# PROTOCOL

## CAPRISA 018

**A phase I/II trial to assess the safety, acceptability, tolerability and pharmacokinetics of a sustained-release tenofovir alafenamide sub-dermal implant for HIV prevention in women**


**Trial Design and Conduct:**
Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa

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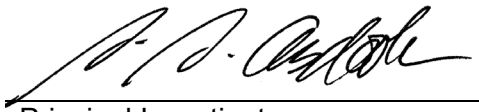

12 August 2019

Principal Investigator
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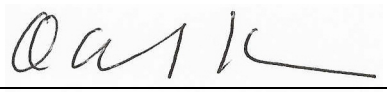
Date of Signature



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## *ABBREVIATIONS AND ACRONYMS*

| | |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| API | Active pharmaceutical ingredient |
| ART | Antiretroviral therapy |
| ARV | Antiretroviral |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| BCRP | Breast cancer resistant protein |
| BMD | Bone mineral density |
| BREC | Biomedical Research Ethics Committee |
| CAB | Community Advisory Board |
| CAPRISA | Centre for the AIDS Programme of Research in South Africa |
| CatA | cathepsin A |
| CES1 | Carboxyesterase 1 |
| CI | Confidence interval |
| COBI/C | Cobicistat |
| $C_{max}$ | Maximum concentration |
| CRO | Contract Research Organisation |
| CRS | Clinical research site |
| CRF | Case Report Form |
| CYP | Cytochrome P450 |
| DAIDS | Division of AIDS |
| DNA | Deoxyribonucleic acid |
| DBS | Dried blood spots |
| DRV | Darunavir |
| DSMB | Data and Safety Monitoring Board |
| EDCTP | European and Developing Countries Clinical Trials Partnership |
| EVG/E | Elvitegravir |
| ECG | Electrocardiogram |
| ECRS | eThekwini Clinical Research Site |
| EU | European Union |
| EMA | European Medicines Agency |
| FBC | Full blood count |
| FDA | (United States) Food and Drug Administration |
| FTC/F | Emtricitabine |
| GCP | Good clinical practice |
| GFR | Glomerular filtration rate |
| HED | Human equivalent dose |
| HIV | Human Immunodeficiency Virus |
| HBsAG | Hepatitis B surface antigen |
| HBV | Hepatitis B Virus |
| HPV | Human papillomavirus |
| HSV-2 | Herpes simplex virus-2 |
| $IC_{50}$ | 50% inhibitory concentrations |
| ICH | International Council on Harmonization |
| IQR | Interquartile range |
| IRB | Institutional Review Board |
| ITT | Intention to treat |
| IVR | Intravaginal ring |
| MCC | Medicines Control Council |

| | |
|---|---|
| MSM | men who have sex with men |
| NOAEL | no observed adverse effect level |
| NRTI | Nucleotide reverse transcriptase inhibitor |
| OATP | Organic anion transporting polypeptide (1B1 and 1B2) |
| PBMC | Peripheral blood mononuclear cells |
| PCR | Polymerase chain reaction |
| PID | Participant identification |
| PK | Pharmacokinetics |
| POC | Point-of-care |
| PrEP | Pre-exposure prophylaxis |
| PSRT | Protocol safety review team |
| QA | Quality assurance |
| QC | Quality control |
| RNA | Ribonucleic Acid |
| RPV | Rilpivirine |
| RT | Reverse transcriptase |
| SAE | Serious adverse event |
| SAHPRA | South African Healthcare Products Regulatory Authority |
| SAP | Statistical analysis plan |
| SAR | Serious Adverse Reaction |
| SHIV | Simian human immunodeficiency virus |
| SOC | System organ class |
| SOP | Standard operating procedure |
| SSF | Specialty Silicon Fabricators |
| SSP | Study Specific Procedures |
| STI | Sexually transmitted infection |
| STR | Single tablet regimen |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TAF | Tenofovir alafenamide |
| TasP | Treatment as Prevention |
| TDF | Tenofovir disoproxil fumarate |
| TFV | Tenofovir |
| TFV-DP | Tenofovir diphosphate |
| $T_{max}$ | Time to maximum concentration |
| UAR | Unexpected Adverse Reaction |
| UKZN | University of KwaZulu-Natal |
| ULN | Upper limit of normal |
| U.S. | United States (of America) |
| VCRS | Vulindlela Clinical research site |

## *CAPRISA 018 STUDY SCHEMA*

| | |
|---|---|
| **Purpose:** | To determine the safety, tolerability, acceptability and pharmacokinetics (PK) of a sustained-release tenofovir alafenamide (TAF) sub-dermal implant for HIV prevention in women. |
| **Design:** | This is a phase I/II trial of a 110mg TAF sub-dermal implant releasing approximately 0.25mg per day. This implant combines two well-established elements; a) TAF, which is a licenced antiretroviral drug widely used in HIV treatment, and b) a sub-dermal implant, which is widely used as a route of administration for contraception.<br><br>The phase I component of the trial initially assesses the safety and PK profile of a single implant over 4 weeks in 6 low risk women (Group 1). Thereafter, the phase I trial progresses to group 2 to assess safety and PK profile of one or two implants in 30 women at low risk (12 single TAF implant, 3 single placebo implant, 12 dual TAF implants and 3 dual placebo implants) over 24 weeks (Group 2). Provided that there are no safety concerns, follow-up of this group will be extended to 48 weeks. The last group of phase I trial (Group 3) is a dose-ranging study, assessing the safety and PK of 2, 3 and 4 implants in 6 low risk women at each dosing level over 24 weeks. In group 2, all women with 2 implants have them inserted in the same arm, while in group 3, all women with 2 implants have them inserted one in each arm in order to assess whether site of insertion influences the safety and PK profile. The PK assessments in group 3 are compared to the PK profile of daily 25mg oral TAF (n=6) over 24 weeks. Progression from one group to the next is dependent on the approval of the Data Safety and Monitoring Board (DSMB) and Protocol Safety Review Team (PSRT).<br><br>The phase II component of the trial (Group 4) assesses extended safety, PK, tolerability and acceptability of the implant in 490 women, randomized 1:1 to the TAF implant with placebo tablet or to the placebo implant with TDF 300mg / FTC 200mg oral tablet. The number of implants, implant location and replacement interval for group 4 will be determined from the phase I data obtained from groups 1-3. |
| **Study Population:** | Healthy, HIV-negative, low risk women aged 18-40 years will be enrolled into groups 1-3, while group 4 comprises healthy, HIV-negative women aged 18-30 years from the general population. |
| **Target Sample Size:** | 550 women (60 in phase I and 490 in phase II) |
| **Treatment Regimen:** | The study product, TAF 110mg, is formulated in a sub-dermal implant, releasing a daily dose of 0.25mg. A total of 1, 2, 3 or 4 implants will be inserted, in the inside of the upper arm, to achieve and test the target daily release of 0.25mg, 0.5mg, 0.75mg and 1mg of TAF, respectively.<br><br>In Group 2, the comparator product for the safety assessment is a placebo implant.<br><br>In Group 3, the comparator for the PK assessment is oral TAF 25mg tablets.<br><br>In Group 4, the active comparator product is daily TDF-FTC 300/200mg oral tablets. The placebo comparators are a placebo implant and a placebo tablet.<br><br>Randomization (1:1) is as follows: |

| | |
|---|---|
| | Arm 1: TAF 110mg implant + daily Placebo oral tablet<br>Arm 2: Placebo implant + daily TDF-FTC 300/200mg oral tablet |
| **Study Duration:** | Group 1: Maximum of 56 days (28 days on product and 28 days off product)<br><br>Groups 2 and 3: Maximum of 52 weeks (48 weeks on product and 4 weeks off product)<br><br>Group 4: Maximum of 120 weeks (116 weeks on product and 4 weeks off product) |
| **Primary Objective:** | To evaluate the safety of the sustained-release TAF 110mg sub-dermal implant/s in HIV uninfected young women at low risk for HIV acquisition |
| **Secondary Objectives:** | • To assess systemic and genital compartment PK of single and multiple TAF 110mg implant/s to determine in-human release rate characteristics<br>• To compare the PK profile of insertion of two implants in one arm compared to insertion of one implant in each arm.<br>• To assess participant acceptability of the implant technology after insertion of one or more TAF implants.<br>• To assess the incidence of HIV infection, as well as other sexually transmitted infections (STIs), including (but not limited to) herpes simplex virus type 2 (HSV-2), human papillomavirus (HPV), gonorrhoea, chlamydia and trichomonas infections.<br>• To assess the viral load and frequency of resistance mutations in HIV seroconverters.<br>• To assess pregnancy rates and outcomes. |
| **Study sites:** | The CAPRISA eThekwini Clinical Research Site (ECRS), Durban and the CAPRISA Vulindlela Clinical Research Site (VCRS), uMgungundlovu (for Group 4 only). These two clinics are in KwaZulu-Natal, South Africa |

# 1 INTRODUCTION

## 1.1 Background and rationale

Although the number of new HIV infections globally have declined by 48% since 2005, the number of people who acquire HIV each year remains unacceptably high (1). In 2016, there were an estimated 1.8 million new HIV infections worldwide. Sub-Saharan Africa continues to experience the highest rates of new HIV infections, accounting for 64% of all new HIV infections in 2016 (1). Young women in this region are particularly vulnerable. In 2016, new infections among young women (aged 15–24 years) were 44% higher than they were among men in the same age group (1). In sub-Saharan Africa, women acquire HIV infection at least 5–7 years earlier than men (2). Adolescent girls and young women in sub-Saharan Africa are therefore especially vulnerable to HIV acquisition, which occurs mostly as a result of unprotected heterosexual intercourse (3).

In addition to biological factors (4-6) that make women more vulnerable than men to acquiring HIV during sex, various sexual coupling patterns place young women at high risk, including partnering with older men who are more likely to be infected (7), multiple concurrent relationships (8), low marriage rates (9), low consistent condom use rates (10, 11), and limited ability to negotiate safer sex practices. Gender-based violence increases vulnerability (12), and poverty increases reliance on transactional sex for survival (13). Women are often unable to convince their male partners, especially husbands and regular partners, to use condoms or to be faithful.

Despite the greater vulnerability of women, they have few options to reduce the transmission and acquisition of HIV. There is an urgent need for new technologies to prevent HIV infection in young women.

## 1.2 HIV prevention technologies for women

The development of technologies that empower women to protect themselves from HIV remains an essential tool in the fight against the HIV epidemic in sub-Saharan Africa. Since July 2010, when antiretrovirals (ARVs) were first shown by the CAPRISA 004 trial (14) to prevent sexual transmission of HIV, the HIV prevention landscape has been transformed, principally through oral (and topical) tenofovir (TFV)-containing pre-exposure prophylaxis (PrEP) (15-20) or through early antiretroviral therapy (ART) initiation in HIV-positive individuals (Treatment as Prevention [TasP]) (21).

Although daily oral tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) has been demonstrated to be consistently effective in men who have sex with men (MSM) and transgender women globally (15, 16), the results of clinical trials in African women have been inconsistent, most likely due to varying adherence (17-20). The lack of protective effect observed in the FEM-PrEP (19) and VOICE trials (20) can partially be explained by suboptimal adherence. In the FEM-PREP trial (19), only 24% of the women allocated to the daily oral TDF/FTC group had detectable drug levels. Similarly, in the VOICE trial, only 25%, 29%, and 30% of women allocated to the daily tenofovir gel, daily oral TDF/FTC and daily oral TDF groups respectively had detectable drug levels (20). In the dapivirine vaginal ring trial, where women were provided with a monthly vaginal ring, higher rates of HIV protection were observed among women over the age of 21 years (56%; 95% Confidence Interval (CI), 31 to 71; $p<0.001$) but not among those 21 years of age or younger (-27%; 95% CI, -133 to 31; $p=0.45$), a difference that was correlated with reduced adherence (22).

Recent approval of TDF/FTC (marketed as Truvada®) by regulatory authorities in South Africa, the European Union (EU), Canada, Kenya and other countries, following on from the United States

(U.S.) Food and Drug Administration (FDA) approval (23, 24) and the 2015 WHO guidelines that recommend the use of TFV-containing PrEP (25), have given impetus to the search for improved formulations to overcome adherence challenges related to daily oral PrEP. However, it also seems that women are more likely than men to require near-perfect adherence to oral TFV-containing HIV prevention therapy and may need to take 5 or 6 out of 7 doses in a week, in order to be protected against HIV (26).

In addition to overcoming adherence challenges, there are concerns that TFV-containing PrEP may predispose individuals to long-term bone and kidney adverse effects, especially in young people who may require years of drug exposure. Data emerging from open label extension PrEP studies indicates a statistically significant impact on renal chemistry (28-30). In the Partners PrEP trial, there was a -1.59 mL/min/1.73 $m^2$ (95% CI, -2.44 to -0.74) decline in creatinine clearance from baseline after median of 18 months (27, 28). In the iPrEx demonstration trial there was a 5% overall decline in creatinine clearance from baseline, translating into a reduction of 6 ml/min at 12 weeks of use (28). Notably, men younger than 25 years showed a greater decline of 7.7ml/min (28) . In both these studies, the declines appear to be non-progressive and not clinically significant. Research into PrEP drugs with better renal and bone safety profiles for long-term use is therefore needed.

Novel long-acting PrEP agents and innovative delivery systems such as sustained-release sub-dermal implants which are successfully and safely used as a delivery mechanism for contraceptives such as Implanon NXT®, Jadelle® and Sino-Implant (II)® have the potential to effectively support adherence and offer independent and discrete use by vulnerable young women. The goal of this trial is to develop and test a new safe and effective sustained-release prevention technology for women in order to impact the course of the HIV epidemic in Africa.

### 1.3 Rationale for a sub-dermal implant device for PrEP

It is well known across different delivery methods for many drugs that medication non-adherence is inversely related to the dosing strategy. Fortunately, sustained-release ARV formulations can potentially reduce the dosing frequency and inherently increase the effectiveness of HIV PrEP. Tenofovir alafenamide (TAF) is particularly promising as a sub-dermal implant for PrEP due to its track record for improved safety compared to TDF, high potency and prolonged intracellular activity (29, 30). A device has been designed for this purpose and is a proposed candidate for HIV prevention. This strategic invention is distinct from both current and recently tested PrEP strategies.

ARV containing intravaginal rings (IVRs) and long-acting injectable ARVs have specific advantages over daily oral PrEP, however their disadvantages present challenges that the implant has the potential to overcome. The dapivirine IVR needs to be replaced monthly and most users are able to remove the product at any time, thereby reducing its effectiveness. Long-acting injectable agents have to be administered every 6 to 12 weeks and adverse drug reactions cannot be countered (or mitigated) once the product is injected. Also, if treatment is interrupted, the long half-life of the drug puts the user at risk for selection of drug resistance should HIV acquisition occur during this time. With the sustained-release TAF implant, user dependence is removed and management of adverse events provider removal of the implant, with rapid waning of drug levels thereafter. These distinct advantages of the TAF implant makes it a substantially improved PrEP technology with potential for wide-scale implementation. While IVRs are for women only, injectables and implants could be used by both men and women. In this project we have focused only on women given the pressing need for a woman-controlled HIV prevention technology. However, a positive signal from the CAPRISA 018 trial will very likely lead to parallel research and development paths for men and women. Its potential infrequent dosing schedule, relative ease of removal and potential applicability to both men

and women, give the implant distinct advantages over IVRs and injectables, constituting a substantial advance for HIV prevention.

This proposed CAPRISA 018 trial will therefore assess a novel sustained-release implant technology (OCIS-001) containing 110mg of TAF for the prevention of HIV infection. The objectives of this project are primarily, to assess the safety of the TAF sub-dermal implant and secondarily, to assess acceptability and PK of different doses, in order to select the optimal dose for an annually administered implant and move forward to phase III trials, assessing efficacy for HIV prevention in young women.

### 1.4 Potential of the clinical trial to achieve maximum impact and advance the field

Sub-dermal implant technology to formulate a sustained-release approach for ARV delivery was not possible previously due to the impractical amounts of drug required. For example, the 300mg of TDF required for PrEP for just one day cannot fit into a sub-dermal implant. However, the high potency of TAF and the consequent small quantities of drug required for several months make an implant product providing 12 months of drug for PrEP feasible now.

A safe and effective sustained-release TAF implant, as an HIV prevention strategy for women to use and control, has the potential to make a significant impact on the HIV epidemic in sub-Saharan Africa. This innovative product offers young women, who are unable to negotiate safer sex, a woman-controlled option to remain HIV-free.

The key benefit that this technology has over oral and topical PrEP is that it overcomes most of the adherence challenges seen in young women from southern Africa that have led to mixed clinical trial results in the past. Low adherence, because of contextual factors including migrant partners, infrequent coital activity and low perception of HIV risk, have had a marked negative effect on drug effectiveness in previous clinical trials and implementation programmes. Poor adherence to PrEP has become the Achilles heel of HIV prevention despite the potency and efficacy of the PrEP drug under study. The provision of a non-user dependent, high potency product once a year, with properties that mitigate some of the renal and bone mineral density concerns associated with TDF/FTC, could provide a safer and higher efficacy PrEP option than any of the current PrEP agents. If so, it could have a major impact on the HIV epidemic in most of Africa, where HIV prevalence is very high in young women. By turning the tide against new HIV infections in young women, an annual PrEP implant could contribute significantly to improved global public health.

### 1.5 Overview of Tenofovir Alafenamide (TAF) Data

TFV is a nucleotide reverse transcriptase inhibitor (NRTI) with potent anti-HIV activity. The phosphonate group contained by TFV contains an altered C-O bond, which is not recognized by host enzymes making it less susceptible to phosphatases (31). TFV is intracellularly phosphorylated to the active metabolite, tenofovir diphosphate (TFV-DP) and incorporated into the viral deoxyribonucleic acid (DNA) by HIV reverse transcriptase (RT) where it functions as a chain terminator (32). Negative charges present in TFV, from its phosphonate moiety reduces its cellular permeability thereby limiting its absorption and oral bioavailability. TDF, is a pro-drug of TFV and is widely used in combination treatment for HIV infection. TDF was developed to improve TFV permeability and permit systemic delivery of TFV for oral administration. However, TDF is rapidly metabolized to TFV by gut and serum esterases *in vivo* and requires high drug exposures for efficient loading of target cells. TAF is a pro-drug of TFV with properties distinct from that of TDF, and has been shown to be significantly more stable in both blood and plasma. Additionally, TAF is

rapidly converted to TFV in lymphocytes resulting in improved intracellular accumulation of TFV-DP within target cells (33). The structural formulae of TFV, TDF and TAF are illustrated in Figure 1 (34).

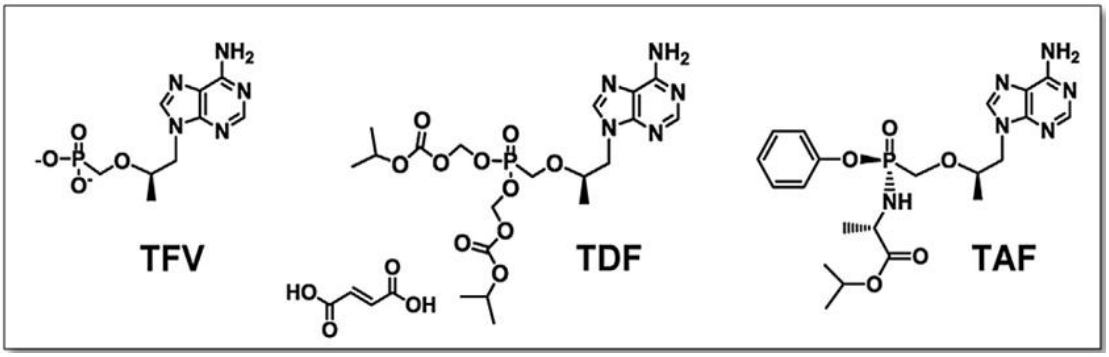


**Figure 1.** Structural formulae for TFV, TDF and TAF (35).

TAF offers many improved properties in comparison to TFV, making it the drug of choice for the development of a sustained-release implant formulation. Firstly, TAF is more stable in plasma than TDF and provides higher intracellular levels of the active phosphorylated metabolite TFV-DP, especially within CD4+ cells, which are the primary target of HIV. Secondly, TAF demonstrates approximately 90% lower circulating levels of TFV when compared to TDF. Furthermore, TAF is not a substrate for renal organic anion transporters (OAT1) offering a more favourable renal safety profile and less impact on bone mineral density compared to TDF (36, 37). Although currently registered for a treatment indication and not for an HIV prevention indication, TAF has long-term potential as a PrEP agent.

There are three forms of the TAF active drug substance. TAF is the synonym for GS-7340 as the free base, TAF monofumarate (GS-7340-02) – 1:1 ratio of GS-7340 to fumaric acid and TAF hemifumarate (GS-7340-03) (2:1 ratio of GS-7340 to fumaric acid. TAF hemifumarate is comparable to TAF monofumarate based on physical, chemical properties and toxicokinetic data. Both forms exist as the free base in blood and biological fluids.

TAF containing products are registered for combination use with other ARVs for the treatment of HIV-1 by the US Food and Drug Administration FDA and the European Medicines Agency (EMA) (38-40), amongst other regulatory authorities.

Table 1: Registered TAF containing drugs

| Trade name® | Drug components and DAILY dosage | Date of first FDA registration | Date of first EMA registration |
|---|---|---|---|
| Genvoya® | EVG 200mg/COBI 150mg/ FTC 200mg and **TAF 10mg** | 2015 | 2015 |
| Descovy® | **TAF 25mg**/ FTC 200mg | 2015 | 2016 |
| Odefsey® | FTC 200 mg/ RPV 25 mg/**TAF 25mg** | 2016 | 2016 |

EVG/E: elvitagravir, COBI/C: cobicistat, FTC/F: emtricitabine, RPV: rilpivirine

### 1.5.1 TAF metabolism

The metabolic pathway for TAF is unique and distinct from that of TDF. TAF passively enters the cell via OATP1B1 and OATP1B3-mediated transport and is subject to ester hydrolysis. In peripheral blood mononuclear cells (PBMC), this is performed by the serine protease cathepsin A (CatA) and in hepatocytes, by carboxyesterase 1 (CES1) (41). Following penetration of TAF into the cells, CatA cleaves the carboxyester bond in the pro-drug moeity and a metastable metabolite is released. The phenol group is eliminated via intramolecular cyclization and hydrolysis, for the formation of the TFV-Ala conjugate. Alanine is then released either by enzymatic or chemical degradation to release

free TFV. TFV is then phosphorylated to TFV-DP, following which TFV is slowly released from cells into plasma for renal elimination by a combination of glomerular filtration and active tubular secretion (35, 42). The TAF metabolic pathway is illustrated in Figure 2.

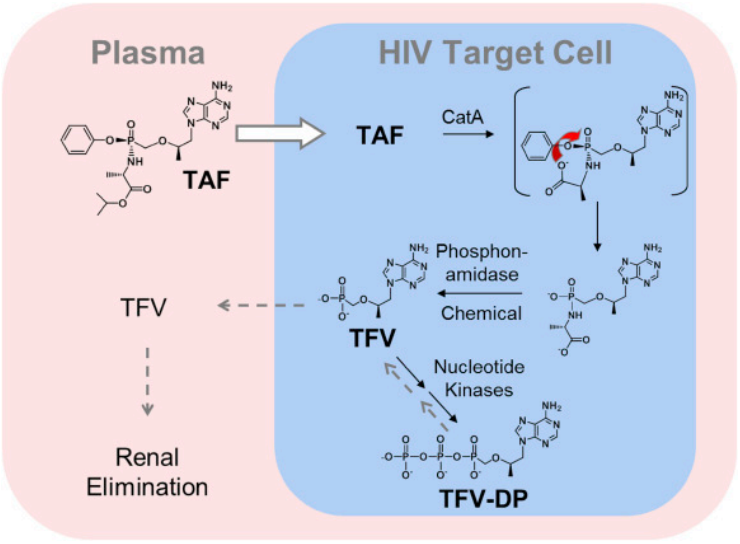


**Figure 2**. Metabolic pathway of TAF (35)

### 1.6 Prior research with TAF

Extensive *in vitro*, pre/non-clinical, clinical safety and efficacy data have been published for TAF and are summarised below.

#### 1.6.1 TAF *in vitro* antiviral activity studies

The antiviral activity of TAF was evaluated in two lymphoblastoid T cells (MT2 and MT4), PBMCs, primary monocyte/macrophage cells and CD4+ T lymphocytes infected with HIV-1 from multiple donors. The anti-HIV potency of TAF was significantly improved in comparison to TFV, possibly attributed to the higher cellular permeability of TAF. The $EC_{50}$ values for TAF were in the 2 to 14 nM range. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, and O), including subtypes A, B, C, D, E, F, and G ($EC_{50}$ values ranged from 0.10 to 12.0 nM) and showed strain specific activity against HIV-2 ($EC_{50}$ values ranged from 0.91 to 2.63 nM). TAF also showed similar antiviral effects with high specificity across all three cells types in comparison to TFV. When TAF and TFV were compared, TAF showed a 500-fold improvement in anti-viral activity compared to TFV in PBMCs (33). TFV weakly inhibited the herpes simplex virus 2 (HSV-2) strain KW (a clinical isolate) with an $EC_{50}$ of 146 µM, which is consistent with data previously published (43). TAF has an $EC_{50}$ of 424 nM for that viral isolate and can be classified as a weak HSV-2 inhibitor.

Other studies with isolated cells have shown efficient TAF activation and potent anti-viral activity in both CD4+ T cells and monocyte-derived macrophages (44). It has also been reported that TAF is 1000 and 10-fold more active against HIV-1 *in vitro* than TFV and TDF, respectively (35). In another study, the antiviral activity of TAF showed declines in serum hepatitis B virus (HBV) DNA levels amongst different TAF dose groups, similar to TDF. The mean changes in HBV DNA by the fourth week were -2.81, -2.55, -2.19 and -2.76 $log_{10}$ IU/ml for TAF at doses of 8, 25, 40 and 120mg respectively and is consistent with the results of TDF at 300mg (45).

### 1.6.2 Pre-clinical (animal) pharmacology of oral TAF and the TAF implant

***Summary of non-clinical findings from the US FDA Genvoya and Descovy Pharmacology/ Toxicology Review (46, 47)***

The main target organs for TAF were kidney and bone in rats and dogs, as well as eye (posterior uveitis) in dogs. Bone and kidney toxicities have also been seen with another TFV-prodrug (TDF) and are believed to be due to TFV exposure, while uveitis has been seen after TAF administration, but not after TDF administration. Further, chronic administration of TAF was associated with reversible PR prolongation and a reversible reduction in heart rate associated with mild QT prolongation and decreased serum T3 levels in dogs***.*** However, no specific concerns were identified from the range of safety pharmacology, genotoxicity, carcinogenicity and reproductive toxicity studies conducted with TAF.

***Renal Toxicity:*** Chronic administration of TAF led to a dose-dependent, slight to moderate renal cortical tubular degeneration/regeneration and karyomegaly in the dog, as well as renal karyomegaly in the rat. In the dog, partial recovery was observed after three months***.***

***Bone toxicity:*** After long term toxicity studies with TAF, dose dependent reductions in bone mineral density and mineral content, as well as changes in bone turnover markers and in related hormones, were observed in rats and dogs. Partial recovery was observed after three months in dogs. Mechanistic toxicity studies suggest that TAF might directly inhibit 25-dihydroxyvitamin D3 production, thus resulting in decreased gastrointestinal absorption of calcium and phosphate and decreased renal reabsorption of calcium***.*** The TAF exposure levels at the NOAEL (no observed adverse effect level) for bone and kidney toxicity in the dog were lower than the human TAF exposure after Genvoya administration. Since TAF has a very short $T_{1/2}$ in rat plasma, no plasma exposure for TAF could be measured. However, the bone and kidney toxicities have also been seen with another TFV-prodrug (TDF) and are believed to be due to TFV exposure. The TFV exposures at the NOAEL was 13 (rats) and 4 (dogs) times the human TFV exposure after Genvoya administration.

***Posterior uveitis:*** In dogs, a minimal to slight infiltration of mononuclear cells of the posterior uvea was seen in the high dose group with similar severity after three- and nine-month administration of TAF. Reversibility was seen after a three-month recovery period. At the NOAEL for eye toxicity, the systemic TAF/TFV exposure in dogs was 5 (TAF) and 15 (TFV) times the exposure seen in humans at the recommended daily Genvoya dosage.

***Cardiac toxicity:*** TAF showed a PR prolongation at the mid and high dose, and a reversible reduction in heart rate associated with mild QT prolongation in the high dose animals at week 39 in the chronic dog study. These changes were associated with decreases in serum T3. Recovery was observed after 13-weeks. At the NOAEL, the systemic TAF exposure was lower in dogs than in humans; therefore, no safety margins were established. The systemic exposure in dogs for TFV was 4 times higher than the exposures seen in humans. No PR prolongation or any change in Electrocardiogram (ECG) results occurred in the single dose safety pharmacology study as well as in the one-month clinical QT study with TAF.

***Embryonic foetal development***

Embryonic foetal development studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to TAF. The embryo-foetal NOAELs in rats and rabbits occurred at TAF exposures similar to and 53 times higher than, respectively, the exposure in humans at the recommended daily dose. TAF is rapidly converted to TFV, the observed TFV exposure in these studies was 59 (rat) and 93 (rabbit) times higher than human TFV exposures at the recommended daily dose.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Since TAF is rapidly converted to TFV and a lower TFV exposure in rats and mice is observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of TDF for HIV-1 infection. The TFV exposure in these studies was approximately 167 times (mice) and 5 times (rat) those observed in humans after daily administration of TAF. At the high dose in female mice, liver adenomas were increased at TFV exposures approximately 10 times (300 mg TDF) and 167 times (10 mg or 20 mg TAF in Descovy®) that in humans. In rats, the study was negative for carcinogenic findings. TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through day seven of gestation.

***Pharmacology of oral TAF in animal models***
*Use of oral TAF in Beagle dogs*
In a group of 5 male Beagle dogs, 10mg/kg of TAF was given orally, and measurable levels of circulating TAF was found in plasma. TAF was only transiently present with a t½ of ± 30 minutes, however the exposure was sufficient to drive high and persistent levels of TFV-DP in PBMCs, while only resulting in low levels of TFV in plasma. The relative efficiency of cell loading by TAF was assessed following administration of equivalent doses of subcutaneous TFV, oral TDF or oral TAF in 2 groups of 5 dogs each. The PBMC to plasma ratio was approx. 1, 5 and 140 for TFV, TDF and TAF respectively, demonstrating, that TAF is highly efficient at concentrating TFV and its metabolites in PBMCS. Oral TAF also resulted in higher levels relative to TDF in on-target tissues, including lymph nodes, mesenteric tissues (5, 7 to 15 fold) and spleen (12.8 fold) in dogs (48).

*Use of oral TAF in macaques*
The PK profile of TAF was investigated at first dose in 12 macaques (mean age, 9.4 years [range, 5–18 years]; mean weight, 9.1 kg [range, 7.8–12.2 kg]). Macaques (4 per dosing group) were given 1 dose of TAF (4.5, 1.5, or 0.5 mg/kg) orally by gavage, after which blood and rectal biopsy specimens were collected. Macaques were exposed rectally to simian human immunodeficiency virus (SHIV) once per week for up to 19 weeks and received saline or FTC/TAF 24 hours before and 2 hours after each virus inoculation. All 6 controls were infected, while the 6 PrEP-treated animals were protected from infection. Target TFV-DP concentrations in PBMCs could be achieved with only 1.5mg/kg of TAF (human equivalent dose for the TAF 25mg). The concentrations of TFV-DP were also measured at 24 hours in rectal biopsy specimens. TFV-DP was detected in all 4 animals that received 4.5 mg/kg of TAF and in 3 of 4 animals that received 1.5 or 0.5 mg/kg of TAF. The authors concluded that FTC/TAF prevents rectal SHIV infection in macaques to a degree similar to that previously found with FTC/TDF, but with a substantially reduced prodrug dose and consequently lower systemic tenofovir exposure. These results suggest that FTC/TAF may be feasible for PrEP against rectal HIV infection and support the clinical investigation of FTC/TAF as a PrEP agent in humans (49).

***Safety and PK of the TAF implant in animal models – systemic and insertion site reactions***
The OCIS-001 TAF implant is proposed for study in the current protocol. Earlier prototypes of the implant, on which early non-clinical work was performed, are listed as generation (GEN) 1 and GEN

2 in the text below and minor differences in physical description of these implants are summarised in the investigators brochure (50).

*Use of the prototype TAF implant (GEN 1) in Beagle dogs*
In the study of four male Beagle dogs (Table 2) aged (13-19 months), a subcutaneous implant containing TAF (0.92mg/day) was given for 40 days, delivering TAF at a rate of 1.07±0.02mg/day, the implant maintained a low systemic exposure to TAF, median 0.85ng $ml^{-1}$ [Interquartile range (IQR): 0.60 to 1.50ng $ml^{-1}$] and TFV median 15ng $ml^{-1}$ [IQR: 8.8 to 23.3ng $ml^{-1}$], the product of *in vivo* TAF hydrolysis. TFV-DP was observed in PBMCs at levels over 30 times higher than those associated with HIV-1 PrEP efficacy in humans. Short plasma t½ of 92 minutes in dogs indicates that significant pro-drug hydrolysis was occurring in the implant. The lower observed levels after day 30 is likely due to the drug depletion from the implant, resulting in a change in release kinetics from zero order to first order. Furthermore, 98% of the TAF payload was delivered over the 40-day period, residual TAF 0.85±0.81mg mean SD. While only traces of TFV mean (0.13mg) were detectable (51).

No adverse treatment related events or significant unusual abnormalities were noted during the 40 days. There were no significant abnormalities present and the majority of clinical observations were considered to be co-incidental, procedure-related or common findings for animals of this species. There was no clinical evidence of inflammation at the implantation site and no evidence of toxicity or poor tolerability was found. In addition, the incision sites appeared healthy on days 2 to 9 following surgery, with staples/sutures removed on day 8 (51).

**Table 2: Summary of major findings from animal studies with the GEN1, GEN2 and OCIS-001 implant extracted from the investigator brochure (50)**

| Study #, implant type, animal, implant location | Implant total TAF dose and daily release rate and duration | Evaluations | Major findings including release rate (RR) |
|---|---|---|---|
| **Study 1**<br>GEN1(51)<br>4 Beagle dogs<br>Dorsal scapular area (surgical implantation) | 40 mg/ implant releasing 0.6mg/day<br>40 days | Residual drug remaining in implant<br>Plasma PK<br>PBMC<br>Incision site observations<br>Body weight assessments | RR: 1.07 mg/day (95%CI: 1.04 – 1.10 mg/day)<br>PK:<br>• Plasma TAF: (median, 0.85 ng/ml; IQR, 0.60 to 1.50 ng/ml)<br>• Plasma TFV: (median, 15.0 ng/ml; IQR, 8.8 to 23.3 ng/ml)<br>• PBMC TFV-DP: median, 512 fmol/$10^6$ cells over the first 35 days<br>Toxicology:<br>• No AEs<br>• No clinical evidence of inflammation, toxicity, or poor tolerability at the implantation sites |
| **Study 2**<br>GEN2<br>12 Beagle dogs, 4 per group<br>Dorsal scapular (Trocar insertion) | Group 1<br>1 implant; 70 mg/implant releasing 0.1 mg/day<br>Group 2<br>2 implants; 70 mg/implant releasing 0.25 mg/day per implant | Residual drug remaining in implant<br>Plasma PK<br>PBMC<br>Drug in vaginal/rectal biopsies and fluids<br>Clinical observations, body weights | Total RR all implants (median, IQR,)<br>Gr 1: 2.1 mg/day, 1.9-2.3 mg/day<br>Gr 2: 2.7, mg/day 2.2-3.4 mg/day<br>Gr 3: 3.1, mg/day 2.4-3.5 mg/day<br>PK: mean plasma levels at steady state (Group 1):<br>• Plasma TAF: 1.4 ng/ml<br>• Plasma TFV: 24.9 ng/ml |

| | | | |
|---|---|---|---|
| | Group 3<br>2 implants 70 mg/implant releasing 1.0 mg/day per implant<br>30 days | Draize scoring of implantation site, and histopathology | • PBMC TFV-DP: 6585 fmol/$10^6$ cells<br><br>Toxicology:<br>• Erythema and/or oedema at the implantation site between the dorsal interscapular region starting on Study Day 14 for all dose groups (largely reversible).<br>• Discharge at the implantation site.<br>• In the Day 30 excisional biopsies, there were macroscopic and/or microscopic findings in all dogs, regardless of the dose or number of implants, consistent with a foreign body tissue reaction due to the TAF implants.<br>• Microscopic alterations were moderate to marked fibrotic capsule formation, minimal to moderate mixed inflammatory cell infiltrates, and minimal or moderate areas of haemorrhage. |
| **Study 4**<br>OCIS-001<br>6 Beagle dogs, 3 per group<br>Dorsal scapular (Trocar insertion) | 1 implant:100mg/ implant releasing low dose/day<br><br>1 implant: 100mg/ implant releasing high dose/day<br>14 days | Residual drug remaining in implant (*in vivo* release rate)<br>Clinical observations, Culture of incision site tissue, and Histopathology | RR:<br>Low: 1.53 +/- 0.65 mg/day<br>High: 7.32 +/- 0.29 mg/day<br>Toxicology:<br>• Clinical observations included oedema at the implantation site and expressible material at the implantation site.<br>• Swabs from the implantation site post implant removal were negative for bacterial contamination.<br>• Histopathology was consistent with a foreign body response. |

*** Study 3 (omitted from table) tested IV TAF and details are contained in the TAF implant IB.**

**Study 1, PK summary**: These data suggest that TAF is stable in the implant for 40 days in vivo, and that this general approach for TAF implants can yield sustained plasma levels of TAF and TFV, and appropriate PBMC TFV-DP concentrations.

**Study 1, Toxicology summary**: Based on clinical observations no adverse events related to treatment were noted during the course of the study. There was no clinical evidence of inflammation at the implantation sites and no evidence of toxicity or poor tolerability at the implantation sites throughout the duration of the study.
Study 2 was conducted with GEN2 implants, which are not directly comparable to the OCIS-001 clinical implants to be used in the clinical trial but is included for completeness.

**Study 2, PK summary**: Group 1 in vivo release rate and plasma and PBMC levels (in Table 2

above). Group 2 and 3 showed in-vivo release rates of 2.7 mg/day and 3.1 mg/day respectively and TFV plasma concentration of 24.9 ng/mL and 15.7 ng/mL and PBMC concentrations of 2810 fmol/$10^6$ cells and 2229 fmol/$10^6$ cells respectively. These findings suggest a saturation effect with higher release rates and lead the optimization of the implant.

**Study 2, Toxicology summary**: Abnormal clinical observations in this study included erythema and/or edema at the implantation site between the dorsal interscapular region starting on Study Day 14 for all dose groups. There were also multiple instances of discharge noted at the implantation site. These noted observations were likely attributed to body's reaction to the implants. Following removal of the implants on Study Day 30, most erythema and/or edema began to resolve and many were completely resolved by the end of the study on Study Day 37.

**Study 4, PK summary**: Data not yet available.

**Study 4, Toxicology summary**: Clinical observations included edema at the implantation site and expressible material at the implantation site. Swabs from the implantation site post implant removal were negative for bacterial contamination. Histopathology was consistent with a foreign body response.

As observed in Study 1, it is expected that when 1 mg per day or less of TAF is administered subdermally, these macroscopic findings will not be observed

### 1.7 Clinical experience with oral TAF in humans

Summary: TAF is registered for use, as part of combination treatment for HIV in several countries globally. Clinical trials with TAF-containing single tablet regimens (STRs) versus TDF-containing STRs for treatment of HIV have successfully demonstrated similarly high rates of virologic suppression in both groups (36, 37). However, for those receiving TAF, there were significantly smaller changes in estimated creatinine clearance, renal tubular proteinuria, and bone mineral density.

#### 1.7.1 TAF Pharmacokinetics

The pharmacokinetics of TAF after multiple doses listed in Table 3.

**Table 3: Pharmacokinetic properties of orally administered TAF (52)**

| **Multiple dose TAF PK Parameters** | |
|---|---|
| **Absorption** | |
| Tmax (h) | 1 |
| Effect of high fat meal (relative to fasting)[a] | Area under the curve (AUC) Ratio = 1.75 (1.64, 1.88) Cmax Ratio = 0.85 (0.75, 0.95) |
| **Distribution** | |
| % Bound to human plasma proteins | ~80 |
| Source of protein binding data | Ex-vivo |
| Blood-to-plasma ratio | 1.0 |
| **Metabolism** | |
| Metabolism | Cathepsin A[b] (PBMCs)<br>CES1 (hepatocytes)<br>CYP3A (minimal) |
| **Elimination** | |
| Major route of elimination | Metabolism (>80% of oral dose) |
| t1/2 (h)[c] | 0.51 |
| % Of dose excreted in urine[d] | <1 |
| % Of dose excreted in faeces[d] | 31.7 |

a. Values refer to geometric mean ratio [High-fat meal/ fasting] in PK parameters and (90% CI). High-calorie/high-fat meal = ~800 kcal, 50% fat.

b. *In vivo*, TAF is hydrolyzed within cells to form TFV (major metabolite), which is phosphorylated to the active metabolite, TFV-DP. *In vitro* studies have shown that TAF is metabolized to TFV by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon co-administration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.
c. $t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, TFV-DP, has a half-life of 150-180 hours within PBMCs.
d. Dosing in mass balance studies: TAF (single dose administration of [14C] tenofovir alafenamide).

In a phase I/II study, amongst 30 HIV-positive treatment naïve subjects, mean age 34 years, TAF was given as 40mg and 120mg and TDF 300mg was given orally for 14 days. The estimated TAF elimination $t_{1/2}$ in plasma was ~ (20 min -1 hour) with concentrations falling to below detectable levels between 2.5 and 8 hours after dosing. The median apparent volume of distribution for TAF was >100L for both dosing cohorts (29). Several phase I, II and III studies have reported on the pharmacokinetics of TAF in HIV-positive individuals often in comparison to TDF and as part of single tablet regimens. Plasma concentrations of TFV were found to be approximately 91% lower in TAF groups than with the TDF group, the TAF group delivering up to 5 to 7 times higher intracellular, physiologically active metabolite (TFV-DP) to PBMCs (36, 53-55).

**Drug interactions with TAF**

TAF is a substrate of P-gp, breast cancer resistant protein (BCRP), organic-anion transporting polypeptide (OATP)1B1 and OATP1B3. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Section 6.4.4). Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect and development of resistance. Co-administration with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A in vitro, but it is not an inhibitor or inducer of CYP3A in vivo (52).

### 1.7.2 Safety and Efficacy of TAF for Treatment of HIV

Two phase III clinical trials for HIV-positive treatment naïve subjects have shown non-inferiority for a regimen containing a 4-drug single tablet regimen (STR) with either TAF or TDF. These results showed that treatment with TFV in either E/C/F/TAF or E/C/F/TDF can exceed the 90% threshold for virological suppression (plasma HIV ribonucleic acid (RNA) < 50 copies/ml) (37). In addition, continued treatment in these trials showed that the high rates of virologic suppression observed at 48 weeks were sustained though 96 weeks (56). These results together show that TAF-based regimens are as effective as TDF-based regimens for first-line treatment of HIV infection.

A Phase I/II study, including 30 subjects, evaluated the PK, safety and antiviral activity of 40 or 120 mg of TAF with 300 mg of TDF when administered as monotherapy once daily for 14 days in HIV-positive, treatment-naive subjects. The most commonly observed adverse events, at these relatively high daily doses of TAF, were headache, nausea and flatulence, which occurred similarly across the three groups (29).

A phase II randomised study comparing one daily dose of the study drug E/C/F/TAF (n=112) to one daily dose of E/C/F/TDF (n=58) found similar 48-week safety profiles in both arms. Nausea and diarrhoea were the most common side effects, and no clinically defined cases of proximal renal tubulopathy were observed in either arm. No treatment discontinuations were reported and both regimens were well tolerated (36). In the 96-week phase III study, 866 patients received TAF and 867 received TDF. A few subjects discontinued treatment due to treatment-related adverse events (AEs) (1.2% TAF vs 2.3% TDF). However, at week 48, a better renal safety profile and bone mineral density (BMD) was observed for the TAF arm in comparison to the TDF arm (56). Similarly, in a phase III trial with 866 treatment naïve adult subjects receiving E/C/F/TAF, diarrhoea (17%), nausea (15%) and headache (14%) were the most frequently reported adverse events and occurred with similar frequency in the TDF arm. AEs leading to treatment discontinuation were infrequent: seven (0.8%)

subjects in the TAF treatment arm and 11 (1.3%) in the TDF arm stopped taking treatment due to adverse treatment-related events (37).

The efficacy observed in treatment-naïve individuals is also consistent for virologically-suppressed adults with mild-moderate renal impairment, who switch regimens and do not have a history of virological failure. Amongst treatment-experienced HIV-positive adults who developed resistance to multiple standard regimens the switch to a regimen containing E/C/F/TAF+ Darunavir (DRV) was associated with maintained virological suppression and an improvement in markers of renal safety. The switch to E/C/F/TAF + DRV also resulted in a higher mean treatment satisfaction scores and improved adherence (57). The nature and frequency of AEs reported for virologically-suppressed subjects who switched to a TAF-containing regimen, were consistent with the findings for treatment-naïve subjects. Rates of discontinuation due to adverse treatment related events were found to be low (1-2%) (58, 59).

***TAF use in HBV co-infection***

A phase IIb open label study consisting of 72 subjects co-infected with HIV/HBV found that after one year of switching treatment from a TDF-containing regimen to EVG/COBI/FTC/TAF, all subjects maintained high rates of HIV and HBV suppression. Furthermore, improved renal function and reduced bone turnover biomarkers were noted. No discontinuations were reported. These results are supportive of EVG/COBI/FTC/TAF in treating HIV/HBV co-infections, although the product is not registered for this indication. Overall, treatment in both arms was well tolerated (36).

***TAF and renal effects***

Amongst 663 HIV virologically-suppressed subjects who were randomized to switch to TAF (n=333) vs remain on TDF (n=330), each co-formulated with FTC, while continuing on a third agent (boosted Protease Inhibitor (PI)/unboosted third agent), the switch TAF was found to be non-inferior and resulted in improved proteinuria, albuminuria and BMD. Additionally, there was an increase in glomerular filtration rate (GFR) and a decrease in protein, especially in the excretion of β2 microglobulin and retinol binding protein markers of proximal renal tubulopathy (60).

A phase III study, described earlier, demonstrated a smaller mean serum creatinine increase (0.08 vs. 0.12mg/dL) ($p< 0.0001$) as well as significantly less proteinuria (median % change in urine protein: creatinine ratio -3 vs 20, respectively; $p<0.0001$), retinol binding protein (median % change urine protein: creatinine ratio 9 vs 51, respectively; $p<0.0001$) and β2 microglobulin (median % change in urine protein: creatinine ratio -32 vs 24, respectively; $p<0.0001$ at week 48 (37). After 48 weeks, there were no cases of proximal renal tubulopathy, including Fanconi syndrome, for either treatment arm. Two subjects in the TDF arm developed proximal tubulopathy at week 96. No discontinuation associated with adverse renal events was reported for the TAF arm, while six were reported for the TDF arm ($p=0.03$). At 96 weeks, the beneficial effects of a TAF inclusive regimen were further confirmed, with sustained kidney function, and more favourable changes in proteinuria, albuminuria, and tubular proteinuria distinct from that of a TDF-containing regimen (56).

A 48-week study evaluated the efficacy and safety of FTC and TAF (10mg) in 242 HIV-positive subjects with mild-moderate renal impairment ($eGFR_{CG}$: 30-69mL/min). Patients were virologically-suppressed for at least six months before being switched to E/C/F/TAF. At baseline, the median eGFR was 56mL/min and 33% of patients had an eGFR between 30 and 49mL/min. There were no significant changes in the creatinine clearance and no evidence of renal tubulopathy. Subjects showed significant improvement in proteinuria, albuminuria and BMD. Overall, the data support the efficacy and safety of once daily E/C/F/TAF in HIV patients with mild-moderate renal impairment without dose adjustment (61).

In another study of treatment-experienced HIV-positive subjects, 199 were screened and 135 were enrolled, with 89 being randomized for E/C/F/TAF + DRV, while 46 remained on the baseline treatment. In this study, the TAF group experienced a higher rate of AEs, which was not unexpected for patients initiating a novel treatment regimen. However, the switch to TAF, similarly to other studies, resulted in improved renal function and was well tolerated overall (57).

***TAF effects on bone mineral density (BMD)***
Studies with HIV-positive individuals have shown an association between TDF and a small but significant reduction in BMD, which in some cases can lead to fragility fractures, specifically amongst young HIV-positive adults (25–54 years) (62). Phase II and III clinical trials have investigated the effect of TAF compared with TDF on bone metabolism, studying changes in BMD. Treatment-naïve adults receiving the TAF-containing regimen displayed significantly smaller reductions in both lumbar spine and hip BMD at week 48 in comparison to those receiving the TDF-containing regimen (37). The mean percentage change in the BMD was -1.30% versus -2.86% for TAF and TDF, respectively ($p<0.0001$). The changes for hip BMD were -0.66% and -2.95%, respectively, ($p<0.0001$). Overall, 76% of subjects who were treated with the TAF-containing regimen had no change in hip BMD and 17% had bone loss (defined as >3%), compared to 46% of those in the TDF arm having no change in BMD and 50% experiencing bone loss. The spine BMD changes were less at 48 weeks, with 68% stable and 26% losing bone mass in the TAF arm versus 51% remaining stable and 45% having BMD loss in the TDF arm.

At week 96, the benefit of the TAF-containing arm on bone metabolism was more evident. Spine BMD increased toward baseline (mean % change at week 48: -1.291% and at week 96: -0.960) for subjects in the TAF arm, while it remained lower for subjects in the TDF arm (mean % change at week 48: -2.830% and at week 96: -2.792%) (56).

***TAF effects on lipid profile***
A phase II, randomized, double-blind, double-dummy, multicentre, active-controlled study comparing two STR regimens, E/C/F/TAF (n=112) and E/C/F/TDF (n = 58), found that patients on E/C/F/TAF had higher increases in total cholesterol, low-density lipoprotein, and high-density lipoprotein, but the total cholesterol/high-density lipoprotein ratio was unchanged for both (36).

***TAF use in pregnancy and lactation***
There are insufficient human data on the use of TAF during pregnancy to inform drug-associated risks of birth defects and miscarriage. Similarly, there are insufficient data on infant exposure in lactating women. For these reasons, pregnant and lactating women will be excluded from the current study.

### 1.8 Dose rationale for the TAF implant (OCIS-001) dosages in the Phase I/ II trial
The TAF implant (OCIS-001) is at an early stage of development for HIV prevention. This trial will primarily evaluate safety and not efficacy of this device. Women at low risk for HIV infection will be enrolled to assess initial safety, PK, acceptability and tolerability. Based on the data produced in the initial safety Phase I part of the study, the optimal number of implants will be selected for testing in the extended safety Phase II part of the trial.

PrEP reduces the risk of sexually-acquired HIV in adults but it is important to be able to estimate a biological correlate of protection. The iPrEx trial studied Truvada® (TDF/FTC) *versus* placebo in MSM at high risk of acquiring HIV infection. Truvada® demonstrated a 42% relative risk reduction relative to placebo (15). A *post hoc* analysis found that a PBMC TFV-DP concentration of 16 fmol/$10^6$ cells was associated with 90% reduction in risk for HIV acquisition (63). It should be noted that the iPrEX study used cryopreserved PBMCs, which leads to 33 to 67% loss of TFV-DP. Therefore, a more conservative $EC_{90}$ lies in the range of 24 to 48 fmol/$10^6$ cells. While this tentative

prophylactic TFV-DP concentration requires further clinical validation, it represents the best available initial target level in PBMCs in the preclinical development of a TAF implant (51).

A subcutaneous implant delivering TAF at a rate of 1.07 ± 0.02 mg/day for 40 days in Beagle dogs achieved and maintained median PBMC TFV-DP levels of 512 fmol/$10^6$ cells over the first 35 days (51). This concentration is 11 to 32 times higher than the protective target from iPrEX (corresponding to a TFV-DP concentration range of 16 to 48 fmol/$10^6$ cells). Simple allometric scaling (exponent, 0.75) from Beagle dogs (mean weight, 10.8 kg) to humans (70 kg) affords a preliminary, lower target daily TAF release rate of 0.14 mg/day in humans to maintain a median TFV-DP PBMC concentration of 16 fmol/$10^6$ cells. The concentration of PBMCs in Beagle dog whole blood (mean, 1.6x$10^6$ cells/ mL; SD, 0.7x$10^6$ cells/m L) was comparable to typical values for HIV-negative humans. Since 0.14 mg TAF per day in humans is estimated to yield TFV-DP PBMC concentrations of 16 fmol/$10^6$ cells (lower end of expected efficacy), the planned clinical study will evaluate a target of 0.25 mg TAF per day per implant, ranging from 1 to 4 implants (0.25 mg/day to 1 mg/day).

Safety at this level is expected based on prior nonclinical studies with TAF (50) and based on conversion to human equivalent dose (HED) and there is at least a 11-fold safety factor based on the NOAEL in the most sensitive species, for a dose of 1 mg/day in humans.

Table 4: Safety factor based on the NOAEL in the most sensitive species

| **Species** | **NOAEL (oral)** mg/kg/day | **HED (oral)** mg/kg/day | **HED (subdermal)** mg/kg/day | **Safety factor for 1 mg/day target subdermal human dose (0.017 mg/kg for 60 kg person)** |
|---|---|---|---|---|
| Rat | 25 | 4.05 | 0.68* | 41 |
| Dog | 2 | 1.08 | 0.18* | 11 |

* Assuming 17% bioavailability when taken orally (48)

### 1.8.1 Scenarios for OCIS-001 implant device failure (dose dumping and dose retention)

Although the active ingredient TAF has been tested extensively in humans as the oral formulation, it has not been formulated or administered as a subcutaneous implant in humans prior to this trial. There is a small but potential risk for device failure that requires examination.

Three scenarios for device failure are considered here:

- Scenario 1: Potential full release of TAF into systemic circulation
- Scenario 2: TAF is released too rapidly into systemic circulation
- Scenario 3: TAF is released too slowly into systemic circulation

***Scenario 1: Full release of TAF from the implant***

Each subdermal implant is expected to contain ca. 110 mg. Up to four implants are planned for use during the proposed clinical study. This risk analysis considers the full release of TAF from up to two implants in a given participant (a greater number of simultaneous unit failures is considered exceedingly unlikely). Full release of two implants would be approximately 200 mg TAF delivered sub-dermally.

This dose of TAF (approximately 200 mg in humans, delivered sub dermally) is expected to exceed NOAEL values based on chronic toxicology studies in rats and dogs:

- 26 week oral toxicology study in rats had a NOAEL of 25 mg/kg/day; 9 month oral toxicology study in dogs had a NOAEL of 2 mg/kg/day (Genvoya® Pharmacology Review) (46, 64).

- Accounting for 70% oral bioavailability (48), this corresponds to a subdermal dose of 17.5 mg/kg/day in rats and 1.4 mg/kg/day in dogs.
- Human equivalent doses are 2.84 mg/kg (based on rat) and 0.76 mg/kg (based on dog). Assuming a 60 kg human, this corresponds to 170 mg (based on rat) and 45 mg (based on dog).
    - However, this “dose dumping” would be expected to be a one-time event (not chronic). Also, blood TAF exposure would decline rapidly as it is hydrolyzed in plasma to TFV; the drug’s half-life in human plasma is approximately 18 min (30).
    - This dose of TAF would result in comparable expected plasma TFV levels as oral 300 mg TDF.
- Following a single dose of Viread® 300 mg to HIV-positive subjects in the fasted state, AUC values for TFV are 2.29±0.69 µg. hr. mL-1 (Viread Package Insert), approximating a serum concentration of 0.1 µg/ml TFV.
- A subdermal dose of 200 mg TAF would be expected to yield a plasma concentration of TFV of approximately 517 ng mL-1, or 0.5 µg mL-1. A 25 mg oral dose in humans, assuming 60 kg human, results in an AUC of 270 ng hr mL-1 (35), approximating 11 ng mL-1. Assuming linearity, an oral dose of 200 mg would result in 88 ng mL-1. Accounting for 17% bioavailability upon oral dosing (48), this yields an estimate of 517 ng mL-1 for 200 mg delivered subdermally.
- No known toxicities from intracellular TFV-DP exist, likely because *in vitro* analyses demonstrate that there is no mitochondrial effect. Clinical studies have confirmed this observation at the standard 25 mg exposure, or even after repeated daily oral dosing of 125 mg TAF (29).

**Scenario 2: Implant delivers TAF too rapidly**

In the extreme case of immediate “dose dumping,” the analysis above applies. In less extreme circumstances, the unit delivers TAF too rapidly over time. The impact of this is that the unit may be implanted for a period of time during which no TAF is remaining for delivery (no efficacy). This will be evaluated in the current study. This is not considered a significant safety risk for the current study, because study participants will be counselled on safer sex practices, and the product is not purported to have efficacy at this time.

**Scenario 3: Implant delivers TAF too slowly**

If the unit delivers TAF too slowly, it may have limited efficacy. The PK and durability of the implant will be evaluated in the current study.

## 2 STUDY SETTING

The study will be conducted at both the urban CAPRISA eThekwini Clinical Research Site (ECRS) in Durban, South Africa, and the rural CAPRISA Vulindlela Clinical Research Site (VCRS) in uMgungundlovu district, South Africa.

CAPRISA ECRS has well-developed clinical trial infrastructure and trained staff with experience in conducting clinical trials. The site is located adjacent to the Prince Cyril Zulu Communicable Disease Centre, which provides services specifically for the diagnosis and treatment of STIs and tuberculosis. The clinic is conveniently situated in the Warwick triangle in the transport hub of Durban, making it readily accessible in terms of the transport infrastructure. Annually, approximately 40,000 cases of STIs are treated at this clinic, approximately 36,000 of which are new cases. The majority of the STI patients accessing these facilities are self-referred either symptomatic with genital ulceration and/or vaginal discharge syndrome or as contacts of patients with a diagnosis of a STI and include both males and females. Given the high prevalence of HIV infection in South Africa and the strong association between STIs and HIV acquisition, these patients are at an increased

risk of acquiring and transmitting HIV through sex (65, 66). Overall, HSV-2 and HPV prevalence in women attending the CAPRISA ECRS is 59.0% (95% CI 53.1 – 64.6) and 74.9 (95% CI 69.3 – 80.5) respectively. Overall, HIV prevalence in women attending the CAPRISA ECRS is 23% (95% CI 21.3 -25.6). The HIV incidence rate at this site during a trial of topical PrEP published in 2010 was 9.0 per 100 women-years (CI: 5.3-14.3) in the placebo arm (14). More recently in the CAPRISA oral PrEP demonstration study, CAPRISA 082, site HIV incidence rate per 100 py was 3.94 (1.73-8.06) amongst PrEP users (unpublished data, January 2018) and the recently released District Health Barometer for the eThekwini district, which is the source population for participants at this clinic, showed HIV prevalence to be 16.8% in 2017 (67).

The CAPRISA VCRS is situated in a rural community, with approximately 90,000 residents, in the uMgungundlovu district in the KwaZulu-Natal midlands, about 150 km north-west of Durban. CAPRISA has conducted several clinical trials at this rural research clinic. VCRS is conveniently located adjacent to a provincial Department of Health run clinic called the Mafakatini Primary Health Care Clinic. Overall HSV-2 and HPV prevalence in women attending the VCRS is 47.9% (95% CI 44.0 – 51.9) and 73.4% (95% CI 69.7 – 77.1), respectively. Overall HIV prevalence in pregnant women in Vulindlela has increased from 35.3% (95% CI 32.3-38.3) in 2001-2003 to 39.3% (95% CI 37.2-41.4) in 2009-2013 (68). The HIV incidence rate at this site during a trial of topical PrEP completed in 2010 was 9.1 per 100 women-years (CI: 6.6-12.3) (14). From the 2015 - 2016 HIV Incidence Provincial Surveillance System (HIPSS) data, HIV incidence for women was 3.54 (95% CI 2.87-4.31) overall, 4.55 (95% CI 3.66-5.58) in 15-24 year-olds and 1.65 (95% CI 0.67 – 2.92) in 24-34 year-olds. The recently released District Health Barometer for the uMgungundlovu district, which is the source population for participants at this clinic, showed HIV prevalence to be 20.6% in 2017 (67).

These HIV prevalence and incidence rate data from the CAPRISA ECRS and VCRS in KwaZulu-Natal, South Africa, underscore the generalized nature of the HIV pandemic in this region of the world. The high HIV prevalence and continued high HIV incidence rates, particularly in younger women, highlight the hyper-endemic characteristic of the epidemic and the importance of developing HIV prevention technologies for young women in this setting.

# 3 STUDY OBJECTIVES

## 3.1 Primary Objective

- To evaluate the safety of the sustained-release TAF 110mg sub-dermal implant/s in HIV-negative young women at low risk for HIV acquisition

## 3.2 Secondary Objectives

- To assess systemic and genital compartment PK of single and multiple TAF 110mg implant/s to determine in-human release rate characteristics.
- To compare the PK profile of insertion of two implants in one arm compared to insertion of one implant in each arm.
- To assess participant acceptability of the implant technology after insertion of one or more TAF implants.
- To assess participant tolerability of the implant technology after insertion of one or more TAF implants.
- To assess the incidence of HIV infection, as well as other sexually transmitted infections (STIs), including (but not limited to) HSV-2, HPV, gonorrhoea, chlamydia and trichomonas infections.
- To assess the viral load and frequency of resistance mutations in HIV seroconverters.
- To assess pregnancy rates and outcomes.

# 4 STUDY DESIGN

## 4.1 Overview

This is a study of a novel formulation of TAF in a sub-dermal implant, OCIS-001. TAF oral tablets are registered in several countries for the treatment of HIV infection and sub-dermal implants are registered and widely used globally for hormonal contraception in women. In the CAPRISA 018 trial, TAF API (active pharmaceutical ingredient), which has an extensive safety profile, has been formulated as a sub-dermal implant for slow, continuous release of drug. Although a prototype of the implant has been tested successfully in Beagle dogs, this is the first human trial to assess release rates, PK and safety of the OCIS-001 TAF implant.

The trial comprises an initial safety assessment in six (Group 1) participants followed by a dose escalation component (Groups 2 and 3) assessing the safety and PK of TAF 110mg implants releasing a daily dose of 0.25mg, 0.5mg, 0.75mg and 1mg in 60 healthy, low risk, HIV-negative women. Comparator drugs include TAF 25mg oral tablets and the placebo implant. Once data from Groups 1 to 3 are available, Group 4 will initiate as an extended safety assessment where 490 HIV-negative women will be randomized in a double-blinded, double-placebo controlled trial to assess safety, acceptability and PK of the TAF implant (Table 5 and Figure 3).

**Table 5: Study drug administration in the CAPRISA 018 trial assessing initial safety and dose escalation followed by an extended safety assessment**

| Group | (n) | Study product | Implant insertion site | Duration of exposure (weeks) | Estimated daily TAF release rate (mg/day) |
|---|---|---|---|---|---|
| **Group 1: Phase I Assessment of initial 4 week intensive safety and PK assessment** | | | | | |
| 1 | 6 | 1 TAF implant rod 110mg | Arm | 4 | 0.25 |
| **Group 2: Assessment of 4 and 24 week safety and PK of 1 and 2 TAF implant rods in one arm** | | | | | |
| 2a | 12 | 1 TAF implant rod 110mg | Arm | 24(48)* | 0.25 |
| 2b | 3 | 1 placebo implant rod | Arm | 24(48)* | 0 |
| 2c | 12 | 2 TAF implant rods 220mg | Both rods in one arm | 24(48)* | 0.50 |
| 2d | 3 | 2 placebo implant rods | Both rods in one arm | 24(48)* | 0 |
| **Group 3: Assessment of 4 and 24 week safety and PK of escalating doses and of varying site of administration** | | | | | |
| 3a | 6 | 2 TAF implant rods 220mg | 1 rod in each arm | 24 | 0.50 |
| 3b | 6 | 3 TAF implant rods 330mg | All 3 rods in one arm | 24(48)* | 0.75 |
| 3c | 6 | Oral 25mg TAF tablets daily | No insertion | 24 | 25 |
| 3d | 6 | 4 TAF implant rods 440mg | All 4 rods in one arm | 24(48)* | 1 |
| **Group 4: Assessment of 48 and 120 week extended safety and PK of optimal implant dose selected from data generated in Groups 1-3** | | | | | |
| 4a | 245 | TAF Implant/s plus placebo oral tablet | 2 rods in one arm** | Up to 116 weeks | 0.50** |
| 4b | 245 | TDF 300mg/FTC 200mg oral tablet + placebo implant/s | 2 rods in one arm** | Up to 116 weeks | 0 |

*Follow-up extended based on safety review of the adverse events occurring during the first 4 weeks after insertion in groups 1-3 **Based on the PK and safety assessment in dog models but is subject to change after PK data becomes available from groups 1- 3 in the trial.

Following screening, women at low risk for HIV, who meet all eligibility criteria will be enrolled sequentially into Group 1.

### 4.1.1 Group 1 (n=6)

Following screening, women at low risk for HIV, who meet all eligibility criteria will be enrolled sequentially into Group 1.

In Group 1 (Table 5), six participants will be enrolled on separate days, after which enrolment will be temporarily suspended pending the outcome of their 28-day safety assessments. During these 28 days, women will have safety and PK assessments, post implant insertion, in accordance with the Schedule of Evaluations for Group 1 (*See Appendix A1*)

Each safety assessment will review AEs at grade 2 or higher for local site reactions and serum chemistry. Product hold or discontinuation will be based on assessment of grade 3 or higher AEs that are deemed to be probably or definitely related to study product.

At Day 28 the implant will be removed and safety assessments will be conducted off–product at days 35, 42 and 49. The final, study exit visit will be held on day 56. During this time the protocol safety review team (PSRT) will review the safety data for each of the listed time points shortly after each of these milestones have been reached by all six participants. Within approximately 14 days of all six participants reaching the 28-day milestone, an independent DSMB review of the data will be undertaken to determine whether or not there are any safety concerns precluding study continuation.

Following DSMB approval to proceed with the study, after assessment of Group 1 four-week safety data, the next 30 eligible low risk HIV-negative women will be enrolled into Group 2.

### 4.1.2 Group 2 (n=30)

Following DSMB approval to proceed with the study, after assessment of Group 1 four-week safety data, the next 30 eligible HIV-negative women will be enrolled into Group 2.

These 30 women will be randomized to one of four sub-groups where they could receive either one or two active or placebo implants in a 4:1 active to placebo ratio. Participants will attend study visits weekly in the first 4 weeks post active/placebo implant insertion and thereafter study visits will be conducted every 4 weeks. Safety and pharmacokinetic assessments will be performed at study visits in accordance with the Schedule of Evaluations for Group 2 (*See Appendix A2*).

During this time the PSRT will review the safety data for each of the listed time points shortly after each of these milestones as they are reached by the 30 participants. The DSMB will independently review week 4 safety data on all group 2 participants to determine whether there are any safety concerns precluding progression to group 3. Group 2 participants will continue follow-up for a minimum of 24 weeks. The DSMB will then independently review safety data up to week 12 to determine whether there are any safety concerns precluding follow-up from being extended to week 48 to enable collection of further safety data or study discontinuation. At week 48, the implant will be removed and the final safety study visit will take place by week 52.

Contingent on DSMB approval to proceed with the study after the review of the week 4 safety data from participants in Group 2, the dose escalation component (Group 3) of the study will proceed in 24 eligible low risk HIV-negative women.

### 4.1.3 Group 3 (n=24)

Contingent on DSMB approval to proceed with the study after the review of the week 4 safety data from participants in Group 2, the dose escalation component (Group 3) of the study will proceed in 24 eligible HIV-negative women.

Participants in Group 3 will be enrolled in parallel in for Groups 3a, 3b and 3c but sequentially for Group 3d pending Group 3b, 7-day safety assessment outcome. Participants will attend study visits

weekly in the first 4 weeks post active implant insertion or receipt of oral TAF tablets and thereafter study visits will be conducted every 4 weeks. Safety and PK assessments will be performed at study visits in accordance with the Schedule of Evaluations for Group 3 (See Appendix A2). During this time, the PSRT will review safety data for each of the listed time points shortly after each of these milestones are reached by the 24 participants.

The first 18 participants will be enrolled into Group 3a, 3b and 3c, where 6 participants will have one implant inserted in each arm, 6 participants will have 3 implants inserted in one arm and 6 participants will receive the oral TAF 25mg tablet daily, respectively. No implants will be inserted for Group 3c. The 7-day safety data from the participants in Group 3b will be assessed by the PSRT to determine whether there are any safety concerns precluding progression to Group 3d. Contingent on PSRT approval, 6 participants will then be enrolled in Group 3d where they will receive 4 implant rods in one arm. The PSRT will review the 7-day safety and PK data from all 3 implant groups (Group 3a, 3b and 3d) to make a determination to proceed as planned or whether a change in the number of rods is warranted.

Participants in Groups 3a and 3c will have the implants removed and oral TAF tablets stopped respectively at week 24 and will continue follow up off-product through to week 48 at which point the final study visit will occur and these participants will be exited from the study.

If the PSRT recommends increasing the number of rods to 3 or 4 then the DSMB will independently review week 4 safety data in Group 3b and 3d to determine whether there are any safety concerns precluding participant continuation with the number of implant rods recommended by the PSRT. Further, this DSMB review of the week 4 safety data will determine whether Groups 3b and 3d should continue follow-up beyond week 24 to week 48 to enable collection of further safety data. Should the DSMB recommend extended follow-up of Groups 3b and 3d, the participants will be followed for safety assessments up to week 48, after which the implants will be removed and the final safety study visit will take place at week 52.

#### 4.1.4 Group 4 (n=490)

Enrolment into Group 4 will proceed with 2 implant rods in one arm provided that the DSMB review of the 4-week safety data in Group 2 recommended study continuation and the PSRT review of the safety and PK data from Group 3 recommended progression to Group 4 without change. In the event that the PSRT recommends increasing the number of implant rods, then enrolment into Group 4 will only proceed after a DSMB review of 4-week safety data in Groups 3b and 3d. With this approach, the review of the PK and safety data by the PSRT and the review of the safety data by the DSMB will determine the dose (number of implants), implant dosing frequency (replacement interval) and implant location. This determination for Group 4 will include both safety assessments and PK modelling of the peripheral blood mononuclear cell (PBMC) TFV-DP concentrations. Safety and pharmacokinetic assessments will be performed at study visits in accordance with the Schedule of Evaluations for Group 4 (*See Appendix A3*).

The extended safety assessment is a randomized, double-blinded, double-placebo controlled trial to assess safety, acceptability and PK of the TAF implant in 490 HIV-negative women from the general population. In addition, this extended safety component will generate data on the potential efficacy of the TAF implant to guide the design of subsequent phase III trials aim to assess the efficacy of this technology for HIV prevention.

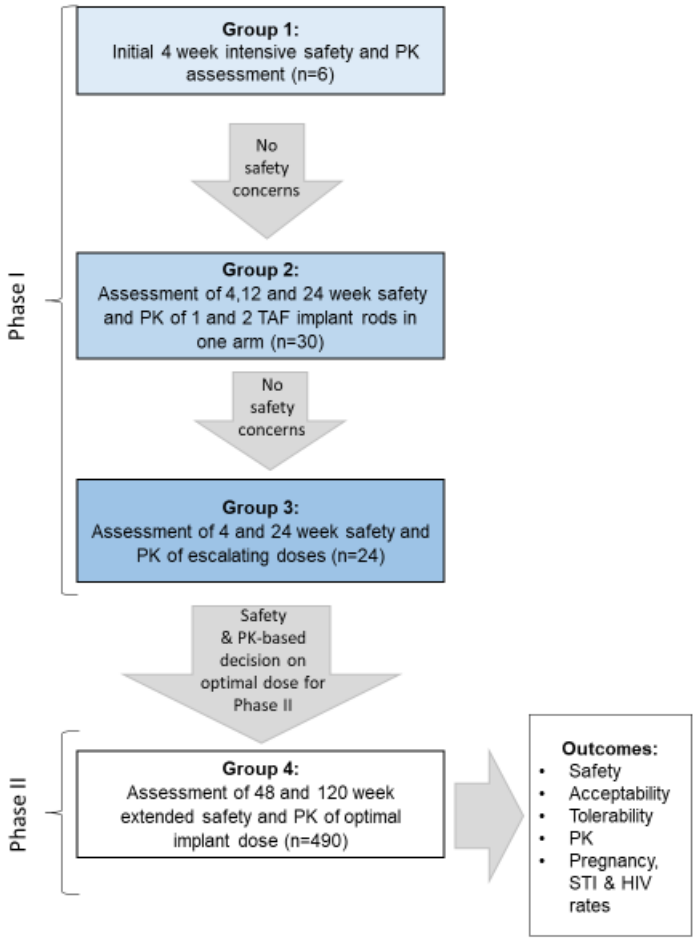


Figure 3: CAPRISA 018, phase I/II trial design summary graphic

### 4.2 Accrual and Follow-up

For the initial safety assessment in Group 1, low risk HIV-negative participants will be enrolled sequentially on different days based on the outcome of safety reviews from each group. Accrual of Group 1 participants will take place over approximately 3 weeks. In Group 1, six participants will be enrolled on separate days and followed for 28 days on product and a further 4 weeks off-product. If the independent DSMB assessment of Group 1 data at week 4 shows no safety concerns, then the next 30 eligible women will be enrolled into Group 2.

Accrual of participants for Group 2 will occur over approximately 12 weeks. Group 2 participants will continue follow-up for a minimum of 24 weeks. If the DSMB review of safety data up to week 12 show no safety concerns, follow-up will be extended to week 48 on product to enable collection of further safety data and a further 4 weeks off-product (week 52). The DSMB will also independently review week 4 safety data on all Group 2 participants to determine whether there are any safety concerns precluding progression to Group 3.

Accrual of participants for Group 3 will occur over approximately 12 – 16 weeks. Participants will be enrolled in parallel into Groups 3a, 3b and 3c. Day 7 safety data from participants in Group 3b will be assessed by the PSRT to determine whether there are any safety concerns precluding progression to Group 3d. Contingent on PSRT approval, enrolment into Group 3d will be authorised. Group 3 participants will continue follow-up for a minimum of 24 weeks. Group 3a and 3c will complete study product use at week 24 and will be followed off-product through week 48, which will also be their study exit visit. For Groups 3b and 3d, if on DSMB review there are no safety concerns

at week 12, then on-product follow-up may be extended to week 48 to enable collection of further safety data. At week 48 the implants will be removed and a final study visit 4 weeks off product will be conducted to assess safety at week 52.

Participant accrual in the extended safety phase component for Group 4 is scheduled to occur over 48 weeks and follow-up will continue through 120 weeks. Participants will be randomized in a 1:1 ratio to either Arm 1 (Group 4a) or Arm 2 (Group 4b). At minimum, the on product participant follow-up time will be 48 weeks along with a 4-week safety assessment period when off-product.

At regular intervals, the Principal Investigator (or designee), in consultation with the study team, will assess progress with regards to accrual and retention at the site. Accrual targets may be adjusted, as deemed necessary to achieve the goals of this trial efficiently.

### 4.3 Enrolment and Randomisation (if applicable)

Potential study participants will be screened for eligibility and eligible participants who consent for enrolment will be enrolled in the study within 56 days of screening. (*See Appendix B1-B3: Study informed consent forms).*

- The first 6 participants in Group 1 (Open-label) will be enrolled sequentially and implant insertions will be scheduled on separate days.
- The 30 participants in Group 2 (Double-blinded) will be randomised to one of four sub-groups where they could receive either one or two active implants or placebo implants in a 4:1 ratio.
- For the dose escalation component, Group 3 (Open-label) will consist of 24 women enrolled in parallel in 3 sub-groups and the maximum dose group will be enrolled sequentially.
- The 490 participants in Group 4 (Double-blinded) will be randomized in a 1:1 ratio and could receive either 2 active implants + placebo tablets or 2 placebo implants + TDF 300mg/FTC 200mg tablets.

### 4.4 Summary of Assessments

Participants enrolled in Group 1 will attend visits daily for the first 3 days after enrolment (implant insertion) to assess safety and PK. Thereafter study visits assessing on-product safety and PK will be scheduled weekly up to week 4 (implant removed) and weekly off-product safety and PK assessments will continue weekly until Week 8 when the participant will be exited. *(Appendix A1: Schedule of Evaluations for Group 1).*

Participants enrolled in Groups 2 and 3 will attend study visits weekly in the first 4 weeks post active/placebo implant insertion to assess safety and PK and thereafter study visits will be conducted every 4 weeks *(Appendix A2: Schedule of Evaluations for Group 2 and Group 3).* Depending on the outcome of DSMB reviews product may be stopped as scheduled at week 24 (Groups 3a, 3c) or use could be extended to week 48 (Groups 2 a-d, Group 3b, 3d) or product may be withdrawn at any time on the discretion of the Principal Investigator or designee in the interests of participant safety.

Participants enrolled in Group 4 will attend a study visit at week 1 after implant insertion and thereafter from week 4 the study visits will be conducted every 4 weeks and old implants will be removed at week 48 or 96 followed by insertion of new implants with exposure in some participants

up to 116 weeks. Implants may be removed without replacement at any time; however, in accordance with study visits, they will be scheduled to be removed four weeks before study exit. *(See Appendix A3: Schedule of Evaluations for Group 4).*

All groups will be subject to administrative procedures, behavioural risk interviews, clinical and pharmacy procedures. In addition, where indicated on the schedule of evaluations, phlebotomy or pelvic exams will be conducted to assess safety and perform PK assessments.

HIV/STI risk reduction counselling messages and condoms will be provided by counsellors trained to administer consistent prevention messages. Similarly, pregnancy prevention counselling and a non-barrier method of contraception will be provided by trained staff.

All scheduled, interim, off-site and participant-initiated study visits will be documented in study records.

### 4.5 Safety Assessments

While clinical safety is assessed as part of each medical history and examination, detailed laboratory-based safety assessments will be undertaken additionally during screening, enrolment and at certain follow-up visits including at study exit and additionally if indicated. The following assessments will be undertaken in accordance with the schedule of evaluations (Appendix A1–A3):

- Pelvic exam
- Physical exam
- Vital signs
- Insertion site reactions
- Insertion site healing time
- PK assessments
- Implant acceptability/tolerability
- Urinalysis
- HIV and other STI incidence
- Sexual behaviour trends
- Pregnancy rates and outcomes
- Bone densitometry (DEXA scan)

For symptoms experienced between scheduled visits, the participant will be instructed to contact the clinic staff at the CAPRISA ECRS or VCRS as soon as possible.

### 4.6 Outcome Assessment

Clinical safety will be assessed by evaluating:

- vital signs
- physical examination
- implant insertion site reactions
- healing time
- urinalysis
- changes in serum chemistry
- clinical laboratory results, and
- AE data.

A PK profile will be developed for each sub-group in the initial safety and dose escalation component and a population PK model will be developed for the TAF implant from the data obtained.

### 4.7 Clinical management of non-study related conditions

Participants who are found to have an STI or other treatable reproductive tract infection at a scheduled or participant-initiated visit will be provided counselling and clinical care in accordance with the South African Department of Health guidelines, at no cost to them. Participants with STIs will be encouraged to refer their partners for treatment and risk reduction counselling. Contraceptives of choice (with the exception of the contraceptive implant) will be provided as part of study visits and at no cost to the participant. Other conditions will be managed if possible at the study clinic and referred for further care where appropriate.

Participants who have a positive pregnancy test at enrolment or at any subsequent study visit will have the TAF implant removed immediately if possible but no later than 7 days from the date of confirmation of pregnancy. The participant will be required to return approximately one week after implant removal to assess healing and thereafter approximately every 12 weeks for review until pregnancy outcome is reached. Participants will also be referred to a local healthcare provider for further management. Product use is prohibited in participants who are currently breastfeeding. *(For more information on the Clinical Management of non-study related conditions refer to the CAPRISA 018 Study Specific Procedures (SSP))*.

Post implant insertion, participants who have confirmed incident or window period HIV infection will be scheduled to have the implant/s removed as soon as possible and in accordance with the HIV testing algorithm in Appendix D. The participant will be referred for further HIV care (*See section 7.9*) and will also be required to return approximately one week after implant removal to assess insertion site healing.

## 5 STUDY POPULATION

Approximately 60 eligible participants will be enrolled collectively in Groups 1-3 and 490 participants will be enrolled in Group 4. The following criteria must be met in order to be eligible for enrolment.

### 5.1 Inclusion Criteria

- Female
- Age 18-40 years (Group 4 participants age criterion is 18-30 years)
- Able and willing to provide written informed consent
- Able and willing to provide adequate locator information for study retention purposes
- HIV-negative on testing performed by study staff
- Negative pregnancy test performed by study staff
- Agree to use a reliable non-barrier form of contraception during the study and for at least 14 days before enrolment and until 30 days after implant removal (even if not currently sexually active).
- In general, be in good health, as assessed clinically
- Group 1, 2 and 3 participants must be at low risk of HIV infection based on the CAPRISA HIV risk assessment tool*

(**See CAPRISA 018 SSP manual for the CAPRISA HIV risk assessment tool*)

## 5.2 Exclusion Criteria

- Pregnant or currently breastfeeding, or intends to become pregnant and/or breastfeed during the study
- Intends relocation from current residential area in the next 12 months
- Haemoglobin < 9.5 g/dL
- Alanine aminotransferase (ALT) > the upper limit of normal (ULN)
- Aspartate aminotransferase (AST) > ULN
- Creatinine clearance < 60 mL/min (Cockcroft and Gault estimation)
- Hepatitis B surface antigen (HBsAg) positive
- LDL or triglycerides or total cholesterol > ULN from a random sample
- Past (< 6 months ago) or current participation in any other research study which may interfere with this study
- Currently on tenofovir-containing oral PrEP drugs
- Currently has a contraceptive implant, only if this would make it difficult to insert the study implant
- Has a tattoo or other dermatological condition overlying the inner arm which in the opinion of the Principal Investigator or designee, may interfere with interpretation of insertion site reactions
- Bleeding abnormality or on anti-coagulants
- Active or planned use of prohibited medications as described in the SSP manual (updated regularly from the OCIS-001 Investigator's Brochure)
- Has any other condition that, based on the opinion of the Principal Investigator or designee, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

## 5.3 Recruitment, Screening and Enrolment

### 5.3.1 Sources for study participants

Participants may be recruited from sexual reproductive/family planning health services or directly from the community. Walk-in participants, who may have heard about the trial during community outreach activities, may also be screened for participation.

### 5.3.2 Screening and enrolment

Eligibility for the study will be assessed at both the study Screening visit and the Enrolment visits which occur over 2 days. Although all required procedures may be completed at these visits, additional visits between screening and enrolment may be conducted if needed.

Regardless of the number of visits required, all screening procedures will be completed within a 56-day period. If a participant is not enrolled within 56 days of providing informed consent for screening, the participant may be re-consented for a second screening attempt and the screening process and tests will need to be repeated. After an unsuccessful second screening attempt, no further attempts will be allowed.

All enrolment procedures will need to be completed within 5 working days of provision of informed consent for enrolment. If enrolment (implant insertion or provision of oral TAF tablets) has not occurred within 5 working days of informed consent provision, then the PI/ designee will need to be contacted immediately to assess further study participation.

### 5.4 Co-Enrolment Guidelines

Participants in this study may not take part in other concurrent research studies that would interfere with the objectives of this study. The determination of whether participation in another study would be exclusionary for a given participant will be made by the Principal Investigator or designee. Approved co-enrolment in other concurrent protocols will be documented.

### 5.5 Participant Retention

The target retention rate will be 90% per annum. The Protocol Team will track retention rates and take any required action to address below-target retention rates. If volunteers do not adhere to scheduled pre-enrolment visits, screening may be discontinued at the discretion of the Principal Investigator or designee. Once a participant is enrolled in the study, study staff will make every reasonable effort to retain her in follow-up. This may include obtaining and checking locator data, conducting off-site visits, issuing telephone and in-person reminders of scheduled visits, and maintaining a scheduler of enrolled participants as part of a strategy to achieve the target.

### 5.6 Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason and at any time. The Principal Investigator or designee may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Continued participation in the study may be terminated by the Principal Investigator or designee based on advice from the Study Sponsor, DSMB, South African Healthcare Products Regulatory Authority (SAHPRA) – known previously as the South African Medicines Control Council (MCC), the U.S. FDA and/or the University of KwaZulu-Natal's (UKZN) Biomedical Research Ethics Committee (BREC).

Study participants who are being withdrawn and who have had an implant inserted will be encouraged to continue follow-up off-product for an additional 4 weeks after implant removal to assess healing. Every reasonable effort will be made to complete a final evaluation of participants who withdraw or are withdrawn from the study. Study staff will record the reason(s) for all withdrawals in participants' study records. Should the participant decline the 4-week post removal safety evaluation then they will be referred out, to a suitable health facility, for further care.

## 6 STUDY TREATMENT CONSIDERATIONS

### 6.1 Product formulation

The OCIS-001 implant is loaded with micro tabletted TAF (free base). The chemical name of TAF L-alanine is N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1- methylethoxy] methyl] phenoxyphosphinyl]-, 1-methylethyl ester. The molecular formula for TAF is $C_{21}H_{29}N_6O_5P$ and has a molecular weight of 476.47.

Description: The free-base TAF is a white to off-white or tan powder and has an approximate aqueous solubility above 1 mg $mL^{-1}$ in water at 20°C.

Molecular formula: $C_{21}H_{29}N_6O_5P$

Molecular weight: 476.47

Manufacturer: TAF free base API, is provided by Gilead Sciences, Foster City, USA.

### 6.1.1 OCIS-001 TAF implant

The OCIS-001 implant is manufactured from Nusil MED-4780 high consistency silicone elastomer, which is of long-term (> 29 days) implantable grade. The implant is manufactured by extrusion with post-extrusion processing for delivery channel formation. The implant consists of a drug core encased in a cylindrical silicone sheath, with two delivery channels mechanically punched perpendicular to the longitudinal axis of the cylindrical sheath. Both ends of the cylinder are sealed.

The dimensions of the implant are as follows (Table 6):

**Table 6:** Dimensions of OCIS-001 TAF implant

| TAF content inserted (mg) | Available TAF (mg) (80% of TAF content) | Dose (mg / day) | Duration (days) | Inner Diameter (mm | Wall thickness (mm) | Outer Diameter (mm) | Length (mm) | # Rods for a single insertion |
|---|---|---|---|---|---|---|---|---|
| 110 (100-120) | 88 (80-96) | 0.25 | 320-384 | 2.01 ± 0.051 | 0.19 +0.051 / -0.25 | 2.5 | 40-45 | 1 to 4 |

A design drawing of OCIS-001 is available in the latest version of the OCIS-001 investigators brochure. The device dimensions are 2.5 mm OD × 40 (40-45) mm length and consist of an impermeable, thin-walled (0.19 mm wall thickness) silicone shell filled with a TAF reservoir consisting of TAF (99.5% w/w), with magnesium stearate (0.5% w/w) admixed as lubricant to form micro tablets.

The mechanically fashioned delivery channels along the device length provide a means for fluids to diffuse in and out of the device.

Subcutaneous fluids diffuse across the exterior, into the delivery channel, and dissolve the solid drug core in the implant to form a saturated solution adjacent to the delivery channel. The dissolved API then diffuses back into the subcutaneous space down a concentration gradient according to Fick's laws of diffusion.

The TAF 110mg implants should be stored below 30°C but should not be frozen. Use within the assigned expiration period. The implants are packaged individually and sealed in moisture barrier foil pouches and terminally sterilized by gamma irradiation.
Product developer: Oak Crest Institute of Science (California, USA). For contract manufacturer details please see the most recent version of the OCIS 001 Investigators Brochure.

### 6.1.2 Placebo implant

The placebo implants are analogous to the TAF-implants, except lactose monohydrate is used instead of TAF for the formulation of the microtablets. There are no microchannel perforations/orifices drilled into the implant shell, ensuring that the lactose monohydrate is retained within the implant and does not diffuse into the subcutaneous space. Due to the very small nature of the perforations in the TAF implants, this difference will not affect the blinding of the placebo implants. The placebo implants will be protected from moisture and storage temperatures should not exceed 30 degrees Celsius. The implants should not be frozen.
Product developer: Oak Crest Institute of Science (California, USA). For contract manufacturer details please see the most recent version of the OCIS 001 Investigators Brochure.

### 6.1.3 TAF 25mg tablets

Each tablet contains TAF 25mg and are pink in colour, round, bi convex, film-coated tablets, plain on both sides. The TAF 25mg tablets should be stored below 30°C, preferably in its original container and used within the assigned expiration period.
Manufacturer: The TAF 25mg tablets will be provided by the Cipla Ltd (Mumbai, India)

### 6.1.4 TDF 300mg/FTC 200mg tablets

Each tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg). The tablets are film-coated tablets, blue in colour, capsule shaped, biconvex and plain on both sides. The tablets should not be divided. The TDF 300mg/FTC200mg tablets should be stored below 30°C, and used within the assigned expiration period. Re-labelling will be allowed to maintain the blind.
Manufacturer: The TDF/FTC tablets will be provided by the Cipla Ltd (Mumbai, India)

### 6.1.5 Placebo tablets for TDF/FTC

The placebo tablets are blue, film-coated, capsule shaped, biconvex and plain on both sides. The placebo tablets should be stored below 30°C, and used within the assigned expiration period. Re-labelling will be allowed to maintain the blind.

Manufacturer: The TDF/FTC Placebo tablets will be provided by the Cipla Ltd (Mumbai, India)

## 6.2 Product use regimen and guidelines for implant insertion

A single implant rod is designed to release 0.25 mg per day of TAF. A maximum of 4 rods will be required for the highest dose of 1 mg per day that is being investigated in this trial. Group 1 participants will be sequentially enrolled into the trial on separate days. Group 2 participants will be blinded and randomised to one of 4 sub-groups in a 1:4 ratio based on safety assessment of Group 1 data. Group 3 participants will be enrolled sequentially based on safety assessments. Group 4 participants will be randomized in a 1:1 ratio to one of two sub-groups and the number of implants for insertion will be determined from Group 1-3 data. Table 7 details the study product dosing for each sub-group.

**Table 7: Study product regimens, dose frequency and routes of administration**

| Study Group (n) | Study drug | Estimated TAF implant daily drug release rate (mg/day) | Insertion site or oral | Duration of study drug exposure |
|---|---|---|---|---|
| **GROUP 1 (n=6)** | | | | |
| 1 (6) | TAF 110mg implant | 0.25 | Arm | Up to 28 days |
| **GROUP 2 (n=30)** | | | | |
| 2a (12) | TAF 110mg implant | 0.25 | Arm | Approximately 24 to 48 weeks |
| 2b (3) | Placebo implant | 0 | Arm | Approximately 24 to 48 weeks |
| 2c (12) | 2 TAF 110mg implants | 0.50mg | One arm | Approximately 24 to 48 weeks |
| 2d (3) | 2 Placebo implants | 0 | One arm | Approximately 24 to 48 weeks |
| **GROUP 3 (n=24)** | | | | |
| 3a (6) | 2 TAF 110mg implants | 0.50 | One implant per arm | Up to 24 weeks |
| 3b (6) | 3 TAF 110mg implants | 0.75 | One arm | Approximately 24 to 48 weeks |
| 3c (6) | TAF 25mg tablet | 25 | Oral | Up to 24 weeks |

| | | | | |
|---|---|---|---|---|
| 3d (6) | 4 TAF 110mg implants | 1.0 | One arm | Approximately 24 to 48 weeks |
| **GROUP 4 (n=490)** | | | | |
| 4a (245) | TAF Implant/s plus placebo oral tablet | 0.50mg* | *Two TAF implants per arm plus oral placebo tablets | Approximately 48 to 120 weeks |
| 4b (245) | TDF 300mg/ FTC 200mg oral tablet + placebo implant/s | 0 | *Two placebo implants per arm plus oral TDF/FTC tablets | Approximately 48 to 120 weeks |

*The number of implants selected is based on the PK and safety assessment in dog models but is subject to change after PK data becomes available from groups 1- 3 in the trial.

The TAF/placebo implant will be inserted sub-dermally using a single, sterile trocar device manufactured by Shinva Ande HealthCare Apparatus Co Ltd, Shandong, China. This insertion device is registered with WHO pre-qualification for use with the contraceptive Sino-Implant (II)®. (*Refer to the CAPRISA 018 SSP manual for detailed instructions for implant insertion and removal).*

## 6.3 Product management

### 6.3.1 Study product procurement

The OCIS-001 TAF implant will be manufactured by Oak Crest Institute of Science, California, USA and TAF 25mg, TDF 300mg/FTC 200mg and matching placebo oral tablets will be provided by Cipla (Ltd), Mumbai, India.

The protocol pharmacist will generate a written order for study product from the manufacturers. Study product will be delivered directly to the site study pharmacies. On receipt of a shipment the transit temperatures will be reviewed by the study pharmacists and shipment receipt confirmation will be sent to the manufacturers. All shipment and receipt records will be housed in each study pharmacy and will be subject to study monitoring and auditing. *(Further detail and instructions are provided in the CAPRISA 018 Pharmacy Standard operating procedure (SOP) and CAPRISA 018 SSP Manual).*

### 6.3.2 Study product accountability

The study pharmacist/s will be unblinded to product assignment in the CAPRISA 018 trial. The study pharmacist/s are required to maintain complete accountability and storage condition records of all study products received from the manufacturer and subsequently dispensed to study participants. All study products will be stored at the site study pharmacy. *(The detailed procedures to be followed are provided in the CAPRISA 018 Pharmacy SOPs and the CAPRISA 018 SSP Manual).*

### 6.3.3 Study product dispensing

The study pharmacist/s will be required to maintain the blind (where required) when product is dispensed for administration. Dispensing of study product will be done either directly to the study participant or to authorized study staff. (*The detailed procedures to be followed are provided in the CAPRISA 018 Pharmacy SOPs and the CAPRISA 018 SSP Manual).*

### 6.3.4 Study product returns

All study product dispensed for a study participant and returned as unused / not administered, must be returned to the study pharmacists for quarantine and safe disposal. All implants that have been removed will be sent for testing of residual drug levels by the CAPRISA laboratory. (*Refer to the CAPRISA 018 SSP Manual for further details*).

### 6.3.5 Study product destruction

Study product may be destroyed only after written authorisation is received from the product manufacturer and/or the Principal Investigator. Destruction will occur in accordance with the institutional procedures and legislative requirements for safe destruction of pharmaceuticals. All study product destruction records will be housed in the study pharmacy and will be subject to study monitoring and auditing.

## 6.4 Adherence counselling

All participants who have had an implant inserted will be instructed to return to the CAPRISA clinic for implant removal (if required). Participants will be counselled not to have the implant removed at any other facility except for the CAPRISA ECRS or CAPRISA VCRS.

Adherence counselling will be provided specifically to study participants in Group 3c (oral TAF group) and for all Group 4 participants. Counselling will address topics such as participant-centred strategies to remember to take the tablets every day, to ensure the availability of the tablets both in the home and away from home; and to identify and discuss various challenges and situations that may impede daily tablet adherence. Counselling will also include reminders to contact study staff with questions about product use and participants will be instructed to return all oral study product in their possession each time they visit the clinic. Group 3c participants will also be required to take a directly observed dose at routine study visits, regardless of the time of day that they usually take their dose (DOT may be omitted if the days' dose was taken before the study visit).

### 6.4.1 Adherence assessment

Adherence to oral study product will be assessed at the study pharmacy at each study visit for Group 3c and Group 4 participants, by means of a pill-count, which will be documented on the relevant case report form (CRF). Participant self-reported reasons for non-adherence will be assessed and adherence counselling will be provided at the study pharmacy, if needed.

### 6.4.2 Study product toxicity management

Study product toxicity management guidelines are detailed in Appendix E.

### 6.4.3 Study product discontinuation

Study product use may be discontinued at any time during the study by removal of the implant or cessation of oral tablet ingestion (Group 3c and Group 4). Participants will be followed up for 4 weeks after implant removal to assess healing and perform a final safety assessment.

### 6.4.4 Concomitant, prohibited and precautionary medications

Information on concomitant medications / preparations (prescription and non-prescription) including alternative / complementary medications / preparations (e.g., herbs, vitamins, etc.) taken within 30 days prior to screening and anytime during study participation will be collected.

A summary of prohibited medications (Table 8) includes, but is not limited to:

**Table 8: Prohibited concomitant medication**

| Drug Class | Drug example |
|---|---|
| **P-glycoprotein inhibitors and inducers** | *Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF. Co-administration of TAF with other drugs that inhibit P-gp and BRCP may increase the absorption and plasma concentration of TAF. |
| **Anticonvulsants** | Carbamazepine<br>Oxcarbazepine<br>Phenobarbital<br>Phenytoin |
| **Antimycobacterials** | Rifabutin<br>Rifampin<br>Rifapentine |
| **Herbal products** | St. John's wort *(Hypericum Perforatum)* |

*A full listing of prohibited concomitant medication is available in the CAPRISA 018 SSP Manual.

# 7 STUDY PROCEDURES

The sequence of study visits and procedure schedules are presented in *Appendix A1 –A3: Schedule of Evaluations*. Study staff will be trained to conduct study procedures in a standardised manner. Study specific SOPs and the CAPRISA 018 SSP manual will guide this process.

## 7.1 Recruitment of study participants

Study staff may conduct targeted recruitment, by focusing study outreach and recruitment efforts on women likely to be between 18 and 40 years of age for Groups 1- 3 and 18- 30 years for Group 4. All possible efforts will be made to maintain the confidentiality of eligibility criteria, so as not to encourage artificial responses from volunteers being screened or to encourage them to change their behaviour in order to be eligible for the study.

## 7.2 Screening (up to 56 days) for ALL GROUPS

If all the required screening procedures cannot be completed in a single visit, then multiple visits may be conducted, if necessary. Only two screening attempts are allowed. For potential participants who do not meet the study eligibility criteria, the screening process will be discontinued when ineligibility is determined.

Screening will be completed in a stepwise manner. The first step includes the provision of:

- Introductory study information and obtaining written informed consent for screening procedures *(See Appendix B1).*
- HIV testing including pre- and post-test counselling will be done first and only HIV-negative participants and those who meet the criteria for low HIV risk *(refer to the CAPRISA 018 SSP manual for the risk assessment tool)* will continue with the screening process.

The following procedures will be completed for all groups:

### 7.2.1 Administrative, Behavioural, and Regulatory Procedures

- Informed consent for screening
- Assignment of a participant identification number (PID)
- Collection of the following:
    - demographic information
    - locator information
    - HIV risk assessment
    - eligibility assessment
    - HIV/STI risk reduction counselling and provision of condoms
- Provision of pre- and post-test HIV counselling

### 7.2.2 Clinical Procedures

- Baseline complete medical and menstrual history
- Contraceptive counselling and provision
- Vitals
- Physical examination
- Pelvic examination
- Blood draw
- Document concomitant medication

### 7.2.3 Laboratory Procedures

- Laboratory tests as defined in the inclusion and exclusion criteria, including:
    - Urinalysis
    - Urine pregnancy test
    - HIV rapid test
    - Full Blood Count (FBC) with differential white cell count
    - Chemistry panel (ALT, AST, alkaline phosphatase (ALP), urea and creatinine, creatinine clearance, calcium, phosphate, vitamin D and para-thyroid hormone)
    - Lipogram
    - HBsAg
    - STI testing as well as vaginal pH
    - Pap smear

**NOTE:**

If a positive result is obtained for any HIV test during Screening, the volunteer is not eligible for the study. Additional testing to confirm suspected HIV infection during Screening will be performed in accordance with local guidelines. If HIV infection is confirmed, participants will receive counselling and be referred for further medical evaluation and appropriate care.

If a volunteer is deemed eligible after Screening, they will be asked to return to the site for Enrolment. Those who are not eligible will be informed that they do not meet the eligibility criteria for the study and will be referred for appropriate medical care, if necessary.

Potential participants may be re-screened once at the discretion of the Principal Investigator or designee. However, potential participants with pre-existing conditions outlined in the exclusion criteria in Section 5.2, or having a positive or discordant HIV test may not be re-screened.

## 7.3 Enrolment Visit (Day -1 and Day 0) for GROUPS 1, 2 AND 3

The enrolment visit will only be commenced for participants who are found to be eligible. Written informed consent for study participation will be obtained before any enrolment (or "on-study") procedures are conducted. Whilst enrolment is split over two days, enrolment into the study is considered to be simultaneous with product administration (implant insertion or oral tablet ingestion).

In accordance with the schedule of evaluations the following procedures must be completed:

### 7.3.1 Administrative, Behavioural, and Regulatory Procedures

**Day -1**

- Informed consent for enrolment and stored specimens and future testing
- Review eligibility
- Group allocation
- Randomization (Group 2 only)
- Update locator information
- Collect baseline behavioural data
- Pre- and post-test HIV counselling
- HIV/STI risk reduction counselling and provision of condoms

**Day 0**

- Update locator information
- Product adherence counselling (oral product Group 3c)
- Eligibility assessment

### 7.3.2 Clinical Procedures

**Day-1**

- Targeted medical history
- Vitals
- Targeted physical examination
- Contraceptive counselling
- Documentation of concomitant medications
- Blood draw
- DEXA scan

**Day 0**

- Directly observed oral TAF dose (Group 3c only)
- Insertion of implant/s (except for Group 3c)
- PK blood draws for plasma levels and dried blood spots (DBS) at time 0.5h, 2h, 6h, 8h post implant insertion and oral TAF tablet ingestion
- PK blood draws for PBMCs at 6h post implant insertion
- Post-insertion implant acceptability /tolerability assessment and photograph of the insertion site. (except for Group 3c)
- Adverse event assessment

### 7.3.3 Laboratory Procedures

**Day-1**

- HIV rapid testing
- Urine pregnancy testing
- Serum, plasma and PBMC archive
- Genital specimen for archive
- Urinalysis

- **Day 0**
- DBS for bloods drawn at time 0.5h, 2h, 6h, 8h post implant insertion or oral TAF tablet ingestion
- Plasma for TAF and TFV concentrations at time 0.5h, 2h, 6h, 8h post implant insertion or oral TAF tablet ingestion
- PBMCs for TFV-DP quantification at time 6h post implant insertion or oral TAF tablet ingestion

### 7.3.4 Pharmacy Procedures

**Day-1**

Not applicable

**Day 0**

- Provision of TAF/placebo implant/s to study staff for insertion or provision of oral TAF to study staff or directly to study participant
- Complete pill count log for Group 3c participants
- Provision of assigned oral study product to study staff or directly to study participants with dosing instructions for Group 3c
- Update study product accountability log/s

## 7.4 Follow-up Visits – GROUP 1

In accordance with the schedule of evaluations the following procedures will be completed.

### 7.4.1 Administrative, Behavioural, and Regulatory Procedures

**Days 1 to 3**

- Update locator information

**Days 7, 14, 21, 28, 35, 42, 49, 56**

- Update locator information
- Pre- and post-test HIV counselling (days 28, 56 ONLY)
- Behavioural risk assessment (days 28 and 56 ONLY)
- HIV/STI risk reduction counselling and provision of condoms (Day 28, 56 ONLY)

### 7.4.2 Pharmacy Procedures

- Not applicable

### 7.4.3 Clinical Procedures

**Days 1 to 3 (unless otherwise specified)**

- Targeted medical history
- Vitals
- Targeted physical examination
- Adverse event assessment
- Pelvic examination (day 1 only)
- Genital specimen collection for archive (day 1 only)
- PK blood draws for plasma levels and DBS at time 24h, 48h, 60h post implant insertion.
- PK blood draws for PBMCs at time 24h post implant insertion
- Post-insertion implant acceptability /tolerability assessment and photograph of the insertion site. (days 1, 7, 14, 28, 35, 42, 56 only)

**Days 7, 14, 21, 28, 35, 42, 49, 56 (unless otherwise specified)**

- Targeted medical history
- Vitals
- HIV rapid testing (days 28 and 56 ONLY)
- Adverse event assessment
- Targeted physical examination
- Pelvic examination (days 7, 28 and 56 ONLY)
- Documentation of concomitant medications (where indicated)
- Contraceptive counselling and provision (if indicated) (days 28 and 56)
- Safety blood draws (days 7,14, 28 and 56 ONLY)
- Genital specimen collection for storage (genital fluid in the Softcup, cytobrush and swabs) (days 7, 28 and 56 and at any visit if suspected seroconversion ONLY)
- Cervico-vaginal tissue biopsy (day 28 ONLY)
- PK blood draws for plasma levels and DBS post implant insertion
- PK blood draws for PBMCs (days 7, 14, 28, 35, 42, and 56 ONLY)
- Post-insertion Implant acceptability /tolerability assessment and photograph of the insertion site. (days 7, 14 and 28 ONLY)
- Implant removal (day 28)
- Post-removal Implant acceptability /tolerability assessment and photograph of the insertion site. (days 28, 35, 42 and 56 ONLY)
- DEXA scan (day 56 only)

### 7.4.4 Laboratory Procedures

**Days 1 to 3 (unless otherwise specified)**

- Genital fluid collected using Softcup, cytobrush samples and vaginal swabs (day 1 ONLY)
- DBS for bloods drawn at time 0.5h, 2h, 6h, 8h post implant insertion

- Plasma for TAF and TFV concentrations at time approximately 24h, 48h, 60h post implant insertion.
- PBMCs for TFV-DP quantification at time approximately 24h post implant insertion.

**Days 7, 14, 21, 28, 35, 42, 49, 56 (unless otherwise specified)**
- Urine pregnancy testing (days 28 and 56 ONLY)
- Urinalysis
- HIV rapid testing (days 28 and 56 ONLY)
- STI testing, including vaginal pH (if clinically indicated, otherwise at days 7, 28 and 56 ONLY)
- DBS
- Plasma for TAF and TFV concentrations
- PBMCs for TFV-DP quantification (days 7, 14, 28, 35, 42, and 56 ONLY)
- Genital fluid collected in a Softcup, Cytobrush and vaginal swabs for storage (days 7, 28 and 56 and at any visit if suspected HIV seroconversion ONLY)
- Cervico-vaginal biopsy for cryopreservation (day 28 ONLY)
- FBC with differential white cell count (days 7, 14, 28 and 56 ONLY)
- Chemistry panel (ALT, AST, ALP, urea and creatinine, creatinine clearance, calcium, phosphate, vitamin D and para-thyroid hormone) (days 7, 14, 28 and 56 ONLY)
- Fasting lipogram (days 7, 28 and 56 ONLY)
- Plasma and serum archive (days 28 and 56 ONLY)
- Hepatitis B (day 56 ONLY)
- HIV confirmatory tests – RNA Polymerase chain reaction (PCR), point-of-care (POC) GeneXpert®, Geenius™, CD4 (if indicated)
- HIV resistance testing in seroconvertors (if indicated)

### 7.5 Follow-up Visits – GROUPS 2 AND 3
In accordance with the schedule of evaluations the following procedures will be completed.

**Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 (unless otherwise specified)**

#### 7.5.1 Administrative, Behavioural, and Regulatory Procedures
- Update locator information
- HIV/STI risk reduction counselling and provision of condoms (week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 ONLY)
- Pre- and post-test HIV counselling (weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 ONLY)
- Behavioural risk assessment (weeks 4, 12, 24, 36, 48 and 52 ONLY)
- Product adherence counselling (oral product Group 3c, weeks 1, 2, 3, 4, 8, 12, 16 and 20 ONLY)
- Unblinding of Group 2 participants (week 48 ONLY)

#### 7.5.2 Pharmacy Procedures
- Provision of assigned oral study product to study staff or directly to study participants and review dosing instructions for Group 3c (weeks 4, 8, 12, 16, 20 ONLY)
- Complete pill count log for Group 3c (weeks 1, 2 ,3, 4, 8, 12, 16, 20, 24 ONLY)
- Update study product accountability log/s (where applicable)

#### 7.5.3 Clinical Procedures
- Targeted medical history
- Vitals
- HIV rapid testing (weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 ONLY)

- Adverse event assessment
- Targeted physical examination
- Pelvic examination (weeks 1, 4, 12, 24, 36, 48, 52 ONLY)
- Directly observed oral TAF dose (Group 3c only) (weeks 1, 2, 3, 4, 8, 12, 16, 20 ONLY)
- Documentation of concomitant medications (where indicated)
- Contraceptive counselling and provision (if indicated) (weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 ONLY)
- Safety blood draws (weeks 1, 4, 12, 24, 36, 48, 52 ONLY)
- Genital specimen collection for archive (weeks 1, 4, 12, 24, 36, 48, 52 and at any visit if suspected HIV seroconversion ONLY)
- Cervico-vaginal tissue biopsy (weeks 12 ONLY)
- PK blood draws for plasma levels and DBS post implant insertion and oral TAF tablet ingestion
- PK blood draws for PBMCs (weeks 1, 2, 4, 8, 12, 24, 36, 48, 52 ONLY)
- Post-insertion implant acceptability /tolerability assessment and photograph of the insertion site. (weeks 1, 4, 8, 12, 24, 36, 48 ONLY)
- Implant removal (Week 24 for Group 3a or if indicated, otherwise week 48 ONLY)
- Post-removal implant acceptability /tolerability assessment and photograph of the insertion site. (weeks 24 and 28 for group 3a, otherwise weeks 48 and 52 ONLY)
- DEXA scan (week 24 (if indicated) or week 52 ONLY)

### 7.5.4 Laboratory Procedures

- Urine pregnancy testing (weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 ONLY)
- Urinalysis
- HIV rapid testing (weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 ONLY)
- STI testing as well as vaginal pH (if clinically indicated, otherwise at weeks 4, 12, 24, 36,48, 52 ONLY)
- DBS
- Plasma for TAF and TFV concentrations
- PBMCs for TFV-DP quantification (weeks 1,2, 4, 8, 12, 24, 36, 48, 52 ONLY)
- Genital fluid collected in a Softcup, cytobrush and vaginal swabs (weeks 1, 4, 12, 24, 36, 48, 52 and at any visit if suspected HIV seroconversion ONLY)
- Cervico-vaginal biopsy for cryopreservation (week 12 ONLY)
- FBC with differential white cell count (weeks 1, 4, 12, 24, 36, 48, 52 ONLY)
- Chemistry panel (ALT, AST, ALP, urea and creatinine, creatinine clearance, calcium, phosphate, vitamin D and para-thyroid hormone) (weeks 1, 4, 12, 24, 36, 48, 52 ONLY)
- Fasting lipogram (weeks 1, 4, 12, 24, 36, 48, 52 ONLY)
- Plasma and serum archive (weeks 4, 12, 24, 36, 48 and 52 ONLY)
- Hepatitis B (weeks 24, 52 ONLY)
- HIV confirmatory tests – RNA PCR, POC GeneXpert®, Geenius™, CD4 (if indicated)
- HIV resistance testing in seroconverters (if indicated)

**NOTE:** All HIV test results (from current and previous visits) and pregnancy test results (from current visit) must be available, reviewed and confirmed to be negative prior to the provision of further study product or scheduling of next appointment. If any of these tests are positive, study drug should be discontinued.

## 7.6 Enrolment Visit (Day -1 and Day 0) for GROUP 4

The enrolment visit will only be commenced for participants who are found to be eligible. Written informed consent for study participation will be obtained before any enrolment (or “on-study”) procedures are conducted. Whilst enrolment is split over two days, enrolment into the study is

considered to be simultaneous with product administration (implant insertion and oral tablet ingestion).

In accordance with the schedule of evaluations the following procedures must be completed:

### 7.6.1 Administrative, Behavioural, and Regulatory Procedures

**Day -1**

- Informed consent for enrolment and stored specimens and future testing
- Review eligibility
- Group allocation
- Randomization
- Update locator information
- Collect baseline behavioural data
- Pre- and post-test HIV counselling
- HIV/STI risk reduction counselling and provision of condoms

**Day 0**

- Update locator information
- Product adherence counselling
- Eligibility assessment

### 7.6.2 Clinical Procedures

**Day-1**

- Targeted medical history
- Vitals
- Targeted physical examination
- Contraceptive counselling
- Documentation of concomitant medications
- Blood draw
- DEXA scan

**Day 0**

- Provide oral TDF/FTC or placebo oral dose
- Insertion of implant/s
- PK blood draws for plasma levels and DBS at time 6h post implant insertion
- PK blood draws for PBMCs at 6h post implant insertion
- Post-insertion implant acceptability /tolerability assessment and photograph of the insertion site.
- Adverse event assessment

### 7.6.3 Laboratory Procedures

**Day-1**

- HIV rapid testing
- Urine pregnancy testing
- Serum, plasma and PBMC archive
- Genital specimen for archive
- Urinalysis

**Day 0**

- DBS for bloods drawn at time 6h post implant insertion and oral TDF/FTC tablet ingestion
- Plasma for TAF and TFV concentrations at time 6h post implant insertion and oral TDF/FTC tablet ingestion

- PBMCs for TFV-DP quantification at time 6h post implant insertion and oral TDF/FTC tablet ingestion

### 7.6.4 Pharmacy Procedures

**Day-1**

Not applicable

**Day 0**

- Provision of TAF/placebo implant/s to study staff for insertion and provision of oral TDF/FTC or Placebo tablets to study staff or directly to study participant
- Complete pill count log for participants
- Update study product accountability log/s

## 7.7 Follow-up Visits – Group 4

In accordance with the schedule of evaluations the following procedures will be completed.

**Week 1, week 4 and then every 4 weeks through week 120 (unless otherwise specified)**

### 7.7.1 Administrative, Behavioural, and Regulatory Procedures

- Update locator information
- HIV/STI risk reduction counselling and provision of condoms (Week 4 to 120)
- Pre- and post-test HIV counselling (weeks 4 to 120)
- Behavioural assessment (weeks 4, 12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY)
- Product adherence counselling (oral product Week 1 to 116)
- Unblinding of Group 4 participants (week 120 ONLY)

### 7.7.2 Pharmacy Procedures

- Provision of TAF/placebo implant (weeks 48, 96 ONLY)
- Provision of assigned oral study product to study staff or directly to study participants and review dosing instructions
- Complete pill count log
- Update study product accountability log/s (where applicable)

### 7.7.3 Clinical Procedures

- Targeted medical history
- Vitals
- HIV rapid testing (weeks 4 to 120)
- Adverse event assessment
- Targeted physical examination
- Pelvic examination (weeks 1, 4, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 ONLY)
- Documentation of concomitant medications (where indicated)
- Contraceptive counselling and provision (if indicated) (weeks 4 to 120)
- Safety blood draws (weeks 1, 4 to 120)
- Genital specimen collection for archive (weeks 1, 4, 12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY and at any visit if suspected HIV seroconversion)
- PK blood draws for plasma levels and DBS post implant insertion and oral TDF/FTC tablet ingestion (weeks 1, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY)
- PK blood draws for PBMCs (weeks 1, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY)
- Implant removal and insertion (weeks 48 and 96 ONLY)
- Post-insertion implant acceptability /tolerability assessment and photograph of the insertion site. (weeks 1, 4, 12, 24, 36 48, 60, 72, 84, 96,108 and 120 ONLY)

- Implant removal (weeks 48, 96, 116 ONLY)
- Post-removal implant acceptability /tolerability assessment and photograph of the insertion site. (weeks 48, 60, 72, 84, 96,108 and 120 ONLY)
- DEXA scan (weeks 52, 100 ONLY)

### 7.7.4 Laboratory Procedures

- Urine pregnancy testing (weeks 4 to 120)
- Urinalysis (weeks 1, 4 to 120)
- HIV rapid testing (weeks 4 to 120)
- STI testing as well as vaginal pH (if clinically indicated, otherwise at weeks 4, 12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY)
- DBS (weeks 1, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY)
- Plasma for TAF and TFV concentrations (weeks 1, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96,108 and 120 only
- PBMCs for TFV-DP quantification (weeks 1, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY
- Genital fluid collected in a Softcup, cytobrush and vaginal swabs (weeks 1, 4, 12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY and at any visit if suspected HIV seroconversion)
- FBC with differential white cell count (weeks 1, 4,12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY)
- Chemistry panel (ALT, AST, ALP, urea and creatinine, creatinine clearance, calcium, phosphate, vitamin D and para-thyroid hormone) weeks 1, 4,12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY)
- Lipogram (weeks 1, 4,12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY)
- Plasma and serum archive (weeks 4,12, 24, 36, 48, 60, 72, 84, 96,108 and 120 ONLY)
- Hepatitis B (weeks 48, 96, 120 ONLY)
- HIV confirmatory tests – RNA PCR, POC GeneXpert®, Geenius™, CD4 (if indicated)
- HIV resistance testing in seroconverters (if indicated)

**NOTE:** All HIV test results (from current and previous visits) and pregnancy test results (from current visit) must be available, reviewed and confirmed to be negative prior to the provision of further study product or scheduling of next appointment. If any of these tests are positive, study drug should be discontinued.

## 7.8 Interim Contacts and Visits and Off-Site visits (ALL GROUPS)

- Interim visits and off-site visits may be performed during the study, for a number of reasons, which include, but may not be limited to, the following:

    - For administrative reasons, e.g., a participant may have questions for study staff or may need to re-schedule a follow-up visit.
    - In response to AEs. When interim contacts or visits are completed in response to participant reports of AEs or laboratory AEs, study staff will assess the reported event and provide or refer the participant to appropriate medical care
    - For interim STI counselling and / or treatment in response to STI symptoms.
    - For interim HIV counselling and testing in response to presumed exposure to HIV or seroconversion symptoms.
    - Contraception counselling and / or provision
    - To provide participants with the results of confirmatory HIV test results, per algorithm in Appendix D.
    - For other reasons at participant / study staff request.

Study Exit Visit

Study exit visits generally occur approximately 4 weeks post implant removal or at any time in the study where a participant is terminated or has reached study exit in accordance with the schedule of evaluations. All test results, related to safety that are available on the day of study exit will be communicated to the participant telephonically within 7 working days post study exit and if necessary referrals for ongoing care will be made.

### 7.8.1 Administrative and Behavioural Procedures

- Update locator information
- Pre- and post-test HIV counselling
- Behavioural risk assessment
- HIV/STI risk reduction counselling and provision of condoms

### 7.8.2 Clinical Procedures

- Targeted medical history
- Vitals
- HIV rapid testing
- Adverse event assessment
- Targeted physical examination
- Pelvic examination
- Documentation of concomitant medications (where indicated)
- Contraceptive counselling and provision (if indicated)
- Safety blood draws
- Genital specimen collection for archive
- PK blood draws for plasma levels and DBS
- PK blood draws for PBMCs
- Post-removal implant acceptability /tolerability assessment and photograph of the insertion site.

### 7.8.3 Pharmacy Procedures

- Update accountability logs (where necessary) and perform final reconciliation of study product

### 7.8.4 Laboratory Procedures

- Urine pregnancy testing
- Urinalysis
- HIV rapid testing
- STI testing as well as vaginal pH
- DBS
- Plasma for TAF and TFV concentrations
- PBMCs for TFV-DP quantification
- Genital fluid collected in a Softcup, Cytobrush and vaginal swabs
- Hepatitis B
- FBC with differential white cell count
- Chemistry panel (ALT, AST, ALP, urea and creatinine, creatinine clearance, calcium, phosphate, vitamin D and para-thyroid hormone)
- Fasting lipogram
- Plasma and serum archive
- HIV confirmatory tests – RNA PCR, POC GeneXpert®, Geenius™, storage bloods (if indicated)
- HIV resistance testing in seroconverters (if indicated)

### 7.9 Planned unblinding of study participants in Groups 2 and 4

At the trial completion, when all participants have completed their study exit visit, Group 2 and 4 study participants will have study product assignment revealed to them.

### 7.10 Participants with suspected or confirmed HIV infection

HIV infection is defined as two positive PCR tests from independent samples obtained post-enrolment, which is defined as post implant insertion or oral TAF tablet ingestion. *(Refer to the HIV testing algorithms at screening, baseline, and at each follow-up visit is included in Appendix D)*.

At screening, participants will undergo two rapid tests for HIV. Those who are negative on both tests and meet all eligibility criteria as assessed within a 56-day period since screening will be eligible to be tested for study enrolment.

At enrolment participants will undergo two rapid tests for HIV even if it has been less than 56 days since their screening rapid tests. Participants will only be enrolled if both rapid tests are negative. Participants who have a positive, discordant or indeterminate result on either or both tests will be excluded from further participation and will be referred for further tests and/or HIV treatment.

At each follow-up visit, enrolled participants will be tested for HIV antibodies with two rapid HIV tests. Participants with two negative rapid tests will continue follow-up in the study. If both tests are not negative, i.e. either of these tests is positive or indeterminate, then the participant is considered a suspected seroconvertor. The participant will immediately have blood drawn (Time 1 sample) for point of care (POC) GeneXpert® viral load testing and POC Geenius™ antibody confirmatory testing. If the results of both these tests are negative, then the participant will be eligible to continue study participation. If any of these tests are positive, discordant or indeterminate then the participant will be booked to return for further testing no earlier than two days later. At this visit, blood (Time 2 sample) will be taken for a lab based HIV RNA PCR and POC Geenius™ antibody confirmatory testing. The PCR results will be available in a further 2 days and the POC Geenius™ result will be available immediately. If both these tests are positive, then study product will be stopped immediately (implant removed and/or tablets withdrawn). The max time allowed between Time 1 and infection confirmation is 7 days. In the rare event PSRT decision is required to assess for acute HIV infection (if either of the Time 2 samples are negative, indeterminate or discordant) then the maximum time between Time 1 and confirmation of ongoing study participation or ineligibility is 14 days.

Upon request, participants can be tested for HIV between scheduled study visits if they feel they have been exposed or are experiencing symptoms compatible with HIV infection.

At the end of the study all new HIV infections will be confirmed by RNA PCR on stored plasma for quality assurance purposes. Non-incident cases will be excluded from the analysis of the secondary objectives. Participants who become infected with HIV will be offered counselling and referral either to the CAPRISA Acute Infection Study (CAPRISA 002), where immediate ART initiation will be provided to the participant or to other treatment programmes or other HIV/AIDS care services.

### 7.11 Pregnancy and breastfeeding

Since TAF is not indicated for use in pregnancy, all participants are required to use a non-barrier method of contraception regardless of whether they are currently sexually inactive. All participants will be counselled to use male or female condoms for prevention of HIV and other STIs. Study staff will provide contraceptive counselling to enrolled participants throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery and/or

active referrals to local service providers. Study staff will also provide participants with male and female condoms and counselling on use of condoms. Participants will have pregnancy testing performed as outlined in the *Schedule of Evaluations (Appendix A1 –A3).* Participants will be encouraged to report any suspicion of pregnancy to study staff as soon as possible.

Any pregnancy that occurs during the course of a participant's participation in the study should be reported to the PSRT upon site awareness (either upon confirming via urine pregnancy testing during a study visit or as reported by the participant between study visits). Participants who have a positive pregnancy test will have study product discontinued (implant removed and/or oral tablets stopped) and the participant will be followed approximately every 12 weeks until pregnancy outcome is reached.

The Site Investigator and/or designee will counsel any participants who become pregnant regarding possible risks to the foetus as detailed in the SOPs and/or SSP manual. Participants may not enrol if they are currently breastfeeding and study product should be discontinued (implant removed or oral tablets stopped) if any participant identifies that she is breastfeeding after enrolment.

Participants who are pregnant at their last study visit will continue to be followed (if they agree) until the pregnancy outcome is ascertained or it is determined that the pregnancy outcome cannot be ascertained. All pregnancy outcomes will be reported on relevant CRFs.

# 8 LABORATORY CONSIDERATIONS

The study laboratory plan will include the procedures for specimen management (e.g. chain of custody, handling, labelling and transport), assay procedures, proficiency testing and quality assurance procedures and specimen storage procedures. (See *Appendix C: Safety laboratory evaluations and radiography)*.

## 8.1 Laboratory Specimens

The following types of specimens will be collected for testing:

- Urine for pregnancy testing, urinalysis, urine microscopy (if indicated) and STI testing
- Blood for haematology, serum chemistry and lipograms
- Blood for HIV testing by rapid tests, HIV confirmatory tests – RNA PCR, POC GeneXpert® Geenius™ (if indicated), CD4 count
- Blood for HBV testing
- Blood for STI testing
- Blood and genital specimens from suspected seroconvertors for virus and tenofovir resistance assays
- Genital specimens for archiving, Pap smear, vaginal pH and STI testing
- Blood for PBMC, plasma PK assessments
- Blood for plasma and serum archive

All the above specimens will be collected with Good Clinical and Laboratory Practice standards and as described in the SOPs for collection of specimens.

## 8.2 On site testing

The study laboratory plan will detail the procedures to be followed for on-site testing, as well as proficiency testing for all on-site testing, for example (but not limited to) urine pregnancy tests, HIV rapid tests, urinalysis and urine microscopy.

### 8.3 Collection and shipping of specimens
All specimens (bloods, urine and genital) will be collected according to methods described in the SSP manual and SOPs for proper collection, processing, labelling, and transport of specimens to the laboratories conducting the assays.

### 8.4 Specimen Storage for Quality Assurance and Potential Future Research Testing
Serum, plasma, PBMC, DBS and genital specimens will be stored for potential post-trial assessments for activity against STIs, markers of safety, risk exposure, and tenofovir resistance. In addition, stored plasma will be used for retrospective RNA PCR or Geenius™ testing to confirm whether early incident cases of HIV infection during the trial occurred post-randomisation. Where possible, stored specimens will be re-tested to assess the validity of unusual or unexpected assays results. For those participants who do not consent to long-term storage of their specimens, any residual specimens will be destroyed at the end of the study after all protocol-required and quality assurance testing has been completed.

### 8.5 Laboratory Quality Control and Quality Assurance Procedures
The laboratories involved in the study will follow the quality assurance and quality control procedures outlined in the study laboratory plan. For the on-site tests, the quality assurance personnel from the CAPRISA laboratory will conduct periodic visits to the ECRS to assess the implementation of on-site quality control procedures, including maintenance of laboratory testing equipment, use of appropriate reagents, proficiency testing records and quality checks of on-site testing procedures.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 Review of study design
This is a phase I/II trial assessing the safety, PK, acceptability and tolerability of the TAF implant in 60 HIV-negative women at low risk for HIV infection and 490 HIV-negative women from the general population.

Clinical safety will be assessed by evaluating insertion site reactions and healing time, changes in creatinine clearance and adverse event data. In addition, a pharmacokinetic profile will be developed for each sub-group to aid selection of the most appropriate dose for future study.

### 9.2 Endpoints

#### 9.2.1 Primary endpoint
The primary study objective is to evaluate the safety of the OCIS-001 TAF 110mg implant. While clinical safety will be assessed by evaluating vital signs, physical examination, and clinical laboratory results, the main safety indicators are insertion site reactions (local) and changes in creatinine clearance (systemic).

#### 9.2.2 Secondary endpoints
Consistent with the study objectives listed in section 3.2, the following secondary endpoints will be assessed:
- Adverse event rates by grade (according to the DAIDS table for grading AEs)
- Adverse event rates by degree of association with study product

- Number of early implant removals (prior to scheduled removal) and the reasons for early removal
- Systemic PK profile
- Genital compartment PK profile
- Acceptability of the insertion of 1, 2, 3 and 4 implants.
- Incidence rates of STIs, including HIV, HSV-2, HPV, gonorrhoea, chlamydia and trichomonas
- Pregnancy rates and outcomes. *Note that a pregnancy is defined as a positive pregnancy test
- TAF resistance in HIV seroconvertors
- Viral load in HIV seroconvertors

### 9.3 Random assignment and allocation concealment

A summary of the randomisation procedures is as follows: Group 1 participants will not be randomized but enrolled sequentially until targeted numbers are reached. In Group 2, participants will be randomised in a 4:1 ratio, stratified by whether participants will be receiving 1 or 2 TAF implant rods. A statistician who is not involved in the study will produce a computer-generated randomisation list for group 2 which will be provided to an unblinded study pharmacist. The study pharmacist will receive sealed, opaque randomization envelopes, sequentially labelled by a treatment code. These envelopes will be assigned in sequential order to eligible study participants. Upon opening the envelope, the pharmacist will add his or her name and signature as well as the time and date the envelope was opened. The treatment assignment of a participant will be known only to the unblinded pharmacist. Group 3 will be enrolled in parallel for groups 3a, 3b and 3c with Group 3d enrolling sequential to Group 3b until targeted numbers are reached.

In Group 4, participants will be assigned at random to one of the two study arms in equal proportions to receive active implant/s and placebo tablets or placebo implants and active tablets. Similar to randomisation procedures for group 2, a statistician who is not involved in the study will produce a computer-generated randomisation list, which will be provided to an unblinded study pharmacist. The statistician will use a randomly permuted block design, with two or more pre-specified block sizes, which will be recorded on a formal randomisation request form, but they will not be written in the protocol or communicated to the clinical staff in order to reduce the chance of the clinical staff anticipating the assignment of the next participant. The study pharmacist will receive sealed, opaque randomization envelopes, sequentially labelled by a treatment code. These envelopes will be assigned in sequential order to eligible study participants. Upon opening the envelope, the pharmacist will add his or her name and signature as well as the time and date the envelope was opened. The treatment assignment of a participant will be known only to the unblinded pharmacist.

Electronic copies of the randomization schedule and the programs used to generate the randomization schedule will be limited in access and password protected. Paper copies of the randomization schedule will be locked in a secure location at the CAPRISA headquarters, where no unauthorized study staff will have access to them. For Groups 2 and 4, individual treatment assignments may be revealed to the study investigators in the event that emergency unblinding of a study participant is required (see Section 9.6 for details). Any instances of unblinding, intentional or otherwise, will be documented in the study files.

### 9.4 Accrual, follow-up, and sample size calculations

**Phase I (Groups 1 to 3)**

This part of the trial is scheduled for approximately 48 weeks, with an additional 4- week post-trial safety observation. Participant accrual is scheduled to occur over 16 weeks. Follow-up of participants while on product is scheduled to continue until the last enrolee has completed her week 48 visit, at which point participants, who have had implants inserted, will have these removed and will continue safety monitoring off-product for an additional 4 weeks.

The goal of the safety evaluation for the Phase I study is to identify safety concerns associated with product administration for dose escalation. No formal sample size calculation is needed. However, given the chosen sample size per group, the ability of the study to detect SAEs for different group sizes is shown in Table 9. This was done by calculating the probabilities of experiencing zero, ≥1 or ≥2 events under different possible true event rates (69, 70) are shown in Table 9. For each of the groups with n=6 (i.e. participants in Group1, Groups 3a, 3b and 3d), there is 26% chance of observing at least one event, if the true event rate is 4.8%. However, when the true event rate is doubled or six fold higher, this probability rises to 47% and 88% respectively.

When we consider the groups that are doubled in size (n=12), who will receive one or two TAF implants (i.e. Groups 2a and 2c), the probabilities of detecting at least one event are also increased. They are 45%, 72% and 95% when event rate is 4.8%, 10% and 30% respectively. The probability of observing 0, 1+ and 2+ events for a range of true event rates among different groups, including all 54 participants who will be receiving active treatment is provided in Table 9.

Since Phase I will help identify the maximally tolerated dose, the chances of detecting rare events will vary depending on the dosing strategy and how big or small the sample size is.

**Table 9: Probability of observing 0 events, 1 or more events, and 2 or more events, for a range of hypothetical true event rates**

| True event rate (%) | Number of participants | 0 events | 1+ events | 2+ events |
|---|---|---|---|---|
| 1 | 6 | 0.94 | 0.06 | <0.01 |
| | 12 | 0.89 | 0.11 | <0.01 |
| | 24 | 0.79 | 0.21 | 0.02 |
| | 54 | 0.58 | 0.42 | 0.1 |
| 4.8 | 6 | 0.74 | 0.26 | 0.03 |
| | 12 | 0.55 | 0.45 | 0.11 |
| | 24 | 0.31 | 0.69 | 0.32 |
| | 54 | 0.07 | 0.93 | 0.74 |
| 6 | 6 | 0.69 | 0.31 | 0.05 |
| | 12 | 0.48 | 0.52 | 0.16 |
| | 24 | 0.23 | 0.77 | 0.43 |
| | 54 | 0.04 | 0.96 | 0.84 |
| 10 | 6 | 0.53 | 0.47 | 0.11 |
| | 12 | 0.28 | 0.72 | 0.34 |
| | 24 | 0.08 | 0.92 | 0.71 |
| | 54 | <0.01 | >0.99 | 0.98 |
| 30 | 6 | 0.12 | 0.88 | 0.58 |
| | 12 | 0.01 | 0.99 | 0.91 |
| | 24 | <0.01 | >0.99 | >0.99 |
| | 54 | <0.01 | >0.99 | >0.99 |

Table 10. shows the two-sided exact 95% confidence interval by the score test method (71) for the observed true event rate. For example, if one of the 6 participants receiving active study product experiences a safety event, the 2-sided confidence interval for this rate will be 3.01-56.3%.

**Table 10: Two-sided 95% confidence intervals based on observing a particular rate of safety endpoints**

| Number of serious events/ sample size | 95% confidence interval |
|---|---|
| 0/6 | 0.0 - 39.0 |
| 1/6 | 3.0 - 56.3 |
| 2/6 | 9.7 - 70.0 |
| 3/6 | 18.8 - 81.2 |
| 4/6 | 30.0 - 90.3 |
| | |
| 0/12 | 0.0 - 24.2 |
| 1/12 | 1.5 -35.4 |
| 2/12 | 4.7 - 44.8 |
| 3/12 | 8.9 - 53.2 |
| 4/12 | 13.8 - 60.9 |
| | |
| 0/24 | 0.0 - 0.13.8 |
| 1/24 | 0.7 - 20.2 |
| 2/24 | 2.3 - 25.8 |
| 3/24 | 4.3 - 31.0 |
| 4/24 | 6.7 - 35.8 |
| | |
| 0/54 | 0.0 - 6.6 |
| 1/54 | 0.3 - 9.8 |
| 2/54 | 1.0 - 12.5 |
| 3/54 | 1.9 - 15.1 |
| 4/54 | 2.9 - 17.6 |

**Phase II (Group 4)**

Participant accrual in the extended safety phase component for Group 4 is scheduled to occur over 48 weeks and follow-up will continue through 120 weeks. Participants will be randomized in a 1:1 ratio to either intervention (Group 4a) or control arm (Group 4b). At minimum, the on-product participant follow-up time will be 48 weeks along with a 4-week off-product safety assessment period.

The primary safety outcome measure is change in creatinine clearance. The sample size calculation is based on data from the iPREX demo project (27, 28), which showed a mean creatinine clearance decline of 5% from baseline to week 12, and preliminary clinical data (37) regarding TAF oral use suggests minimal creatinine clearance alterations. Assumptions in calculating sample size include a mean decline of 5% from baseline in the TDF/FTC group and a mean decline of 1% in the TAF group, with a common standard deviation of 13%, using a two group t-test with 0.05 2-sided significance. Loss to follow-up was set at 10%. A sample size of 245 in each arm will have 90% power to detect a 5-fold difference in the mean decline in creatinine clearance from baseline to 12 weeks between the two groups.

In Table 11, the statistical power for varying declines in mean creatinine clearance in both TAF and TDF/FTC groups is presented when overall sample size is fixed at 490. These estimates are subject

to differences in adherence to daily oral TDF/FTC in the control group. If adherence is sub-optimal then we are unlikely to see the anticipated declines in creatinine clearance in the control group. TDF/FTC usage will then be determined by assessing drug level data and the per protocol analysis will come into effect (see section 9.5)

**Table 11: Power calculation at a constant sample size of 490, allowing for varying percentage declines in creatinine clearance (CrCl) estimates in the TAF implant and TDF/FTC oral groups**

| | | Mean CrCl % decline in TDF/FTC group | | | | |
|---|---|---|---|---|---|---|
| | | **3** | **4** | **5** | **6** | **7** |
| **Mean CrCl % decline in the TAF group** | **0.5** | 56% | 84% | >95% | >95% | >95% |
| | **1** | 39% | 72% | 90% | >95% | >95% |
| | **1.5** | 24% | 56% | 84% | >95% | >95% |

## 9.5 Data analysis

This section covers the statistical analyses for primary and secondary objectives. An expanded Statistical Analysis Plan (SAP), covering both the final analysis and the planned interim analysis, will be finalized before the first participant is enrolled.

The primary and secondary analyses will be performed on an intention to treat (ITT) basis. Other analyses excluding participants with protocol violations, very low adherence or participants who provided no safety data will also be performed. Statistical analysis will be carried out using either SAS version 9.4 or higher (SAS Institute, Cary, North Carolina).

**Phase I (Groups 1 to 3)**

**Participant demographics**

Demographic data of all participants enrolled in the study will be summarized using descriptive statistics. These will be reported by treatment assignment (where participants were randomized), study group and overall.

**Laboratory test evaluations**

Laboratory test results will be summarised by study arm, group and time-point post enrolment (i.e. weeks 4, 12, 24, 36 and 48). Creatinine clearance is one of the most important laboratory markers in this trial. Percentage change in creatinine clearance will be calculated from baseline to week 4, 12, 24, 36 and 48. The percentage change at weeks 12, 24 and 48, will be compared to controls receiving oral TAF 25mg daily.

**AEs and SAEs**

AEs and SAEs will be coded into MedDRA system organ class (SOC) and preferred terms. Laboratory values meeting grade 1 and above as specified in the Division of AIDS (DAIDS) toxicity grading table, V2.1, March 2017 (or later version) will be reported as AEs. Summaries by treatment arm (active or placebo) and group will show number and percentage of participants experiencing AEs within each of the SOC and preferred term. Moreover, number and percentages of participants experiencing each specific AE will be tabulated by severity and relationship to study product. For the calculations in these tables, each participant's adverse experience will be counted once under the maximum severity or strongest recorded causal relationship to study product. A complete listing of adverse experiences for each participant will provide details including severity, relationship to study product, onset, duration and outcome.

**Study product discontinuation, premature withdrawal from study and product acceptability and tolerability**
The number and percentage of participants who discontinue study product or withdraw from the study along with acceptability of study product will be reported by study group (active or placebo), with reasons for discontinuation summarised.

Acceptability and tolerability of the TAF implant will be determined by participant views on the implant, by summarizing the insertion site reactions, by number of participants who report various insertion site reactions and by summarizing the mean healing time for both insertions and removals of one or more implants. The same information will be summarized for the placebo group, with the same insertion site reactions are expected as a result of the insertion of the placebo implant.

**HIV and STIs**
Due to the enrolment of low HIV risk women enrolled in phase I, new HIV infections and rates of STIs are expected to be low. The number and percentage of participants who acquire HIV and/or other STIs, will be reported by study group and overall. The effect of the sustained-release TAF implant on behavioural risk compensation will be evaluated by assessing the frequency of new STI infections during the study period and comparison with behavioural assessment responses.

**PK of the TAF implant and TAF oral tablets**
The PK analysis will use TAF, TFV and TFV-DP concentrations at various intervals post-insertion in plasma, PBMCs and in the genital tract to generate PK parameters (AUC, half-life, clearance and volume of distribution) for the TAF implant utilizing a non-compartmental PK model. In addition, drug exposure in the peripheral and genital compartments, at various time intervals, will be compared with concentrations achieved after daily oral TAF. These will also include comparisons with literature-based estimates of tenofovir exposure from daily oral TDF/FTC. The implant dose that provides intracellular PBMC concentrations of the active intracellular metabolite, TFV-DP, closest to those levels shown to have a high probability of providing protection against HIV based on the available literature will be selected for Phase II provided it also has a good safety profile during the study.

**Phase II – Group 4**
Any key decisions regarding the timing of outcomes, the appropriateness of test statistics or model assumptions, the eligibility of participants to be included in the various populations or any other statistical issues will be made in a blind review meeting. At the blind review at least the following people will be present: protocol statisticians; Principal Investigators; medical officer; and data manager. Only after this group documents that all data are sufficiently clean and all decisions about individual participant outcomes have been made will the study be unblinded to the true randomization assignments.

**Definitions of study populations**
**Intention to treat (ITT) population:** ITT population includes all randomised participants analysed according to the treatment arm they were randomised to regardless of adherence, protocol deviations, withdrawal or compliance. The only participants excluded from this primary analysis population will be women without a post-randomization HIV test result, and women whose stored baseline blood samples were later found to be HIV positive.

**Safety population:** The safety population is a subset of the ITT population, which will include all participants with implants ever inserted and retained for at least 4 weeks.

**Per protocol population**: Per protocol population is also a subset of ITT but includes only participants with >50% of their bloods samples having detectable drug levels.

Detailed description of the populations, primary and secondary analyses will be provided in the trial SAP. All primary and secondary analyses will be two-sided and will be performed at the 0.05 level of significance (adjusted to account for the two planned interim analyses).

**Safety and efficacy**
All safety analyses will be performed on the safety and per protocol populations. Analyses of drug effect will be performed on ITT population.

To evaluate the safety of the sustained-release TAF sub-dermal implant in HIV-negative young women, the mean percentage change from baseline in creatinine clearance will be calculated from baseline to week 4, 12, 24, 36, 48, 72, 96 and 120. The percentage change at week 12 will be compared between the two treatment groups using a t-test for independent groups. In addition, linear mixed models or generalised estimating equations, accounting for repeated measurements will be used to assess changes in creatinine clearance over time. These models will be adjusted for baseline prognostic covariates.

The efficacy of the sustained-release TAF implant against HIV infection will be measured by comparing the incidence of HIV in the sustained-release TAF implant (placebo tablet) arm with that in the TDF/FTC (placebo implant) arm. Women who test positive on the PCR result from the enrolment visit will be excluded in this analysis. Date of HIV infection will be estimated as the midpoint between the last negative HIV test date and the first confirmed positive HIV test date. Where a participant has a positive PCR and a negative rapid test on the same date, the date of infection is calculated as 14 days prior to this date. Participants who do not become HIV positive before their last study visit will be censored on the day of their last negative HIV test. Time at risk in days, will be computed as the difference between the estimated date of HIV infection or date of censoring and the randomization date, plus one. To assess the effectiveness of TAF implant, the cumulative probability of HIV infection will be calculated for each group using the Kaplan-Meier method. The difference in survival curves will primarily be evaluated with a log-rank test, whereas HIV incidence rates will be compared using a z-test. Secondarily, proportional hazards regression models will be used to estimate the hazard rate ratio, along with a 95% confidence interval, comparing the groups for HIV outcome, controlling for baseline prognostic variables.

The effectiveness of the sustained-release TAF implant against other STIs as well as pregnancies will be evaluated in the same way. Where testing for STIs is infrequent and time to STI infection cannot be determined accurately, the analysis will also be done by comparing the number of new STI infections during the study period between the two treatment arms, using a Fisher's exact test.

The number of women who have HIV resistance mutations will be assessed and compared between the two treatment arms using a Fisher's exact test. HIV viral load (on a $\log_{10}$ scale) will be summarized using means or medians in the two treatment arms and will be compared using a linear mixed model analysis at all-time points including time since HIV infection as covariate to account for correlated responses.

**Adverse events**
Adverse events will be summarized in frequency tables (including both the number of each type of adverse event and the number of distinct participants with each type of adverse event) by body system and treatment group. Listings of all adverse events will include information on duration, outcome, severity, and any relation to product use. Adverse events will be coded using the MedDRA system. Adverse events occurring in >5% of the study population will be compared in the two groups using Fisher's exact test. All laboratory endpoints will be summarized by time point, treatment arm and severity.

**Acceptability and tolerability**
Acceptability of the TAF implant will be determined by participant views on the implant, by summarizing the insertion site reactions, by number of participants who report various insertion site reactions and by summarizing the mean healing time. The same information will be summarized for the placebo arm as the same insertion site reactions are expected as a result of insertion of the placebo implant.

**PK analysis**
The PK analysis in the extended safety part of the trial will use TAF, TFV and TFV-DP concentrations at various intervals post-insertion in plasma, PBMCs and in the genital tract to generate PK parameters (AUC, half-life, clearance and volume of distribution) for the TAF implant utilizing a non-compartmental PK model. The TFV-DP active intracellular metabolite assayed in the PBMCs and genital tract cells along with TFV assayed from the genital fluid will be assessed for evaluating protection against HIV infection.

## 9.6 Blinding
Both study staff (except for the study pharmacists) and participants will be blinded to active or placebo treatment assignments for Groups 2 and 4. However, it will not be possible to blind the number of implants received in Group 2. Blinding will be maintained until the last participant reaches study exit.

In the event that an Investigator is aware that a participant could be put at undue risk by continuing product use, the Principal Investigator or designee may discontinue product use by this participant, without knowledge of the actual treatment assignment. In the event that knowledge of the received study product is necessary to protect a participant's safety, the Principal Investigator or designee will give permission for emergency unblinding. This emergency unblinding will be documented in study records. Emergency unblinding will be done by contacting the study pharmacist who will provide the dispensing history of all study product over the duration of the study, including the dates of product dispensing and whether active or placebo was dispensed.

All study participants and clinic staff inserting or removing implants will be administered a brief unblinding assessment at the study exit visits in which they will be asked to report which study product they think was used.

## 9.7 Data management
All data management activities will be undertaken under the applicable regulatory frameworks. This includes the U.S Food and Drug Administration (FDA) regulations, European Medicines Agency (EMA) regulations and the SAHPRA regulations. All studies will also abide by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC) regulations. The Data management systems in CAPRISA meet FDA requirements as they are CFR Part 11 compliant. The Data Management standard processes are aligned with the Good Clinical Data Management Processes (GCDMP).

CRFs are checked for completeness and accuracy at two levels before they are captured into the system with the presence of a data manager at each site, enabling instant support and clarification on issues. Discrepancy rates and discrepancy resolution turn-around constitute a core metric on the performance management of study staff. The discrepancy rate has to be below 4 per 100 pages faxed in for all CAPRISA internal studies. Discrepancy reports are sent on a weekly basis to the clinical trial site and the staff responsible have to resolve these within an average of 7 working days.

Both CAPRISA ECRS and VCRS will undertake the study and have secure, double-locked rooms for the storage of study forms, with a high capacity fire-proof walk-in safe at the central CAPRISA data management department. All access is electronically or key controlled and only authorized staff has access to these areas (e.g. data management staff and specified study staff). Logs are maintained for monitoring access to the facilities and for tracking the removal and return of study forms from the storage area. The data management systems in use require a username and password for access, which is strictly controlled by the data manager who liaises with the site clinical data management team to grant/revoke access privileges to any users at the appropriate functional levels. Certain users, such as statisticians and site QC officers are given read only rights to the data management system. The systems also maintain audit trails which track and record any changes made to the data after capture, the type of change made, the date and time of the change as well as the person who changed the data.

The data management systems used in CAPRISA are all hosted on the secure CAPRISA network, which is firewalled and access controlled, with the servers backed up on a daily basis to a secure off-site facility. CAPRISA backup and restorations are done in line with the CAPRISA IT Disaster Recovery and Business Continuity.

Data will be collected on one-ply case report forms (CRFs) that will be developed by the study team. All site study staff will be trained in the correct completion of CRFs. If data entered on the CRFs are taken from an external source (e.g., laboratory reports, patient records), the source documents will be maintained in the participant's medical chart or study file at the site, and will be available for review. The CRFs will be faxed into the database management system which is iDataFax 2014.1.1 (or higher) running on SuSe Linux V11. DataFax has optical character recognition, which will read the check boxes and numerical fields on the CRFs and store them in the study database. Any fields not recognized by the optical character recognition system will be entered manually by the Data Encoders. Data Encoders will verify all data by cross-checking the faxed version with what is entered into the database.

Queries arising during validation of the data will be recorded in quality control (QC) reports sent to the sites on a regular basis. Any queries resulting in a change to the database will be documented and attached to the original CRF. The data management centre staff will perform periodic QC and validation checks on the data. Database files will be password-protected and access to the files will be limited to authorised study staff members only. All data will be backed up at regular intervals with backups stored in secure areas with limited access.

The original CRFs and the DataFax version of the CRFs and related documents will be stored securely at the sites for both during and after the completion of the study. At all sites, the forms will be stored in locked cupboards in a secure room with restricted access. Upon completion of the study, the close-out site monitoring visit and finalisation of the database for analysis, the original forms will be bound and kept for long-term storage.

A detailed data management plan will be included in the study SSP manual.

The trial data will be made available to researchers at all the participating partner institutions in order to encourage the preparation of manuscripts from the trial dataset. All data will be owned jointly by the consortium conducting the project and each consortium member will have a complete set of the data for independent analysis after publication of the primary manuscript. Other researchers seeking to access the data for verification and/or re-use will be able to submit data access requests for review by the Study PI and the Head of Statistics & Data Management in CAPRISA. In line with standard data access principles, CAPRISA will ensure that:

- Metadata on the datasets will be made available.
- Anonymization and other measures will be taken to protect individual and personally identifiable information in the datasets.

Conference abstracts and manuscripts written that include the analysis of any data from this trial will follow standard CAPRISA procedures. The abstracts and manuscripts must be submitted to the CAPRISA Scientific Review Committee (CSRC) for approval prior to submission.

## 10 SAFETY MONITORING AND ADVERSE EVENT REPORTING

### 10.1 Adverse Events (AEs) and Reporting Requirements

An AE is defined as any untoward medical or social occurrence in a clinical research participant that may or may not have a causal relationship with the study product. Study product refers to oral TAF and TAF formulated in the OCIS-001 implant and the placebo implant. The above-listed definition of an AE will be applied as soon as the implant is inserted or oral TAF is ingested.

New information regarding symptoms or conditions that occur prior to enrolment will be recorded in the participant's medical history as pre-existing conditions. All new or worsening symptoms or conditions that occur following enrolment will be considered AEs and will be recorded on the AE CRF.

**Adverse drug reaction (ADR):** is defined as a response to a medicine in humans that is noxious and unintended, including lack of efficacy, and that occurs at doses normally used in man and that can also result from overdose, misuse or abuse of a medicine. All adverse events judged by either the investigator as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. ADRs that occur following enrolment will be considered AEs and will be recorded on the AE CRF.

**Unexpected Adverse Reaction (UAR):** is a reaction in which the nature, specificity, severity and outcome is not consistent with the approved package insert for a registered medicine (or investigator's brochure for an investigational product). When the outcome of the adverse reaction is not consistent with the applicable product information, this adverse reaction should be considered as unexpected**.** UARs that occur following enrolment will be considered AEs and will be recorded on the AE CRF.

### 10.2 Adverse Event Reporting

Study participants will be provided with 24-hour contact telephone numbers and instructed to contact a study clinic to report any AEs they may experience, except for life-threatening events, for which they will be instructed to seek immediate emergency care. Depending on the severity of the event, the clinician may instruct the participant to present to the study site or to a hospital casualty department for immediate evaluation.

Participants who present to the study site with AEs that cannot be appropriately managed at the study site will be referred to a local hospital for additional care and management. With appropriate permission of the participant, records from all non-study medical providers related to AEs will be attempted to be obtained and required data elements will be recorded on study CRFs. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline/non-gradable range). AEs that are ongoing at the time of study exit will be followed up for up to 30 days

after study exit and then, if not resolved, will be referred to a health care provider for further follow-up.

The Principal Investigator or designee must determine the severity of the AE and document it on the appropriate CRF (AE Form). Each AE that the participant is aware of should be graded for severity using the DAIDS Adverse Event Grading Tables, version 2.1, dated March 2017 (or latest version):

AEs related to Implant insertion or removal will be graded in accordance with parameters outlined in the DAIDS adverse event grading table for site reactions to injections and infusions for insertion site pain, insertion site erythema, insertion site swelling or insertion site pruritus. Example for insertion site pain:

- Grade 1 (Mild): pain or tenderness causing no or minimal limitation of use of limb.
- Grade 2 (Moderate): pain or tenderness causing greater than minimal limitation of use of limb.
- Grade 3 (Severe): Pain or tenderness causing inability to perform social and functional activities
- Grade 4 (Potentially life-threatening): Pain or tenderness causing inability to perform basic self-care function OR hospitalization indicated.
- Grade 5 (Death)

Other AEs including abnormal serum chemistries will be graded in accordance with the guidance in the DAIDS Adverse Event Grading Tables.

An AE **does not** include:

- pre-existing diseases or conditions present or detected prior to start of study drug administration that does not increase in grade;
- medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions).

The Principal Investigator or designee must determine the relationship of the AE to the product under investigation and document on the appropriate CRF (AE Form). For each AE, an assessment of the relatedness to the study drug will be made using the criteria and scale as outlined in the study SSP manual.

All AEs will be captured regardless of the association or otherwise to the study product and reported on the AE CRF in accordance with study specific procedures. All AE reports will contain at least the date the AE occurred, a brief description of the event, the relationship to study drug, the study drug action taken, the outcome, date resolved, and the seriousness of the event.

### 10.3 Serious Adverse Event (SAE) Reporting

An **SAE** or **Serious Adverse Reaction (SAR)** or **Suspected Unexpected Serious Adverse Reaction (SUSAR)** includes an experience where any AE, AR or UAR that at any dose:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in a congenital anomaly or birth defect;
- results in persistent or significant disability or incapacity; or is a medically significant / important event or reaction that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

A potentially life-threatening AE means that the participant was, in the view of the designated study staff, at immediate risk of death from the condition as it occurred. Notification of deaths will be recorded by reflecting the medical condition that led to the death on the AE CRF and also reported on the SAE report. Reporting SAEs may require additional detailed reports and follow-up, depending upon the study clinician's estimate of a causal relationship between the study product and the AE(s), and whether the AE(s) is identified in nature, severity, and frequency in the Investigator's Brochure or other risk information supplied to the Principal Investigator or designee. SAE reporting must take into account the assessment of the seriousness, the assessment of causality and the assessment of expectedness.

All SAEs will be reported to the Principal Investigator or designee within 48 hours of the research clinic becoming aware of the problem. In cases where the Principal Investigator or designee cannot be informed of a SAE using the report form within 48 hours, the designated study staff will report the SAE via telephone and the SAE report form will be completed as soon as possible after the verbal report. The Principal Investigator or designee will complete a SAE report form and submit it to the relevant regulatory oversight committees, as required. *(Further details for SAE assessment and reporting is contained in the CAPRISA 018 study SOP on SAE reporting and in the CAPRISA 018 SSP Manual).*

These reporting requirements apply to each study participant from enrolment (day 0 on receipt of study product) until their follow-up in the study ends. After this time, the site must report serious, unexpected, clinically suspected adverse drug reactions if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

### 10.4 Safety Monitoring

Participant safety will be closely monitored both internally by the protocol safety review team (PSRT) and externally by the data safety and monitoring board (DSMB). Designated study staff will be responsible for continuous close safety monitoring of all study participants. The study statisticians will prepare routine study progress reports for review by the Protocol Team. In addition, the study statisticians will prepare routine study progress reports which include reports of AEs experienced by study participants (blinded to treatment assignment) for review by the PSRT. The membership, scope of responsibility, role and modus operandi of the PSRT will be outlined in the SSP manual.

PSRT members will meet in-person and/or via teleconference regularly throughout the period of study implementation. The PSRT will review incoming safety data for completeness and consistency on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. Any deaths of study participants or other SAEs must be reviewed and a decision taken by the PSRT with regard to whether a DSMB review is warranted.

In addition to monitoring performed by the PSRT, the study DSMB will review the study data during the period of study implementation. Following its review of the trial, the DSMB may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

### 10.5 Data, Safety, Monitoring Board

An independent DSMB will be established before the clinical trial begins in order to independently monitor the safety of the trial. The DSMB will be comprised of independent medical experts as well as other experts, such as statisticians, in the conduct of clinical trials. The details for the operation and responsibilities of the DSMB will be defined in a separate DSMB Charter. The Charter will delineate the composition, duties, responsibilities and procedures of the DSMB, data required at each meeting, as well as the analyses that will be conducted, i.e. interim comparisons of the safety of the study products.

It is anticipated that there will be an initial DSMB meeting prior to trial initiation and approximately 10 DSMB meetings during the trial conduct. More frequent or ad hoc reviews of safety reports may be conducted by the DSMB as needed. A recommendation to stop the trial may be made by the DSMB at any such time that the board agrees an unacceptable type and/or frequency of AEs has been observed.

After each DSMB meeting, the Chairperson will issue a written report describing all recommendations. The DSMB could recommend that the study should proceed as designed, should proceed with design modifications, or should be discontinued. All reports created by the independent statistician will be distributed password-protected to the members of the DSMB. Some data that goes to the DSMB will be “open” and available to the study team. DSMB reports will be kept in a locked file with restricted access.

## 11 HUMAN SUBJECTS CONSIDERATIONS

### 11.1 Regulatory and Ethical Review

This study will be conducted under the oversight of the SAHPRA in accordance with South African Good Clinical Practice Guidelines, International Council on Harmonization (ICH) standards of Good Clinical Practice (GCP) and Good Participatory Practice (GPP). The Principal Investigator or designee will be responsible for reporting study-related information to the SAHPRA.

The study also will be conducted under the oversight of the University of KwaZulu-Natal (UKZN) Biomedical Research Ethics Committee (BREC) in South Africa. The study will only be initiated after it has been approved by both the UKZN BREC and the SAHPRA. The study will be conducted in accordance with all conditions of approval by the ethics committee.

### 11.2 Informed Consent

Written informed consent will be obtained from each study participant in English or isiZulu prior to screening and enrolment (see Appendix B), in accordance with South African GCP guidelines, 21 CFR Part 50 and ICH GCP guidelines. Separate written informed consents will be obtained for trial screening, specimen storage and possible future testing, enrolment into the trial and off-site visits. Neither consent for long-term specimen storage nor off-site study visits are required for study participation. Potential participants will be provided with informed consents (*See Appendix B1-B3*) and detailed patient information sheets, if they are willing to receive them, (*Refer to the CAPRISA 018 SSP Manual)* to help them make their decision to participate. These documents will be in a language that is understandable to them and an educational level that they can comprehend.

Standard methods will be used for document translation that ensure comparability to the original English. All translated materials will be submitted to the ethics committee for approval and not be put to use until approval is received. The informed consent forms will describe the research in adequate detail, including the nature of participation, any benefits, risks and discomfort that may be

experienced. In addition, information will be provided on how biological samples are stored, anonymized and whether they will be destroyed or re-used subsequently.

The process for obtaining informed consent is detailed in the *CAPRISA SOP on obtaining informed consent and CAPRISA 018 SSP Manual.*

### 11.3 Risks

- Participants may experience side effects related to the insertion and removal of the sub-dermal implants. The majority of clinical experience are with contraceptive use. The frequency of insertion complications is uncommon, around <1%. Removal complications are slightly higher ranging from 1-2%.
- Study participants may also experience discomfort when having pelvic examinations, which would be similar to those experienced by women undergoing routine gynaecological examinations.
- During phlebotomy, participants may feel dizzy or faint, and/or develop a bruise, swelling, or infection where the needle is inserted.
- Participants may become embarrassed, worried, or anxious when completing their HIV-related interviews and/or receiving HIV/STI counselling. They also may become worried or anxious while waiting for their HIV test results or after receiving HIV-positive test results. Trained study staff will be available to help participants deal with these feelings.
- Study personnel will make every effort to protect participant privacy and confidentiality, but it is possible that participants may disclose their HIV status to non-study participants and could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. Participants also could have problems in their partner relationships associated with use or attempted use of condoms and/or the study product.

Data on participant risk behaviours and the occurrence of other potential social harms will be collected from all participants. The Protocol Team will monitor trends in risk behaviours over time based on these data, as well as the occurrence of social harms, and initiate any required follow-up action.

### 11.4 Benefits

There may be no direct benefits to participants in this study. However, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of a safe and effective sub-dermal implant that prevents HIV infection.

Study participants will receive Pap smears, HIV and STI counselling and testing, a physical examination and gynaecological assessments. Contraception will also be available to study participants. They will be provided syndromic STI treatment free-of-charge, and will be offered STI treatment for their partners. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Study participants will also receive condoms and risk reduction counselling and will be reimbursed for time, transport and inconvenience costs for each scheduled visit. Study personnel will make every effort to protect participant privacy and confidentiality.

### 11.5 Access to HIV-related care

Potential study participants who volunteer to undergo HIV testing as part of the study screening process may discover that they are HIV-positive. Study staff will provide all HIV test results with post-test counselling. Potential study participants who have been identified as HIV-positive will be

referred to local HIV treatment services, which will provide medical and psychosocial AIDS care and support. HIV-negative study participants who become infected during follow-up will be referred to one of the long-term CAPRISA Acute Infection cohort studies, which have provisions for care, ART and support for those infected with HIV. These services are provided at no cost to the participant. Those who do not wish to continue in any of these studies post-seroconversion will be referred to their preferred AIDS care provider, which could include government or non-governmental AIDS care services for ongoing clinical management and care.

### 11.5.1 HIV counselling and testing

HIV counselling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV testing time point. HIV test results will be provided with post-test counselling. Condoms will be provided to participants throughout the duration of their participation in the trial.

## 11.6 Community involvement and consultation

The main channel of formal communication with communities takes place with the support of the CAPRISA Community Advisory Board (CAB) that has been established at CAPRISA's CRSs. Key messages about the study will be provided to this group, as well as civil society groups through regular meetings and community events, as appropriate.

The CAB membership includes local community leaders, traditional leaders, leadership of local HIV/AIDS organisations, previous study participants, local health service provider representatives and HIV-positive local community members. CAPRISA's Community Programme in partnership with the CAB will involve the community and local community based organisations in preparation for this trial. Specifically, the CAPRISA Community Programme will inform, educate and mobilise the community to enhance community input into the research process. The local CAB at the CAPRISA CRS's plays an active role as an interface between the researchers and community members serving as advocates for the community's best interests and ensuring that the researchers are aware of any concerns within the community about the research being conducted. The CAB also play an important role in reviewing study educational materials, consent forms and isiZulu translations of documents, which will be shared with study participants.

During the trial, regular update meetings will be held with the CAB where study status accrual and retention challenges, study progress and any other relevant challenges is reported to the CAB by the study leadership. In addition, the CAB reports any concerns that they have noted in the community back to the study management. Then there is an exchange of ideas and discussions commence towards mutual resolution. Participant interaction outside of clinic study procedure visits is essential, in our setting, to ensure that all voices are heard. Experience has revealed that sometimes group events raise issues that individual interaction may not illicit. These events involve inviting study participants to the site outside of a study visit to discuss study updates and feedback to the participants on how the trial is progressing. Participants are given an opportunity to also voice their opinions and are empowered to exercise their rights as study volunteers.

## 11.7 Confidentiality

Every effort will be made to protect participant privacy and confidentiality to the extent permitted by law. Study-related information will be stored securely at the study site. All participant information will be stored in lockable file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only, to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number.

All databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link PID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participants' study data, as identified by PID number only, will not be released without their written permission, except as necessary for review and monitoring by regulatory agencies or study monitors. Where participants provide consent for photography to document post-insertion or post-removal implant insertion site healing, photography will be limited to the arm and no other physically identifiable features of participants will be photographed.

### 11.8 Study discontinuation

This study may be discontinued at any time by the SAHPRA, US FDA, EMA, UKZN BREC, or the Protocol Team (e.g., in response to recommendations from the DSMB or the study sponsor).

## 12 ADMINISTRATIVE PROCEDURES

### 12.1 Protocol Compliance

The study will be conducted in full compliance with the protocol. Amendments to the protocol will be required to follow an SOP which stipulates the levels of approval required prior to submission to regulatory bodies and the steps to be followed prior to implementation of a protocol amendment.

### 12.2 Protocol deviations and violations

A Protocol deviation is related to any change, divergence, or departure from the Institutional Review Board (IRB)/BREC -approved protocol including study design, procedure or schedule of events that:

- is under the investigator's control and that has not been approved by the IRB.
- affects a participant's rights, safety, or well-being
- affects the completeness, accuracy and reliability of the study data but that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

**Definition of a Protocol violation**

A Protocol Violation is an event with potentially severe consequence that could significantly affect data analysis and/ or participant safety. Any change, divergence or departure from the IRB/BREC approved protocol that affects a participant's rights, or safety, or well-being and/or the completeness, accuracy and reliability of the study data, is also considered as a Protocol violation.

The difference between protocol deviation versus protocol violation is based on the severity of its impact on a participant's rights, safety and welfare or study data integrity and credibility. If an event has harmed or posed a significant or substantive risk of harm to the research participant, it is considered a protocol violation.

Examples:

- omission or inadequate administration of informed consent
- inclusion/exclusion errors, including legal age limit
- receipt of an excluded concomitant medication by a research participant
- wrong treatment or incorrect dose received by the participant.
- failure to withdraw a research participant when she meets withdrawal criteria.
- failure to discontinue product use according to protocol criteria
- missing or incorrectly timed study procedures and assessments

In an emergency, the Investigator may make departures from the protocol to eliminate an apparent immediate hazard for a particular participant. In such a case, he/she will notify the relevant regulatory authorities Ethics Committee and SAHPRA, in writing as soon as possible and document reasons for the violation (unless solely caused by participant non-compliance such as not attending for study visits).

## 12.3 Quality Assurance and Study Monitoring

### 12.3.1 Quality assurance

Quality assurance (QA) in the trial will be undertaken according to the Study QA Plan *(Refer to CAP018 SSP manual for further details)*. The QA Plan will include ongoing monitoring of study progress and safety by the Protocol Team, study monitoring in accordance with ICH GCP and South African GCP guidelines by trained Triclinium monitoring staff and/or other outside QA contractors. The Investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. The Investigators will also allow inspection of all study-related documentation by authorized representatives of the SAHPRA, the FDA, the EMA and the study sponsors. A site visit log will be maintained at the study site to document all visits.

### 12.3.2 Study Monitoring

Study monitoring will be conducted by representatives of Triclinium Clinical ~~Trial Project Management~~ Development (TCD-Global), an independent Contract Research Organisation (CRO). Pre-initiation site monitoring will be undertaken to establish study site readiness for study initiation. Thereafter ongoing monitoring will be undertaken after enrollment of the first participants and at regular intervals thereafter. A site visit log will be maintained at the study site to document all visits.

Monitor findings will be documented in accordance with Triclinium monitoring SOPs. The Principal Investigator (or designee) will be notified of the findings. If the monitor discovers issues related to safety, he/she is to report their findings immediately to the Principal Investigator or designee.

## 12.4 Study Records

Complete, accurate, and current study records will be maintained and stored in a secure manner throughout the study. All study records will be maintained for at least 15 years after the termination of the trial and extended to 2 years following the date of marketing approval for the study product for the indication in which it was studied and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of the development of the study product.

The European and Developing Countries Clinical Trials Partnership (EDCTP) will be consulted by the Principal Investigator (or designee) to determine if this storage period needs to be extended.

## 12.5 Use of Information and Publications Policy

Before this trial is initiated, its details will be registered in a publicly available, free to access, searchable clinical trial registry. Information about this trial will be registered with ClinicalTrials.gov and the South African National Clinical Trials Registry (SANCTR - http://www.sanctr.gov.za/).

During the study, the scientists involved in this study will disseminate the results from this research as broadly as possible. We expect that all the research personnel involved in this study will attend local, national and international conferences periodically and present the results from this research to the scientific community. Because of the multidisciplinary nature of the work, different group members will present at various conferences, such as the Conference on Retrovirus and Opportunistic Infections, International AIDS Society, and South African HIV Clinicians conferences, HIV Research for Prevention Conference as appropriate for the different aspects of the research. The results from this research may also be disseminated through presentations at public lectures, scientific institutions and meetings. In addition to the dissemination of the research findings with the scientific community, the findings will also be shared with the study participants, communities and lay persons.

After the study is completed, results from this research will be published in peer-reviewed journals. Summary results of the trial will also be made publicly available in a timely manner by posting to the results section of the clinical trial registry. Other results will also be made available to investigators whose proposed use of the data has been approved by the CAPRISA Scientific Review Committee. Requests to access the data can be made through the CAPRISA website (www.caprisa.org).

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# 14 APPENDICES

## 14.1 Appendix A1: Schedule of evaluations – GROUP1

| Study Procedures (Group 1) V2.0, 12 Aug19 | Screening (up to 56 days) | Day -1 to 7 | | | | | | Weekly follow-up | | | | | | Post trial safety follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Enrolment (Day -1) | Enrolment (Day 0) | DAY 1 | DAY 2 | Day 3 | DAY 7 Week 1 | Day 14 Week 2 | Day 21 Week 3 | Day 28 Week 4 | Day 35 Week 5 | Day 42 week 6 | Day 49 week 7 | Day 56 Final visit |
| **Administrative, Behavioural and Regulatory Procedures** | | | | | | | | | | | | | | |
| Informed consent for screening | X | | | | | | | | | | | | | |
| PID assignment | X | | | | | | | | | | | | | |
| Informed consent for enrolment | | X | | | | | | | | | | | | |
| Informed consent for storage & future testing | | X | | | | | | | | | | | | |
| Demographic information | X | | | | | | | | | | | | | |
| Locator information | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Eligibility assessment | X | X | X | | | | | | | | | | | |
| HIV risk assessment | X | | | | | | | | | | | | | |
| Behavioural assessment | | X | | | | | | | | X | | | | X |
| Pre- and post-test HIV counselling | X | X | | | | | | | | X | | | | X |
| Risk reduction counselling & condom supplies | X | X | | | | | | | | X | | | | X |
| **Clinical Procedures** | | | | | | | | | | | | | | |
| Medical history, physical examination, vitals | X | X | | X | X | X | X | X | X | X | X | X | X | X |
| Contraceptive counselling and provision (if indicated) | X | X | | | | | | | | X | | | | X |
| Adverse event assessment | | | X | X | X | X | X | X | X | X | X | X | X | X |
| Phlebotomy | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pelvic examination | X | | | X | | | X | | | X | | | | X |
| Document concomitant medication | X | X | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Implant insertion | | | X | | | | | | | | | | | |
| Implant removal | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | X | | | | |
| DEXA scan | | X | | | | | | | | | | | | X |
| Post-insertion Implant acceptability/tolerability assessment | | | X | X | | | X | X | | X | X | X | | X |
| Provide test results | X | X | 0 | 0 | 0 | 0 | X | X | X | X | X | X | X | X |
| **Pharmacy procedures** | | | | | | | | | | | | | | |
| Provide TAF implant/s | | | X | | | | | | | | | | | |
| Update accountability logs | | | X | | | | | | | | | | | |
| **Perform laboratory evaluations:** | | | | | | | | | | | | | | |
| Urine pregnancy test | X | X | | | | | | | | X | | | | X |
| Urinalysis | X | X | | | | | X | X | X | X | X | X | X | X |
| HIV serology (rapid tests) | X | X | | | | | | | | X | | | | X |
| Dried blood spots | | | X | X | X | X | X | X | X | X | X | X | X | X |
| PK blood (Storage) | | | X | X | X | X | X | X | X | X | X | X | X | X |
| Lipogram | X | | | | | | X | | | X | | | | X |
| HIV RNA POC GenXpert/Lab PCR | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Geenius [a] + CD4 counts | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PBMCs[a] | | X | X | X | | | X | X | | X | X | X | | X |
| Plasma and serum archive[a, b] | | X | | | | | | | | X | | | | X |
| Hepatitis B[a] | X | | | | | | | | | | | | | X |
| STI testing as well as vaginal pH (Urine, plasma/serum and genital specimen) | X | 0 | 0 | 0 | 0 | 0 | X | 0 | 0 | X | 0 | 0 | 0 | X |
| Haematology[a] (full blood count) & Blood chemistry (LFT, U & E with creatinine clearance, Ca,PO4, Vit D, PTH) | X | | | | 0 | 0 | X | X | 0 | X | 0 | 0 | 0 | X |
| Pap smear | X | | | | | | | | | | | | | |
| Genital specimen for archive[b] | | X | | X | | | X | | | X | | | | X |
| Cervico-vaginal biopsy | | | | | | | | | | X | | | | |
| Resistance testing in seroconvertors[c] | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Amount of blood collected in mls[b] : | 36 | 76(86) | 54(104) | 46(96) | 12(62) | 12(62) | 75(125) | 66(116) | 12(62) | 115(125) | 12(96) | 46(96) | 12(62) | 120(130) |

**Footnotes:**

[a]Blood volumes: HIV Confirmatory tests (PCR, CD4 counts, POC GenXpert, Geenius, Storage ) (40ml EDTA) (only if indicated); Rapid tests (2mls EDTA); PBMCs (34mls CPT); Storage (20 mls, EDTA); Safety bloods (10 mls EDTA); Vit D, PTh (5ml SST), Lipogram (5ml SST), HBV assays (10 mls); Resistance assays (10mls) (only if indicated); PK levels (20mls); STI testing (4mls EDTA).

[b]The stored serum, plasma and genital specimens will be used for potential post-trial assessments for markers of safety, risk exposure, product adherence, suspected HIV seroconversion and tenofovir resistance. In addition, stored plasma will be used for retrospective RNA PCR testing to confirm whether incident cases of early HIV infection during the trial occurred post-randomisation. Vaginal tissue biopsy is considered part of genital specimen collection and will only be taken on Day 28. Other genital specimens collected are genital fluid from the soft cup and e-swabs and cells from cytobrush.

[c]Performed on first positive HIV specimen and exit sample

0 = if indicated ( )= includes additional bloods for suspected HIV seronverters (i.e. HIV confirmatory tests, CD4 counts,storage)

## 14.2 Appendix A2: Schedule of evaluations – GROUP 2 and GROUP 3

| Study procedures Phase I(Groups 2 and 3) V2.0, 12 Aug19 | Screen | Enrolment | | Weekly follow-up | | | | Monthly Follow up | | | | | | | | | | | Post trial safety follow-up (GROUPS 2, 3b,3d) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening (up to 56 days) | Enrolment (Day -1) | Enrolment (Day 0) | DAY 7 Week 1 | Day 14 Week 2 | Day 21 Week 3 | Day 28 Week 4 | Week 8 | Week 12 | Week 16 | week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 (FINAL VISIT GROUPS 3a, 3c) | Week 52 FINAL VISIT |
| **Administrative, Behavioural and Regulatory Procedures** | | | | | | | | | | | | | | | | | | | |
| Informed consent for screening | X | | | | | | | | | | | | | | | | | | |
| PID assignment | X | | | | | | | | | | | | | | | | | | |
| Informed consent for enrolment | | X | | | | | | | | | | | | | | | | | |
| Informed consent for storage & future testing | | X | | | | | | | | | | | | | | | | | |
| Randomisation for Group 2 | | X | | | | | | | | | | | | | | | | | |
| Demographic information | X | | | | | | | | | | | | | | | | | | |
| Locator information | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Eligibility assessment | X | X | X | | | | | | | | | | | | | | | | |
| Pre and post HIV test counselling | X | X | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Risk reduction counselling & condom supplies | X | X | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HIV risk assessment | X | | | | | | | | | | | | | | | | | | |
| Behavioural assessment | | X | | | | | X | | X | | | X | | | X | | | X | X |
| Adherence counselling tablet arm | | | X | X | X | X | X | X | X | X | X | | | | | | | | |
| Unblinding **(GROUP 2 ONLY)** | | | | | | | | | | | | | | | | | | X | |
| **Clinical Procedures** | | | | | | | | | | | | | | | | | | | |
| Medical history, physical examination, vitals | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Contraceptive counselling and provision (if indicated) | X | X | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse event assessment | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Phlebotomy | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pelvic examination | X | | | X | | | X | | X | | | X | | | X | | | X | X |
| Document concomitant medication | X | X | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DOT dose TAF oral | | | X | X | X | X | X | X | X | X | X | | | | | | | | |
| Implant insertion | | | X | | | | | | | | | | | | | | | | |
| Implant removal* | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | X | |
| DEXA scan | | X | | | | | | | | | | 0 | | | | | | | X |
| Post-insertion Implant acceptability/tolerability assessment | | | X | X | | | X | X | X | | | X | | | X | | | X | X |
| Provide test results | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Pharmacy procedures** | | | | | | | | | | | | | | | | | | | |
| Provide oral study product & dosing instructions to participant **(GROUP 3C ONLY)**** | | | X | | | | X | X | X | X | X | | | | | | | | |
| Provide TAF implant/s **(EXCLUDE GROUP 3C)** | | | X | | | | | | | | | | | | | | | | |
| Update accountability logs (where applicable) | | | X | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adherence assessment /pill count **(GROUP 3C ONLY)** | | | X | X | X | X | X | X | X | X | X | X | | | | | | | |
| **Perform laboratory evaluations:** | | | | | | | | | | | | | | | | | | | |
| Urine pregnancy test | X | X | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HIV serology (rapid tests) | X | X | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dried blood spots | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK blood (Storage) | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Lipogram | X | | | X | | | X | | X | | | X | | | X | | | X | X |
| HIV RNA POC GenXpert/Lab PCR | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Geenius [a] + CD4 counts | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PBMCs[a] | | X | X | X | X | | X | X | X | | | X | | | X | | | X | X |
| Plasma and serum archive[a, b] | | X | | | | | X | | X | | | X | | | X | | | X | X |
| Hepatitis B[a] | X | | | | | | | | | | | X | | | | | | | X |
| STI testing as well as vaginal pH (Urine, plasma/serum and genital specimen) | X | 0 | 0 | 0 | 0 | 0 | X | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | X |
| Haematology[a] (full blood count) & Blood chemistry (LFT, U & E with creatinine clearance, Ca,PO4, Vit D, PTH) | X | | | X | 0 | 0 | X | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | X |
| Pap smear | X | | | | | | | | | | | | | | | | | | |
| Genital specimen for archive[b] | | X | 0 | X | 0 | 0 | X | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | X |
| Cervico-vaginal biopsy | | | | | | | | | X | | | | | | | | | | |
| Resistance testing in seroconvertors[c] | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Amount of blood collected in mls[b] | 36 | 76 | 54 | 71(121) | 46(96) | 12(62) | 117(127) | 48(62) | 117(127) | 14(64) | 14(64) | 122(132) | 14(64) | 14(64) | 117(127) | 14(64) | 14(64) | 117(127) | 122(132) |

**Footnotes:**

* Group 3A implants will be removed at week 24 AND monthly study visits OFF product will continue through week 48.

** Group 3C oral TAF tablets will be stopped at week 24 AND monthly study visits OFF product will continue through week 48.

aBlood volumes: HIV Confirmatory tests (PCR, CD4 counts, POC GenXpert, Geenius, Storage ) (40ml EDTA) (only if indicated); Rapid tests (2mls EDTA); PBMCs (34mls CPT); Storage (20 mls, EDTA); Safety bloods (10 mls EDTA); Vit D, PTh (5ml SST), Lipogram (5ml SST), HBV assays (10 mls); Resistance assays (10mls) (only if indicated); PK levels (20mls); STI testing (4mls EDTA).

bThe stored serum, plasma and genital specimens will be used for potential post-trial assessments for markers of safety, risk exposure, product adherence, suspected HIV seroconversion and tenofovir resistance. In addition, stored plasma will be used for retrospective RNA PCR testing to confirm whether incident cases of early HIV infection during the trial occurred post-randomisation. Vaginal tissue biopsy is considered part of genital specimen collection and will only be taken at Month 3. Other genital specimens collected are genital fluid from the soft cup and e-swabs and cells from cytobrush.

[c]Performed on first positive HIV specimen and exit sample

0 = if indicated  Quarterly visit  ( )= includes additional bloods for suspected HIV seronverters (i.e. HIV confirmatory tests, CD4 counts, storage)

## 14.3 Appendix A3: Schedule of evaluations – GROUP 4

| Procedures Phase II (Group 4) V2.0, 12AUG19 | Screen | Enrolment | | Weekly follow-up | | Monthly follow-up | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening (up to 56 days) | Enrolment (Day -1) | Enrolment (Day 0) | DAY 7 Week 1 | DAY 28 Week 4 | Week 8 | Week 12 | Week 16 | week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 | Week 52 | Week 56 | Week 60 | Week 64 | Week 68 | Week 72 | Week 76 | Week 80 | Week 84 | Week 88 | Week 92 | Week 96 | Week 100 | Week 104 | Week 108 | Week 112 | Week 116 | Week 120 Study exit |
| **Administrative, Behavioural and Regulatory Procedures** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent for screening | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PID assignment | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent for enrolment | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent for storage | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Demographic information | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Locator information | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pre and post test HIV counselling | X | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Eligibility assessment | X | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Risk reduction counselling & condom supplies | X | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HIV risk assessment | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Behavioural assessment | | X | | | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | |
| Adherence counselling | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Unblinding | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X |
| **Clinical Procedures** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical history, physical examination, vitals | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Contraceptive counselling and provision (if indicated) | X | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse event assessment | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Phlebotomy | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pelvic examination | X | | | X | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| Document concomitant medication | X | X | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Implant insertion | | | X | | | | | | | | | | | | | X | | | | | | | | | | | | X | | | | | | | | | | |
| Implant removal | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | X | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | X | 0 | 0 | 0 | 0 | X | | | | | | |
| DEXA scan | | X | | | | | | | | | | | | | | | X | | | | | | | | | | | | X | | | | | | | | | X |
| Post-insertion Implant acceptability/ tolerability assessment | | | X | X | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X |
| Provide test results | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Pharmacy procedures** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Provide oral TDF/FTC OR Placebo tablet | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Provide TAF OR Placebo implant | | | X | | | | | | | | | | | | | X | | | | | | | | | | | | X | | | | | | | | | | |
| Update accountability logs | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adherence assessment / pill count | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| **Perform laboratory evaluations:** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urine pregnancy test | X | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HIV serology (rapid tests) | X | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dried blood spots | | | X | X | X | X | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| PK blood (Storage) | | | X | X | X | X | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| Lipogram | X | | | X | X | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | X |
| HIV RNA POC GenXpert/Lab PCR | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Geenius [a] + CD4 counts | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PBMCs[a] | | X | X | X | X | X | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| Plasma and serum archive[a, b] | X | X | | | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| Hepatitis B[a] | X | | | | | | | | | | | | | | | X | | | | | | | | | | | | X | | | | | | | | | | X |
| STI testing as well as vaginal pH (Urine, plasma/serum and genital | X | 0 | 0 | 0 | X | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | X |
| Haematology[a] (full blood count) & Blood chemistry (LFT, U & Ewith creatinine clearance, Ca,PO4, Vit D, | X | | | X | X | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | X |
| Pap smear | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital specimen for archive[b] | | X | 0 | X | X | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | 0 | 0 | X | X |
| Resistance testing in seroconvertors[c] | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Amount of blood collected in mls[b]** | 36 | 76 | 54 | 66(116) | 117(127) | 48(98) | 117(127) | 2(52) | 2(52) | 117(127) | 2(52) | 2(52) | 117(127) | 2(52) | 2(52) | 122(132) | 2(52) | 2(52) | 117(127) | 2(52) | 2(52) | 117(127) | 2(52) | 2(52) | 117(127) | 2(52) | 2(52) | 122(132) | 2(52) | 2(52) | 117(127) | 2(52) | 2(52) | 122(132) | | | | |

**Footnotes:**

[a]Blood volumes: HIV Confirmatory tests (PCR, CD4 counts, POC GenXpert, Geenius, Storage ) (40ml EDTA) (only if indicated); Rapid tests (2mls EDTA); PBMCs (34mls CPT); Storage (20 mls, EDTA); Safety bloods (10 mls EDTA); Vit D, PTh (5ml SST), Lipogram (5ml SST), HBV assays (10 mls); Resistance assays (10mls) (only if indicated); PK levels (20mls); STI testing (4mls EDTA).

[b]The stored serum, plasma and genital specimens will be used for potential post-trial assessments for markers of safety, risk exposure, product adherence, suspected HIV seroconversion and tenofovir resistance. In addition, stored plasma will be used for retrospective RNA PCR testing to confirm whether incident cases of early HIV infection during the trial occurred post-randomisation. Genital specimens collected are genital fluid from the soft cup and e-swabs and cells from cytobrush.

[c]Performed on first positive HIV specimen and exit sample

0 = if indicated  Quarterly visit  ( )= includes additional bloods for suspected HIV seronverters (i.e. HIV confirmatory tests, CD4 counts, storage)

## 14.4 Appendix B: Informed consent forms

### 14.4.1 Appendix B1: Screening informed consent

(Attached as separate documents)

### 14.4.2 Appendix B2: Enrolment informed consents

**14.4.2.1 Enrolment informed consent for GROUP 1**
**14.4.2.2 Enrolment informed consent for GROUP 2**
**14.4.2.3 Enrolment informed consent for GROUP 3**
**14.4.2.4 Enrolment informed consent for GROUP 4**
(Attached as separate documents)

### 14.4.3 Appendix B3: Specimen storage and possible future research testing informed consent

(Attached as separate documents)

## 14.5 Appendix C: Safety laboratory evaluations and radiography

- **HIV RNA PCR**
  - Point of care and lab-based

- **HEAMATOLOGY TESTS**
  - FBC (with differential count)

- **BLOOD CHEMISTRY**
  - Liver chemistry tests
    - Alkaline phosphatase
    - ALT
    - AST
    - Total bilirubin
  - Renal function tests
    - Urea
    - Electrolytes
    - Creatinine clearance
  - Calcium
  - Vitamin D
  - Parathyroid hormone
  - Lipogram

- **STI TESTING**
  - HSV-2
  - Syphilis
  - Gonorrhoea
  - Chlamydia
  - Trichomonas
  - Bacterial vaginosis
  - Vaginal pH

- **OTHER**
  - Hepatitis B

- **BLOOD FOR PK ASSESSMENTS**

- **BONE DENSITOMETRY**
  - DEXA scan

## 14.6 Appendix D: CAPRISA 018 HIV antibody testing algorithm

The HIV testing algorithm at baseline and at each follow-up visit is provided below (Figures 4 and 5).

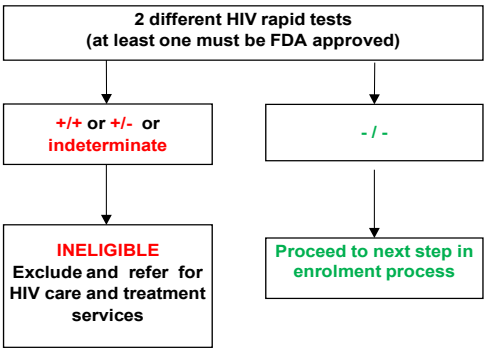


**Figure 4: Algorithm for HIV antibody testing for Screening & Enrolment visits**

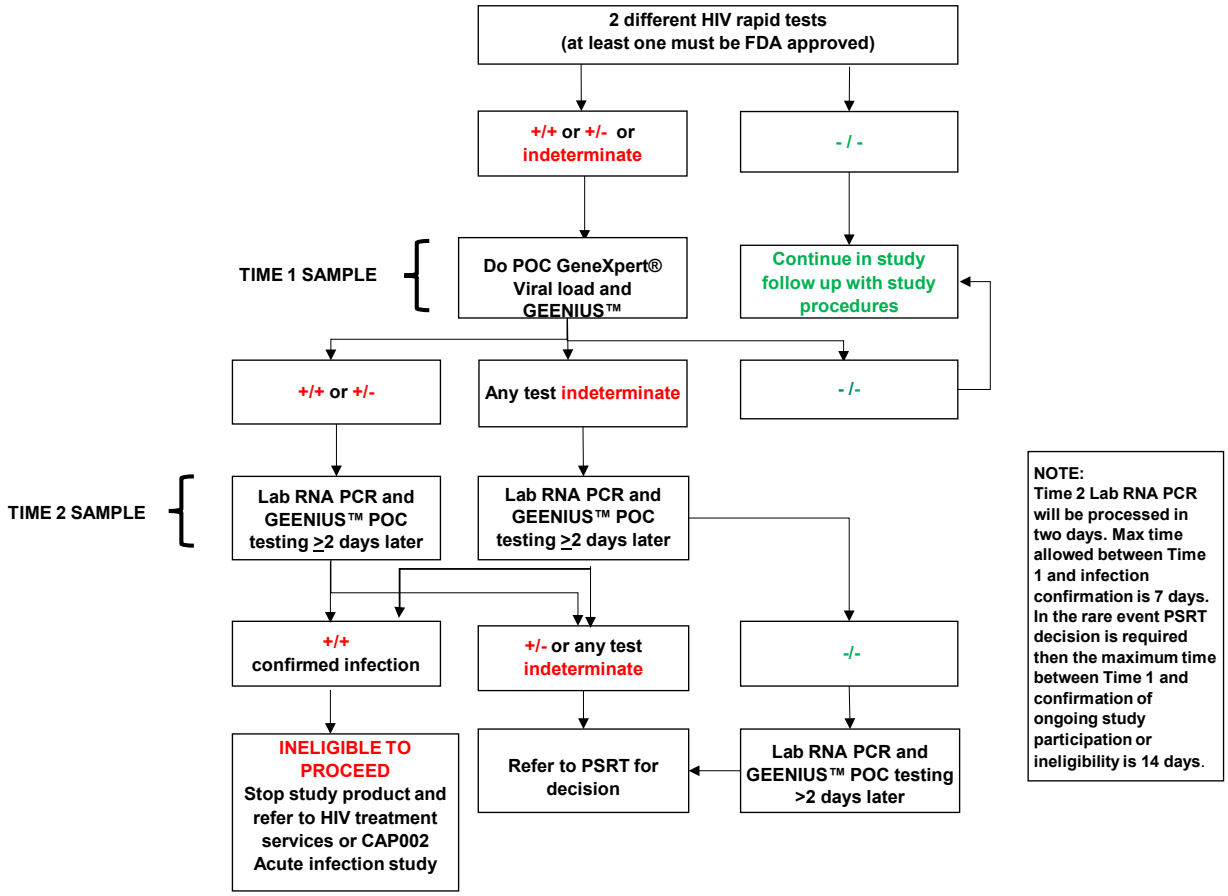


**Figure 5 : Algorithm for HIV antibody testing for Follow-up visits**

## 14.7 Appendix E: Management of insertion site reactions and study product toxicity management

- Use the DAIDS Adverse Event Grading Tables, version 2.1, dated March 2017 (or latest version) criteria for site reactions and injections to assess insertion related adverse events.
    - For Grade 3 (Severe Pain or tenderness causing inability to perform usual social & functional activities) or
    - Grade 4 (Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated) for local insertion site reactions.

Manage patients symptomatically and decisions to remove implant/s will be made by the PSRT in consultation with the Principal Investigator or designee.

- Use DAIDS Adverse Event Grading Tables, version 2.1, dated March 2017 (or latest version) criteria for chemistries to assess systemic effects.
    - Affected chemistries will be repeated to confirm results and the participants with Grade 3 or higher will be asked to return to site for further assessment.
    - Participants with Grade 1-2 chemistry will be closely monitored until chemistries return to normal.

Manage patients symptomatically and the decision to remove implant/s will be made by the PSRT in consultation with the Principal Investigator.