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Title: 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

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Abstract

Introduction

Young African women bear a disproportionately high risk for HIV acquisition. HIV technologies that empower women to protect themselves are needed. Safe, potent antiretroviral agents such as tenofovir alafenamide (TAF), formulated as long-acting sub-dermal implants, offer an innovative solution.

Methods and analysis

CAPRISA 018 is a phase I/II trial to evaluate the safety, acceptability, tolerability, and pharmacokinetics (PK) of a TAF *free base* subdermal silicone implant containing 110mg of TAF with an anticipated 0.25mg/day release rate.

The Phase I trial (n=60) will assess the safety of one implant inserted in six participants (Group 1), followed by dose escalation components (Groups 2 and 3) assessing the safety, tolerability, and PK of one to four TAF 110mg implants releasing between 0.25mg to 1mg daily in 54 healthy women at low risk for HIV infection. Data from this Phase I trial will be used to determine the dosing, implant location, and implant replacement interval for the Phase II trial.

The Phase II component (Group 4) will assess extended safety, PK, tolerability, and acceptability of the implant in 490 women, randomized in a 1:1 ratio to the TAF implant and placebo tablet or to the placebo implant and an oral PrEP (pre-exposure prophylaxis) tablet. Safety will be assessed by calculating the percentage change in creatinine clearance from baseline at weeks 4, 12, 24, 36, 72, 96 and 120, compared to the percentage change in the control group.

Ethics and dissemination

The South African Health Products Regulatory Authority and the University of KwaZulu-Natal's Biomedical Research Ethics Committee have approved the trial. Results will be disseminated through open access peer reviewed publications, conference presentations, public stakeholder engagement and upload of data into the clinical trials registry.

Trial registration number: PACTR201809520959443. Status: recruiting.

Article summary

Strengths and limitations of this study

- This first-in-human trial to assess the safety and PK of a TAF free-base sub-dermal implant formulation.
- This trial adopts a master protocol design, where dose selection for Phase II is based on Phase I data within the same trial.
- Phase I is dose ranging and is designed to provide early safety, tolerability, acceptability, and PK data.
- The potential for implant mechanical failure cannot be assessed until sufficient participant follow up PK data are collected in Group 2 and subsequent groups.
- The Phase II trial, powered on a safety endpoint, adopts a randomised, double-dummy design, and has the potential to show a signal for efficacy against HIV infection, if adherence to the oral study product is low and implant drug release is adequate.

INTRODUCTION

Despite the global decline in HIV infections by 23% since 2010, the number of people who acquire HIV each year remains unacceptably high (1). Adolescent girls and young women (AGYW) in sub-Saharan Africa account for approximately 25% of all new HIV infections globally (1). Young women in this region are particularly vulnerable and acquire HIV infection 3 to 5 years earlier than their male peers (2, 3). Despite their greater vulnerability, young women have limited access to non-user-dependent prevention options to reduce their risk for HIV acquisition.

Since antiretrovirals (ARVs) were first shown by the CAPRISA 004 trial (4) in 2010 to prevent sexual transmission of HIV, the HIV prevention landscape has been transformed, principally through oral tenofovir (TFV)-containing pre-exposure prophylaxis (PrEP) (5-10) or through early antiretroviral therapy (ART) initiation in HIV-positive individuals (Treatment as Prevention [TasP]) (11). Although daily oral PrEP has been shown to be consistently effective in men who have sex with men (MSM) and transgender women globally (5, 6), results have been inconsistent in African women, most likely due to varying adherence (7-10).

Pharmacological models suggest that while an individual only needs 2-3 doses per week of oral TDF/FTC to successfully prevent HIV infection via receptive anal intercourse, 6-7 doses per week are needed to successfully prevent HIV infection via receptive vaginal intercourse, because drug concentrations in the lower female genital tract after oral administration are 10 times lower than those found in the colorectal mucosa (12). Unless adherence improves, many women and men using oral TDF/ FTC will remain unprotected. An effective, low-cost, method of HIV prevention that overcomes adherence challenges is needed. Furthermore, products that have fewer renal and bone mineral density side effects are also desirable given that TDF/FTC oral PrEP has been shown to decrease creatinine clearance and lower bone density (13-16).

This protocol focuses on the study of tenofovir alafenamide (TAF), a phosphonamidate prodrug of the HIV-1 nucleotide reverse transcriptase inhibitor (NtRTI) TAF(17). TAF 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) (18). Following penetration of TAF into the cells and hydrolysis of the isopropyl ester, the TFV-Ala conjugate is formed eventually releasing free TFV. TFV is then phosphorylated by intracellular kinases to the active metabolite tenofovir diphosphate (TFV-DP). Residual TFV is slowly released from cells into plasma for renal elimination by a combination of glomerular filtration and active tubular secretion (19, 20). TFV-DP inhibits HIV-1 replication through incorporation into viral DNA by HIV reverse transcriptase, resulting in DNA chain-termination.

While oral emtricitabine and TAF hemifumarate (F/TAF) in combination with other ARVs has long been established to be safe and effective for HIV treatment (21), the DISCOVER trial reported that daily oral F/TAF was similarly effective in reducing incident HIV infections compared to TFV disoproxil fumarate and emtricitabine (TDF/FTC) in 5,387 men and transgender women (22). While the number of adverse events for both regimens was low, F/TAF had favorable outcomes on bone mineral density and biomarkers of renal safety (23).

In a study of four Beagle dogs, an early prototype of the current implant under study, was assessed over 40 days. The implant delivered TAF free-base at a rate of 1.07±0.02mg/day. TFV-DP was observed in PBMCs at levels over 30 times higher than those associated with HIV-1 PrEP efficacy in humans. No adverse treatment related events or clinical evidence of inflammation at the implantation site was reported. Importantly, there was no evidence of toxicity or poor tolerability. In addition, the incision sites appeared healthy on days 2 to 9 following surgery, with staples/sutures removed on day 8 (24). In contrast, a reservoir polyurethane implant delivering TAF hemifumarate demonstrated local inflammation and in

some instances, severe necrosis around the active implants in white rabbits and rhesus macaques (25).

The CAPRISA 018 implant consists of TAF free-base micro-tablets encased in a cylindrical medical grade silicone elastomer sheath, with two delivery channels mechanically punched perpendicular to the longitudinal axis of the sheath (26). The rationale for the 0.25mg daily release was extrapolated from the earlier described Beagle dog study in which median PBMC TFV-DP levels of 512 fmol/10^6 cells were achieved and maintained over the first 35 days (24). 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) (27). 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, 1.6x10^6 cells/ mL; SD, 0.7x10^6 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).

Recent PK modelling simulations of a potential TAF implant have estimated that multiple implants deliver a total of 1.4 mg/day of TAF subcutaneously and predict protection against HIV for approximately 6-months to 1 year (28). Innovative research into biodegradable, reservoir style TAF implants (29) has also shown promise for future application.

TAF is 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 (14, 30). The CAPRISA 018 trial will assess a novel sustained-release implant technology containing 110mg of TAF for the prevention of HIV infection. The 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.

METHODS AND ANALYSIS

Trial setting

The Phase I (Groups 1 to 3) component of the trial will be conducted at the urban CAPRISA eThekwini Clinical Research Site in Durban, South Africa. The Phase II, which is a randomised controlled trial (Group 4), will continue at this urban site and include the rural CAPRISA Vulindlela Clinical Research Site in uMgungundlovu district, South Africa.

Trial population

The Phase I study will enrol 60 healthy, HIV negative women at low risk for HIV into Groups 1-3, while Phase II, Group 4 comprises 490 healthy, HIV-negative women from the general population. 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 providing informed consent for screening**.** Enrolment into the trial is contingent on strict eligibility criteria being met (Table 1).

Table 1: Eligibility Criteria

Inclusion Criteria	Exclusion criteria
• Female sex at birth • 18-40 years of age (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). • Must be in general good health based on clinical assessment • Group 1, 2 and 3 participants must be deemed to be at low risk of HIV infection on completion of an HIV risk assessment tool	• 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 but 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 study specific procedures manual • 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

Trial design

The trial comprises an initial safety assessment in six participants (Group 1) 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 (1 implant), 0.5mg (2 implants), 0.75mg (3 implants) and 1mg (4 implants) in 54 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, the phase II component (group 4) of the trial will be initiated. A total of 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 2 and Figure 1). Study 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).

Table 2: Study drug administration in the CAPRISA 018 trial assessing initial safety and dose escalation followed by an extended safety assessment.

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

*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 become available from groups 1- 3 in the trial. TDF: tenofovir disoproxil fumarate, FTC: emtricitabine, TAF: tenofovir alafenamide fumarate

Implants will be inserted subcutaneously in the upper arm/s, similar to the contraceptive implant, in a controlled sequence as follows (also see Figure 1 for a graphical representation):

Phase I:

- The first six participants in Group 1 (open-label) will have one active implant inserted and will be enrolled sequentially on separate days. Participants will be followed up daily for the first three days following insertion and weekly thereafter. At the Day 28 visit, the implant will be removed and participant will be followed up weekly for a further four weeks.
- Following DSMB approval to proceed with the trial, the next 30 eligible low risk HIV-negative women will be enrolled into Group 2 (double-blinded). Group 2 participants 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, active to placebo ratio. Participants will attend study visits weekly in the first four weeks post active/placebo implant insertion and thereafter study visits will be conducted every four weeks through week 24 or 48 if safety reviews conducted at weeks 4, 12 and 24 permit. Participant will be followed up weekly for a further four weeks after implant removal.
- 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. Group 3

participants will be enrolled in parallel in three sub-groups (one implant in each arm, three implants in one arm, and an oral TAF 25mg control group) while the maximum dose group (four implants in one arm) will be enrolled sequentially. Participants follow a similar visit schedule and safety review time points to Group 2 participants.

Phase II:

- Enrolment into Phase II (Group 4) may proceed with two 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.
- Group 4 participants (double-blinded, double-dummy design) will be randomized in a 1:1 ratio and could receive either two active implants + daily placebo tablets or two placebo implants + TDF 300mg/FTC 200mg tablets. While the trial protocol allows for insertion of two active/placebo implants in this group, the actual number of implants for insertion will be determined from the PK and safety data that emerge from the Group 1-3 experience.

Trial objectives

Primary objective:

- To evaluate the safety and tolerability of sustained-release TAF 110mg sub-dermal implant/s in HIV uninfected young women

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 profiles of insertion of two implants in one arm versus insertion of one implant in each arm.
- To assess participant acceptability of 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) herpes simplex virus type 2 (HSV-2), human papillomavirus (HPV), gonorrhoea, chlamydia and trichomonas infections.
- To assess viral load and frequency of resistance mutations in HIV seroconverters.
- To assess pregnancy rates and outcomes.

Trial endpoints

Primary endpoint

- To evaluate the safety of the TAF 110mg implant.

Secondary endpoints

- Adverse event rates by grade (according to the National Institutes of Health (NIH) Division of AIDS (DAIDS) table for grading adverse events)
- Adverse event rates by degree of association with study product
- Number of early implant removals (prior to scheduled removal) and the reasons for 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

- TAF resistance in HIV seroconverters
- Viral load in HIV seroconverters

Sample size calculation

Phase I (Groups 1 to 3)

The goal of the Phase I study is to identify safety concerns associated with product administration during dose escalation. No formal sample size calculation is needed. However, given the chosen sample size per group, the ability of the study to detect serious adverse events (SAEs) for different group sizes is shown in Table 3. Sample sizes were selected by calculating the probabilities of experiencing zero, ≥1 or ≥2 events under different possible true event rates (31, 32) as shown in Table 3. For each of the groups with n=6 (i.e. participants in Group1, Groups 3a, 3b and 3d), there is a 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 the 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 3.

Table 3: 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

Since the Phase I trial 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.

Phase II (Group 4)

In the Phase II study, the primary safety endpoint is a change in creatinine clearance from baseline to week 12 post randomisation. The sample size calculation was based on data from the iPrEx study (13, 15), which showed a mean creatinine clearance decline of 5% from baseline to week 12. Preliminary clinical data (33) regarding TAF oral use suggest 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 4, 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.

Table 4: 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%

Trial procedures

Informed Consent

Written informed consent will be obtained from each study participant in English or isiZulu prior to screening and enrolment, in accordance with South African Good Clinical Practice (GCP) guidelines, 21 CFR Part 50 and ICH GCP guidelines. Separate written informed consent will be obtained for trial screening, specimen storage and possible future testing, enrolment into the trial and permissions for off-site visits. Study participation will be permitted even if consent for long-term specimen storage or off-site study visits is declined by study participants.

Recruitment, Screening and Enrolment

Study staff will conduct targeted recruitment, by focusing study outreach on women likely to be between 18 and 40 years of age for Groups 1 to 3 and are between 18 and 30 years for Group 4. 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.

To prevent deliberate or inadvertent co-enrolment in multiple trials, each participant's identification will be verified against the Biometric Co-Enrolment Prevention System (BCEPS) database at the screening visit and at each subsequent contact visit. Screening is completed in a stepwise manner. The first step is to provide introductory study information and obtain written informed consent. A unique participant identification number is assigned. HIV testing and counselling, using two rapid antibody test kits and/or antibody/antigen, one of which must be a fourth generation test, is conducted at the outset. HIV-infected participants or those with discordant results will be linked to immediate care and treatment. Only HIV-negative

participants will continue with screening. A complete medical and contraceptive use history will be recorded along with a full physical examination, urine collection and phlebotomy to assess laboratory test results for further participation. These tests include urinalysis, urine pregnancy, pap smear, sexually transmitted and reproductive tract infection testing, haematology, and serum chemistries.

If all screening parameters conform to the trial inclusion criteria, enrolment into the trial, defined as implant insertion, must take place within 56 days of the first screening attempt. A separate enrolment informed consent is conducted prior to implant insertion along with a physical examination and review of contraceptive and medical history. Additional testing includes an assessment of bone densitometry, genital specimen collection and bloods for PK assessments. The implant insertion procedure is conducted under local anaesthetic, by a trained study clinician or professional nurse.

Randomisation

Group 1 participants will not be randomized but are 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 one or two TAF implants. Group 3 participants are not randomised but will be enrolled in parallel for groups 3a, 3b and 3c with Group 3d enrolling sequentially 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 implants and placebo tablets or placebo implants and active tablets.

A statistician who is not involved in the study will produce a computer-generated randomisation list for Groups 2 and 4, which will then be provided to the unblinded study pharmacist. For Group 4, the statistician will use a randomly permuted block design, with two or more pre-specified block sizes. The study pharmacist will also receive sealed, sequentially numbered opaque randomization envelopes. These envelopes will be assigned in sequence to eligible study participants by the study pharmacist. Electronic copies of the randomization schedule and the programs used to generate the randomization schedule will be access controlled and password protected.

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 within their assigned group.

If knowledge of the received study product is necessary to protect a participant's safety, the Principal Investigator and/or designee will give permission for emergency unblinding.

Safety monitoring

Clinical safety and adverse events

While clinical safety will be assessed by evaluating vital signs, weight, physical examination, and clinical laboratory results, the main safety indicators are implant insertion site reactions (local) and changes in creatinine clearance (systemic). Each safety assessment will review adverse events (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.

All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline/non-gradable range). Each AE will be graded for severity using the DAIDS Adverse Event Grading Tables, version 2.1, dated March 2017 (or latest version). Laboratory values

meeting grade 1 and above will be reported as AEs. AEs related to implant insertion or removal will be graded using a study modified interpretation of the DAIDS AE grading table for site reactions to injections and infusions for insertion site pain, insertion site erythema, insertion site swelling or insertion site pruritus. All AE reports will be captured regardless of the association to the study product and will contain at least the date the AE occurred, a brief description of the event, the relationship to study drug, any treatment given, the outcome, date resolved, and the seriousness of the event. AEs and serious adverse events (SAEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.1) terminology, i.e., system organ class (SOC) and preferred terms.

Protocol safety review team (PSRT) and Data Safety Monitoring Board (DSMB)

PSRT

Participant safety will be closely monitored both internally by the PSRT (designated study staff will be responsible for continuous close safety monitoring of all study participants) and externally by the DSMB. PSRT members will meet in-person and/or via teleconference regularly throughout the period of study implementation.

DSMB

An independent DSMB will be established before the clinical trial begins to monitor the safety of the trial participants. The DSMB will convene regularly to review cumulative safety data prior to opening enrolment into each of the four study groups. Following periodic review of the trial data, the DSMB may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. 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.

Data management and statistical analysis

Data management

Data will be collected on case report forms (CRFs) that have been developed by the study team. 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 central CAPRISA database management system (DataFax Discover database) running on SuSe Linux V11. 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. Database files will be password-protected and access to the files will be limited to authorised study staff. All data will be backed up at regular intervals. Upon completion, 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.

Statistical analysis

Demographic data of all participants enrolled in the study will be summarized using descriptive statistics. These will be reported by treatment assignment, study group and overall. The primary and secondary analyses will be performed on an intention to treat (ITT) basis.

Laboratory test results will be summarised by study arm, group and time-point post enrolment. Creatinine clearance is an important laboratory marker in this trial. For Group 4, the mean percentage change 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.

Summaries of AEs by treatment arm (active or placebo) and group will show number and percentage of participants experiencing AEs within each of the SOC and preferred terms. Moreover, number and percentages of participants experiencing each specific AE will be tabulated by severity and relationship to study product.

To assess the efficacy of TAF implant, the cumulative probability of HIV infection will be calculated for each treatment group using the Kaplan-Meier method and the curves will be compared using the log-rank test. The overall HIV incidence rates will be calculated for each treatment group and compared using a z-test. TAF implant efficacy will be calculated as 1 minus (HIV incidence rate in the TAF implant group/HIV incidence rate in the placebo group).

Pharmacokinetic analysis

The PK analysis will involve analysis of TAF, TFV and TFV-DP concentrations at predetermined timepoints post-insertion in plasma, PBMCs, subdermal fluid on the removed implant and in the genital tract in both Phase I and II of the trial. These data will be used to calculate PK parameters (AUC, half-life, clearance, and volume of distribution) for the TAF implant utilizing a non-compartmental PK model analysis. 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 to evaluate protection against HIV infection.

Patient and public involvement

CAPRISA, the study sponsor, has established a Community Advisory Board (CAB) at both trial sites, informed by Good Participatory Practice guidelines (34). CAB members consist of individuals who reside in the communities from where trial participants will be screened and recruited. They include community leaders, traditional leaders, previous trial participants, representatives of local HIV/AIDS organizations and people living with HIV (PLWH) from the community. The CAB meets at least bi-monthly to review concepts, protocols, provide input into study materials, alert researchers to concerns from the community, prepare messaging for the outcome of DSMB meetings, and plan for the dissemination of study results. Trial staff, designated as community liaison officers, work closely with the CAB and plan, with CAB support, participating in community-driven events within current COVID-19 restrictions.

Ethics and dissemination

Ethics and regulatory approval

Ethics approval was granted by the University of KwaZulu-Natal's Biomedical Research Ethics Committee (UKZN BREC) (reference number: BFC107/18) on 16 October 2019 and regulatory approval by the South African Health Products Regulatory Authority (SAHPRA) (trial reference number: 20180523) on 19 September 2019 for the study protocol (V 2.0, dated 12 August 2019). Any future protocol modifications will be submitted to the relevant regulatory and ethics authorities for approval prior to implementation.

Trial results dissemination plan

Results from this research will be published in open access peer-reviewed journals. In addition, investigators will disseminate the results as broadly as possible to the scientific community by attending presenting the findings at local, national and international conferences and through presentations at public lectures, scientific institutions and stakeholder/partner meetings. The findings will be shared and discussed with the study participants, communities and lay persons. 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.

SPIRIT guidelines
This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

Trial Status
Enrolment commenced on 4 August 2020 and is currently recruiting. The trial is anticipated to be completed in June 2024.

Authors' contributions
SAK, TG conceived the trial. SAK, QAK, TG designed the trial. TG, SAK, QAK, LEM, NYZ and CB contributed to writing the study protocol. CH critically reviewed the protocol. NYZ performed sample size calculations and the statistical analysis strategy. PR designed data collection tools and programmed the study database. MB and JM are the implant product developers and will conduct the PK simulations and analysis. BP will assay the PK samples. All authors contributed to the planning of the trial. All authors reviewed the final version of this manuscript and consented to publication.

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The study is funded by the European and Developing Countries Trial Partnership (EDCTP Grant No: SRIA2015-1061) which is a part of the EDCTP2 programme supported by the European Union Horizon 2020 framework. This research is also supported by a joint initiative between the South African National Department of Health, the South African Medical Research Council and the Centre for the AIDS Programme of Research in South Africa. Cipla Ltd (India) has donated the oral drugs being studied in the CAPRISA 018 trial and Gilead Sciences donated the tenofovir alafenamide free base active pharmaceutical ingredient (API) used to formulate the TAF implants.

Competing interests
None

Patient consent for publication
Not required

Provenance and peer review
Not commissioned, externally peer reviewed.

Data availability
After study completion and publication of the primary results, study data sets 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).

REFERENCES

1. Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2020 Geneva. Switzerland2020 [Available from: https://www.unaids.org/sites/default/files/media_asset/2020_aids-data-book_en.pdf.
2. UNAIDS. The Gap Report 2014 [Available from: http://www.who.int/tb/publications/global_report/en/.
3. Abdool Karim Q, Baxter C, Birx D. Prevention of HIV in Adolescent Girls and Young Women: Key to an AIDS-Free Generation. J Acquir Immune Defic Syndr. 2017;75 Suppl 1:S17-S26.
4. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. Science. 2010;329:1168-74.
5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587-99.
6. McCormack S et al. Pragmatic Open-Label Randomised Trial of Preexposure Prophylaxis: The PROUD Study abstract 22LB. Conference on Retroviruses and Opportunistic Infections (CROI); Seattle, USA2015.
7. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423-34.
8. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399-410.
9. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure Prophylaxis for HIV Infection among African Women. New England Journal of Medicine. 2012;367:411-22.
10. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. New England Journal of Medicine. 2015;372(6):509-18.
11. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493-505.
12. Cottrell ML, Yang KH, Prince HM, Sykes C, White N, Malone S, et al. A translational pharmacology approach to predicting outcomes of preexposure prophylaxis against HIV in men and women using tenofovir disoproxil fumarate with or without emtricitabine. The Journal of infectious diseases. 2016;214(1):55-64.
13. Tang EC, Vittinghoff E, Anderson PL, Cohen SE, Doblecki-Lewis S, Bacon O, et al. Changes in Kidney Function Associated With Daily Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Preexposure Prophylaxis Use in the United States Demonstration Project. Journal of acquired immune deficiency syndromes. 2018;77(2):193-8.
14. Markowitz M, Zolopa A, Squires K, Ruane P, Coakley D, Kearney B, et al. Phase I/II study of the pharmacokinetics, safety and antiretroviral activity of tenofovir alafenamide, a new prodrug of the HIV reverse transcriptase inhibitor tenofovir, in HIV-infected adults. The Journal of antimicrobial chemotherapy. 2014;69(5):1362-9.
15. Liu AY, Vittinghoff E, Anderson PL, Cohen S, Doblecki-Lewis S, Bacon O, et al. Changes in Renal Function Associated With TDF/FTC PrEP Use in the US Demo Project. Abstract number: 867. Conference on Retroviruses and Opportunistic Infections; February 22–25; Boston, Massachusetts2016.
16. Mulligan K, Glidden DV, Anderson PL, Liu A, McMahan V, Gonzales P, et al. Effects of Emtricitabine/Tenofovir on Bone Mineral Density in HIV-Negative Persons in a Randomized, Double-Blind, Placebo-Controlled Trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61(4):572-80.

17. Suo Z, Johnson KA. Selective inhibition of HIV-1 reverse transcriptase by an antiviral inhibitor, (R)-9-(2-Phosphonylmethoxypropyl)adenine. The Journal of biological chemistry. 1998;273(42):27250-8.
18. Birkus G, Wang R, Liu X, Kutty N, MacArthur H, Cihlar T, et al. Cathepsin A is the major hydrolase catalyzing the intracellular hydrolysis of the antiretroviral nucleotide phosphonoamidate prodrugs GS-7340 and GS-9131. Antimicrobial agents and chemotherapy. 2007;51(2):543-50.
19. Ray AS, Fordyce MW, Hitchcock MJ. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus. Antiviral research. 2016;125:63-70.
20. Birkus G, Bam RA, Willkom M, Frey CR, Tsai L, Stray KM, et al. Intracellular Activation of Tenofovir Alafenamide and the Effect of Viral and Host Protease Inhibitors. Antimicrobial agents and chemotherapy. 2015;60(1):316-22.
21. De Clercq E. Role of tenofovir alafenamide (TAF) in the treatment and prophylaxis of HIV and HBV infections. Biochem Pharmacol. 2018;153:2-11.
22. Abbasi J. Long-acting Cabotegravir Shot Prevents HIV Among Women. JAMA. 2020;324(22):2247.
23. Mayer KH, Molina JM, Thompson MA, Anderson PL, Mounzer KC, De Wet JJ, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet. 2020;396(10246):239-54.
24. Gunawardana M, Remedios-Chan M, Miller CS, Fanter R, Yang F, Marzinke MA, et al. Pharmacokinetics of Long-Acting Tenofovir Alafenamide (GS-7340) Subdermal Implant for HIV Prophylaxis. Antimicrobial agents and chemotherapy. 2015;59(7):3913-9.
25. Su JT, Simpson SM, Sung S, Tfaily EB, Veazey R, Marzinke M, et al. A Subcutaneous Implant of Tenofovir Alafenamide Fumarate Causes Local Inflammation and Tissue Necrosis in Rabbits and Macaques. Antimicrobial agents and chemotherapy. 2020;64(3).
26. Oak Crest Institute of Science. Investigators Brochure: OCIS-001 Tenofovir alafenamide (TAF) implant. Second edition. 29 July 2019. 2019.
27. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med. 2012;4(151):151ra25.
28. Rajoli RKR, Demkovich ZR, Flexner C, Owen A, Siccardi M. Predicting pharmacokinetics of a tenofovir alafenamide subcutaneous implant using PBPK modelling. Antimicrobial agents and chemotherapy. 2020.
29. Li L, Johnson LM, Krovi SA, Demkovich ZR, van der Straten A. Performance and Stability of Tenofovir Alafenamide Formulations within Subcutaneous Biodegradable Implants for HIV Pre-Exposure Prophylaxis (PrEP). Pharmaceutics. 2020;12(11).
30. Babusis D, Phan TK, Lee WA, Watkins WJ, Ray AS. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. Mol Pharm. 2013;10(2):459-66.
31. Power J, French R, Cowan F. Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods of preventing pregnancy. Cochrane Database Syst Rev. 2007(3):CD001326.
32. Pillay D, Chersich M, Morroni C, Pleaner M, Adeagbo OA, Naidoo N, et al. User perspectives on Implanon NXT in South Africa: A survey of 12 public-sector facilities. S Afr Med J. 2017;107(10):815-21.
33. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606-15.

34. UNAIDS. Good participatory practice: Guidelines for biomedical HIV prevention trials, https://www.unaids.org/en/resources/documents/2011/20110629_JC1853_GPP_Guidelines_2011%20OK. 2011.

Figure 1: CAPRISA 018, phase I/II trial design summary graphic (extracted from the study protocol version 2.0, 12 Aug 2019)

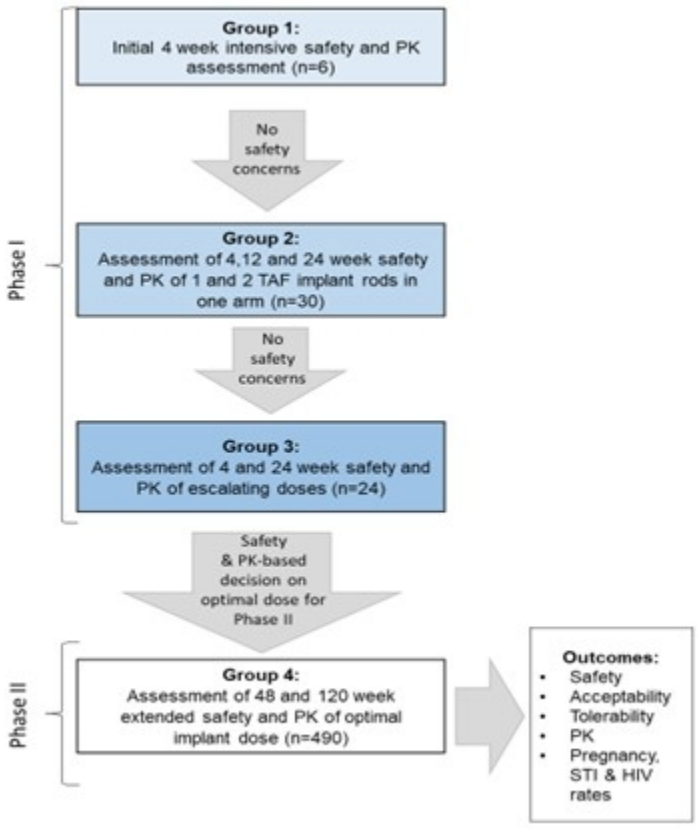

Figure 1: CAPRISA 018, phase I/II trial design summary graphic (extracted from the study protocol version 2.0, 12 Aug 2019)

30x35mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on protocol v2.0 page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	73
	2b	All items from the World Health Organization Trial Registration Data Set	1-4
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	3-4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	2-4
	5b	Name and contact information for the trial sponsor	1-2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	73,88
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	In SSP
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	15-28
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	30
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	31
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	29
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	37
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	45-55
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	31, 66
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	43
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	43
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	36

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	34,80-82
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	58
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	58
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	58
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	58
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	58
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	64
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	64
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	64
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	72
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	64
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	57
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	61
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	62
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	69
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	69

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	66-68
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	73
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	69
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	69
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	69
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	69
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	71
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	72
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	73
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	70
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	73

	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	73
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	84-85
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	80-82

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license

BMJ Open

CAPRISA 018: A phase I/II clinical trial study protocol to assess the safety, acceptability, tolerability and pharmacokinetics of a sustained- tenofovir alafenamide sub-dermal implant for HIV prevention in women

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Secondary Subject Heading:	Pharmacology and therapeutics, Public health, HIV/AIDS, Infectious diseases
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CAPRISA 018: A phase I/II clinical trial study protocol to assess the safety, acceptability, tolerability and pharmacokinetics of a sustained- tenofovir alafenamide sub-dermal implant for HIV prevention in women

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Key words: HIV prevention, tenofovir alafenamide, implant, safety, tolerability

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Manuscript: 4597 excluding abstract, article summary, tables and figure

Abstract

Introduction

Young African women bear a disproportionately high risk for HIV acquisition. HIV technologies that empower women to protect themselves are needed. Safe, potent antiretroviral agents such as tenofovir alafenamide (TAF), formulated as long-acting sub-dermal implants, offer an innovative solution.

Methods and analysis

CAPRISA 018 is a phase I/II trial to evaluate the safety, acceptability, tolerability, and pharmacokinetics (PK) of a TAF *free base* subdermal silicone implant containing 110mg of TAF with an anticipated 0.25mg/day release rate.

The Phase I trial (n=60) will assess the safety of one implant inserted in six participants (Group 1), followed by dose escalation components (Groups 2 and 3) assessing the safety, tolerability, and PK of one to four TAF 110mg implants releasing between 0.25mg to 1mg daily in 54 healthy women at low risk for HIV infection. Data from this Phase I trial will be used to determine the dosing, implant location, and implant replacement interval for the Phase II trial.

The Phase II component (Group 4) will assess extended safety, PK, tolerability, and acceptability of the implant in 490 at risk women, randomized in a 1:1 ratio to the TAF implant and placebo tablet or to the placebo implant and an oral PrEP (pre-exposure prophylaxis) tablet. Safety will be assessed by calculating the percentage change in creatinine clearance from baseline at weeks 4, 12, 24, 36, 72, 96 and 120, compared to the percentage change in the control group.

Ethics and dissemination

The South African Health Products Regulatory Authority and the University of KwaZulu-Natal's Biomedical Research Ethics Committee have approved the trial. Results will be disseminated through open access peer reviewed publications, conference presentations, public stakeholder engagement and upload of data into the clinical trials registry.

Trial registration number: PACTR201809520959443.

Article summary

Strengths and limitations of this study

- CAPRISA 018 is a first-in-human trial assessing the safety, acceptability, tolerability, and pharmacokinetics of a tenofovir alafenamide free-base sub-dermal implant formulation.
- This trial adopts a master protocol design, where Phase I and Phase II studies are conducted sequentially under a single protocol.
- Optimal dosing selected for the Phase II trial is generated from Phase I safety and pharmacokinetic data.
- The Phase II part of the trial is powered on a safety endpoint using a randomised, double-dummy design.
- The study is not powered to show efficacy of the tenofovir alafenamide implant against HIV.

INTRODUCTION

Despite the global decline in HIV infections by 23% since 2010, the number of people who acquire HIV each year remains unacceptably high (1). Adolescent girls and young women (AGYW) in sub-Saharan Africa account for approximately 25% of all new HIV infections globally (1). Young women in this region are particularly vulnerable and acquire HIV infection 3 to 5 years earlier than their male peers (2, 3). Despite their greater vulnerability, young women have limited access to non-user-dependent prevention options to reduce their risk for HIV acquisition.

Since antiretrovirals (ARVs) were first shown by the CAPRISA 004 trial (4) in 2010 to prevent sexual transmission of HIV, the HIV prevention landscape has been transformed, principally through oral tenofovir (TFV)-containing pre-exposure prophylaxis (PrEP) (5-10) or through early antiretroviral therapy (ART) initiation in HIV-positive individuals (Treatment as Prevention [TasP]) (11).Although daily oral PrEP has been shown to be consistently effective in men who have sex with men (MSM) and transgender women globally (5, 6), results have been inconsistent in African women, most likely due to varying adherence (7-10). Other novel long-acting PrEP agents and innovative delivery systems such as ARV containing intravaginal rings (IVRs), viz. the Dapivirine ring (12) and possibly long-acting injectable ARVs (13), are poised to be accessible soon. These formulations along with the implant under study offer specific adherence advantages over daily oral PrEP

Pharmacological models suggest that while an individual only needs 2-3 doses per week of oral TDF/FTC to successfully prevent HIV infection via receptive anal intercourse, 6-7 doses per week are needed to successfully prevent HIV infection via receptive vaginal intercourse, because drug concentrations in the lower female genital tract after oral administration are 10 times lower than those found in the colorectal mucosa (14). Unless adherence improves, many women and men using oral TDF/ FTC will remain unprotected. An effective, low-cost, method of HIV prevention that overcomes adherence challenges is needed. Furthermore, products that have fewer renal and bone mineral density side effects are also desirable given that TDF/FTC oral PrEP has been shown to decrease creatinine clearance and lower bone density (15-18).

This protocol focuses on the study of tenofovir alafenamide (TAF), a phosphonamidate prodrug of the HIV-1 nucleotide reverse transcriptase inhibitor (NtRTI) TAF(19). TAF 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) (20). Following penetration of TAF into the cells and hydrolysis of the isopropyl ester, the TFV-Ala conjugate is formed eventually releasing free TFV. TFV is then phosphorylated by intracellular kinases to the active metabolite tenofovir diphosphate (TFV-DP). Residual TFV is slowly released from cells into plasma for renal elimination by a combination of glomerular filtration and active tubular secretion (21, 22). TFV-DP inhibits HIV-1 replication through incorporation into viral DNA by HIV reverse transcriptase, resulting in DNA chain-termination.

While oral emtricitabine and TAF hemifumarate (F/TAF) in combination with other ARVs has long been established to be safe and effective for HIV treatment (23), the DISCOVER trial reported that daily oral F/TAF was similarly effective in reducing incident HIV infections compared to TFV disoproxil fumarate and emtricitabine (TDF/FTC) in 5,387 men and transgender women (24). While the number of adverse events for both regimens was low, F/TAF had favorable outcomes on bone mineral density and biomarkers of renal safety (25).

In a study of four Beagle dogs, an early prototype of the current implant under study, was assessed over 40 days. The implant delivered TAF free-base at a rate of 1.07±0.02mg/day. TFV-DP was observed in PBMCs at levels over 30 times higher than those associated with HIV-1 PrEP efficacy in humans. No adverse treatment related events or clinical evidence of

inflammation at the implantation site was reported. Importantly, there was no evidence of toxicity or poor tolerability. In addition, the incision sites appeared healthy on days 2 to 9 following surgery, with staples/sutures removed on day 8 (26). In contrast, a reservoir polyurethane implant delivering TAF hemifumarate demonstrated local inflammation and in some instances, severe necrosis around the active implants in white rabbits and rhesus macaques (27).

The CAPRISA 018 implant consists of TAF free-base micro-tablets encased in a cylindrical medical grade silicone elastomer sheath, with two delivery channels mechanically punched perpendicular to the longitudinal axis of the sheath (28). Each implant is approximately 40-45mm in length with an inner diameter of 2.01 ± 0.051mm and a wall thickness of 0.19 +0.051/-0.25 mm (28). The rationale for the 0.25mg daily release was extrapolated from the earlier described Beagle dog study in which median PBMC TFV-DP levels of 512 fmol/10^6 cells were achieved and maintained over the first 35 days (26). 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) (29). 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, 1.6x10^6 cells/ mL; SD, 0.7x10^6 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).

Recent PK modelling simulations of a potential TAF implant have estimated that multiple implants deliver a total of 1.4 mg/day of TAF subcutaneously and predict protection against HIV for approximately 6-months to 1 year (30). Innovative research into biodegradable, reservoir style TAF implants (31) has also shown promise for future application. The use of sub-dermal implants as the drug delivery mechanism in this trial is supported by several studies showing that the contraceptive implant is highly acceptable to young women (32), with continuation rates of ~80% after 1 year, including in studies from sub-Saharan Africa (33, 34).

TAF is 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 (16, 35). The CAPRISA 018 trial will assess a novel sustained-release implant technology containing 110mg of TAF for the prevention of HIV infection. The 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.

METHODS AND ANALYSIS

Trial setting

The Phase I (Groups 1 to 3) component of the trial will be conducted at the urban CAPRISA eThekwini Clinical Research Site in Durban, South Africa. The Phase II, which is a randomised controlled trial (Group 4), will continue at this urban site and include the rural CAPRISA Vulindlela Clinical Research Site in uMgungundlovu district, South Africa.

Trial population

The Phase I study will enrol 60 healthy, HIV negative women at low risk for HIV into Groups 1-3, while Phase II, Group 4 comprises 490 healthy, HIV-negative women from the general population. Potential study participants who consent for screening to assess for eligibility and subsequently participants who consent for enrolment will be enrolled in the study within 56

days of providing informed consent for screening. Enrolment into the trial is contingent on strict eligibility criteria being met (Table 1).

Table 1: Eligibility Criteria

Inclusion Criteria	Exclusion criteria
• Female sex at birth • 18-40 years of age (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). • Must be in general good health based on clinical assessment • Group 1, 2 and 3 participants must be deemed to be at low risk of HIV infection on completion of an HIV risk assessment tool (e.g., no current STIs, no concurrent sex partners and other criteria linked to HIV risk) which will be assessed by the investigators when confirming eligibility to enrol.	• 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 but 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 study specific procedures manual • 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

Trial design

The trial comprises an initial safety assessment in six participants (Group 1) 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 (1 implant), 0.5mg (2 implants), 0.75mg (3 implants) and 1mg (4 implants) in 54 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, the phase II component (group 4) of the trial will be initiated. A total of 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 2 and Figure 1). Study 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).

Table 2: Study drug administration in the CAPRISA 018 trial assessing initial safety and dose escalation followed by an extended safety assessment.

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

*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 become available from groups 1- 3 in the trial. TDF: tenofovir disoproxil fumarate, FTC: emtricitabine, TAF: tenofovir alafenamide fumarate

Implants will be inserted sub dermally in the upper arm/s, similar to the contraceptive implant, in a controlled sequence as follows (also see Figure 1 for a graphical representation):

Phase I:

- The first six participants in Group 1 (open-label) will have one active implant inserted and will be enrolled sequentially on separate days. Participants will be followed up daily for the first three days following insertion and weekly thereafter. At the Day 28 visit, the implant will be removed, and participant will be followed up weekly for a further four weeks.
- Following DSMB approval to proceed with the trial, the next 30 eligible low risk HIV-negative women will be enrolled into Group 2 (double-blinded). Group 2 participants 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, active to placebo ratio. Participants will attend study visits weekly in the first four weeks post active/placebo implant insertion and thereafter study visits will be conducted every four weeks through week 24 or 48 if safety reviews conducted at weeks 4, 12 and 24 permit. Participants will be followed up weekly for a further four weeks after implant removal.
- 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. Group 3

participants will be enrolled in parallel in three sub-groups (one implant in each arm, three implants in one arm, and an oral TAF 25mg control group) while the maximum dose group (four implants in one arm) will be enrolled sequentially. Participants follow a similar visit schedule and safety review time points to Group 2 participants.

Phase II:

- Enrolment into Phase II (Group 4) may proceed with two 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.
- Group 4 participants (double-blinded, double-dummy design) will be randomized in a 1:1 ratio and could receive either two active implants + daily placebo tablets or two placebo implants + TDF 300mg/FTC 200mg tablets. While the trial protocol allows for insertion of two active/placebo implants in this group, the actual number of implants for insertion will be determined from the PK and safety data that emerge from the Group 1-3 experience.
  Participants enrolled in Group 4 will attend a study visit one week after implant insertion and thereafter from week 4 the study visits will be conducted monthly. The minimum follow-up period for Group 4 is 48 weeks. Implants will be removed at week 48 and replacement implants will be inserted. These participants will have implants removed at week 116 and will be exited from the study at week 120. 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.

Trial objectives

Primary objective:

- To evaluate the safety and tolerability of sustained-release TAF 110mg sub-dermal implant/s in HIV uninfected women

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 profiles of insertion of two implants in one arm versus insertion of one implant in each arm.
- To assess participant acceptability of 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) herpes simplex virus type 2 (HSV-2), human papillomavirus (HPV), gonorrhoea, chlamydia and trichomonas infections.
- To assess viral load and frequency of resistance mutations in HIV seroconverters.
- To assess pregnancy rates and outcomes.

Trial endpoints

Primary endpoint

- To evaluate the safety of the TAF 110mg implant.

Secondary endpoints

- Adverse event rates by grade (according to the National Institutes of Health (NIH) Division of AIDS (DAIDS) table for grading adverse events)
- Adverse event rates by degree of association with study product

- Number of early implant removals (prior to scheduled removal) and the reasons for 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
- TAF resistance in HIV seroconverters
- Viral load in HIV seroconverters

Sample size calculation

Phase I (Groups 1 to 3)

The goal of the Phase I study is to identify safety concerns associated with product administration during dose escalation. No formal sample size calculation is needed. However, given the chosen sample size per group, the ability of the study to detect serious adverse events (SAEs) for different group sizes is shown in Table 3. Sample sizes were selected by calculating the probabilities of experiencing zero, ≥1 or ≥2 events under different possible true event rates (33, 36) as shown in Table 3. For each of the groups with n=6 (i.e., participants in Group1, Groups 3a, 3b and 3d), there is a 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 the 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 3.

Table 3: 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

Since the Phase I trial 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.

Phase II (Group 4)

In the Phase II study, the primary safety endpoint is a change in creatinine clearance from baseline to week 12 post randomisation. The sample size calculation was based on data from the iPrEx study (15, 17), which showed a mean creatinine clearance decline of 5% from baseline to week 12. Preliminary clinical data (37) regarding TAF oral use suggest 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 4, 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.

Table 4: 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%

Trial procedures

Informed Consent

Written informed consent will be obtained from each study participant in English or isiZulu prior to screening and enrolment, in accordance with South African Good Clinical Practice (GCP) guidelines, 21 CFR Part 50 and ICH GCP guidelines. Separate written informed consent will be obtained for trial screening, specimen storage and possible future testing, enrolment into the trial and permissions for off-site visits. Study participation will be permitted even if consent for long-term specimen storage or off-site study visits is declined by study participants.

Recruitment, Screening and Enrolment

Study staff will conduct targeted recruitment, by focusing study outreach on women likely to be between 18 and 40 years of age for Groups 1 to 3 and are between 18 and 30 years for Group 4. 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.

To prevent deliberate or inadvertent co-enrolment in multiple trials, each participant's identification will be verified against the Biometric Co-Enrolment Prevention System (BCEPS) database at the screening visit and at each subsequent contact visit. Screening is completed in a stepwise manner. The first step is to provide introductory study information and obtain written informed consent. A unique participant identification number is assigned. HIV testing and counselling, using two rapid antibody test kits and/or antibody/antigen, one of which must be a fourth generation test, is conducted at the outset. HIV-infected participants or those with discordant results will be linked to immediate care and treatment. Only HIV-negative participants will continue with screening. A complete medical and contraceptive use history will be recorded along with a full physical examination, urine collection and phlebotomy to assess laboratory test results for further participation. These tests include urinalysis, urine pregnancy, pap smear, sexually transmitted and reproductive tract infection testing, haematology, and serum chemistries.

If all screening parameters conform to the trial inclusion criteria, enrolment into the trial, defined as implant insertion, must take place within 56 days of the first screening attempt. A separate enrolment informed consent is conducted prior to implant insertion along with a physical examination and review of contraceptive and medical history. Additional testing includes an assessment of bone densitometry, genital specimen collection and bloods for PK assessments. The implant insertion procedure is conducted under local anaesthetic, by a trained study clinician or professional nurse.

Randomisation

Group 1 participants will not be randomized but are 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 one or two TAF implants. Group 3 participants are not randomised but will be enrolled in parallel for groups 3a, 3b and 3c with Group 3d enrolling sequentially 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 implants and placebo tablets or placebo implants and active tablets.

A statistician who is not involved in the study will produce a computer-generated randomisation list for Groups 2 and 4, which will then be provided to the unblinded study pharmacist. For Group 4, the statistician will use a randomly permuted block design, with two or more pre-specified block sizes. The study pharmacist will also receive sealed, sequentially numbered opaque randomization envelopes. These envelopes will be assigned in sequence to eligible study participants by the study pharmacist. Electronic copies of the randomization schedule and the programs used to generate the randomization schedule will be access controlled and password protected.

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 within their assigned group.

If knowledge of the received study product is necessary to protect a participant's safety, the Principal Investigator and/or designee will give permission for emergency unblinding.

Safety monitoring

Clinical safety and adverse events

While clinical safety will be assessed by evaluating vital signs, weight, physical examination, and clinical laboratory results, the main safety indicators are implant insertion site reactions

(local) and changes in creatinine clearance (systemic). Each safety assessment will include a review of adverse events (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.

All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline/non-gradable range). Each AE will be graded for severity using the DAIDS Adverse Event Grading Tables, version 2.1, dated March 2017 (or latest version). Laboratory values meeting grade 1 and above will be reported as AEs. AEs related to implant insertion or removal will be graded using a study modified interpretation of the DAIDS AE grading table for site reactions to injections and infusions for insertion site pain, insertion site erythema, insertion site swelling or insertion site pruritus. All AE reports will be captured regardless of the association to the study product and will contain at least the date the AE occurred, a brief description of the event, the relationship to study drug, any treatment given, the outcome, date resolved, and the seriousness of the event. AEs and serious adverse events (SAEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.1) terminology, i.e., system organ class (SOC) and preferred terms.

Protocol safety review team (PSRT) and Data Safety Monitoring Board (DSMB)

PSRT

Participant safety will be closely monitored both internally by the PSRT (designated study staff will be responsible for continuous close safety monitoring of all study participants) and externally by the DSMB. PSRT members will meet in-person and/or via teleconference regularly throughout the period of study implementation.

DSMB

An independent DSMB will be established before the clinical trial begins to monitor the safety of the trial participants. The DSMB will convene regularly to review cumulative safety data prior to opening enrolment into each of the four study groups. Following periodic review of the trial data, the DSMB may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. 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.

Data management and statistical analysis

Data management

Data will be collected on paper-based case report forms (CRFs) that have been developed by the study team. 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 central CAPRISA database management system (DataFax Discover database) running on SuSe Linux V11. 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. Database files will be password-protected and access to the files will be limited to authorised study staff. All data will be backed up at regular intervals. Upon completion, 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.

Statistical analysis

Demographic data of all participants enrolled in the study will be summarized using descriptive statistics. These will be reported by treatment assignment, study group and overall. The primary and secondary analyses will be performed on an intention to treat (ITT) basis.

Laboratory test results will be summarised by study arm, group and time-point post enrolment. Creatinine clearance is an important laboratory marker in this trial. For Group 4, the mean percentage change 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.

Summaries of AEs by treatment arm (active or placebo) and group will show number and percentage of participants experiencing AEs within each of the SOC and preferred terms. Moreover, number and percentages of participants experiencing each specific AE will be tabulated by severity and relationship to study product.

To assess the efficacy of TAF implant, the cumulative probability of HIV infection will be calculated for each treatment group using the Kaplan-Meier method and the curves will be compared using the log-rank test. The overall HIV incidence rates will be calculated for each treatment group and compared using a z-test. TAF implant efficacy will be calculated as 1 minus (HIV incidence rate in the TAF implant group/HIV incidence rate in the placebo group).

Pharmacokinetic analysis

The PK analysis will involve analysis of TAF, TFV and TFV-DP concentrations at predetermined timepoints post-insertion in plasma, PBMCs, subdermal fluid on the removed implant and in the genital tract in both Phase I and II of the trial. These data will be used to calculate PK parameters (AUC, half-life, clearance, and volume of distribution) for the TAF implant utilizing a non-compartmental PK model analysis. 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 to evaluate protection against HIV infection.

Patient and public involvement

CAPRISA, the study sponsor, has established a Community Advisory Board (CAB) at both trial sites, informed by Good Participatory Practice guidelines (38). CAB members consist of individuals who reside in the communities from where trial participants will be screened and recruited. They include community leaders, traditional leaders, previous trial participants, representatives of local HIV/AIDS organizations and people living with HIV (PLWH) from the community. The CAB meets at least bi-monthly to review concepts, protocols, provide input into study materials, alert researchers to concerns from the community, prepare messaging for the outcome of DSMB meetings, and plan for the dissemination of study results. Trial staff, designated as community liaison officers, work closely with the CAB and plan, with CAB support, participating in community-driven events within current COVID-19 restrictions.

Ethics and dissemination

Ethics and regulatory approval

Ethics approval was granted by the University of KwaZulu-Natal's Biomedical Research Ethics Committee (UKZN BREC) (reference number: BFC107/18) on 16 October 2019 and regulatory approval by the South African Health Products Regulatory Authority (SAHPRA) (trial reference number: 20180523) on 19 September 2019 for the study protocol (V 2.0,

dated 12 August 2019). Any future protocol modifications will be submitted to the relevant regulatory and ethics authorities for approval prior to implementation.

Trial results dissemination plan
Results from this research will be published in open access peer-reviewed journals. In addition, investigators will disseminate the results as broadly as possible to the scientific community by attending presenting the findings at local, national and international conferences and through presentations at public lectures, scientific institutions and stakeholder/partner meetings. The findings will be shared and discussed with the study participants, communities and lay persons. 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.

SPIRIT guidelines
This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

Trial Status
Enrolment commenced on 4 August 2020 and is currently recruiting. The trial is anticipated to be completed in June 2024.

Authors' contributions
SSAK, TNG conceived the trial. SAK, QAK, TNG designed the trial. TNG, SAK, QAK, LEM, NYZ and CB contributed to writing the study protocol. CH critically reviewed the protocol. NYZ performed sample size calculations and the statistical analysis strategy for the study protocol. PR, the study data manager, designed data collection tools and programmed the study database. MMB and JAM are the implant product developers, wrote the study dose rationale and provided the technical information on the study implant and generated the preclinical safety data. BP will assay the PK samples. LEM is the trial project manager, IH is responsible for clinical oversight, NS is responsible for the setup of all laboratory procedures and BM is the study pharmacist. All authors contributed to the planning of the trial. TNG wrote the first draft of the protocol paper and SSAK, QAK, CB, LEM, NYZ, CH, NS, PR, IH, BM, JAM, MMB and BP contributed to critical edits to the manuscript. All authors reviewed the final version of this manuscript and consented to publication.

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Competing interests
None

Patient consent for publication
Not required

Provenance and peer review
Not commissioned, externally peer reviewed.

Data availability

After study completion and publication of the primary results, study data sets 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).

REFERENCES

1. Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2020 Geneva. Switzerland2020 [Available from: https://www.unaids.org/sites/default/files/media_asset/2020_aids-data-book_en.pdf.
2. UNAIDS. The Gap Report 2014 [Available from: http://www.who.int/tb/publications/global_report/en/.
3. Abdool Karim Q, Baxter C, Birx D. Prevention of HIV in Adolescent Girls and Young Women: Key to an AIDS-Free Generation. J Acquir Immune Defic Syndr. 2017;75 Suppl 1:S17-S26.
4. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. Science. 2010;329:1168-74.
5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587-99.
6. McCormack S et al. Pragmatic Open-Label Randomised Trial of Preexposure Prophylaxis: The PROUD Study abstract 22LB. Conference on Retroviruses and Opportunistic Infections (CROI); Seattle, USA2015.
7. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423-34.
8. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399-410.
9. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure Prophylaxis for HIV Infection among African Women. New England Journal of Medicine. 2012;367:411-22.
10. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. New England Journal of Medicine. 2015;372(6):509-18.
11. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493-505.
12. PrEPWatch an initiative of AVAC. About the Dapivirine Ring. 2021 [Available from: https://www.prepwatch.org/about-prep/dapivirine-ring/.
13. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. N Engl J Med. 2021;385(7):595-608.
14. Cottrell ML, Yang KH, Prince HM, Sykes C, White N, Malone S, et al. A translational pharmacology approach to predicting outcomes of preexposure prophylaxis against HIV in men and women using tenofovir disoproxil fumarate with or without emtricitabine. The Journal of infectious diseases. 2016;214(1):55-64.
15. Tang EC, Vittinghoff E, Anderson PL, Cohen SE, Doblecki-Lewis S, Bacon O, et al. Changes in Kidney Function Associated With Daily Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Preexposure Prophylaxis Use in the United States Demonstration Project. Journal of acquired immune deficiency syndromes. 2018;77(2):193-8.
16. Markowitz M, Zolopa A, Squires K, Ruane P, Coakley D, Kearney B, et al. Phase I/II study of the pharmacokinetics, safety and antiretroviral activity of tenofovir alafenamide, a new prodrug of the HIV reverse transcriptase inhibitor tenofovir, in HIV-infected adults. The Journal of antimicrobial chemotherapy. 2014;69(5):1362-9.
17. Liu AY, Vittinghoff E, Anderson PL, Cohen S, Doblecki-Lewis S, Bacon O, et al. Changes in Renal Function Associated With TDF/FTC PrEP Use in the US Demo Project. Abstract number: 867. Conference on Retroviruses and Opportunistic Infections; February 22–25; Boston, Massachusetts2016.

18. Mulligan K, Glidden DV, Anderson PL, Liu A, McMahan V, Gonzales P, et al. Effects of Emtricitabine/Tenofovir on Bone Mineral Density in HIV-Negative Persons in a Randomized, Double-Blind, Placebo-Controlled Trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61(4):572-80.
19. Suo Z, Johnson KA. Selective inhibition of HIV-1 reverse transcriptase by an antiviral inhibitor, (R)-9-(2-Phosphonylmethoxypropyl)adenine. The Journal of biological chemistry. 1998;273(42):27250-8.
20. Birkus G, Wang R, Liu X, Kutty N, MacArthur H, Cihlar T, et al. Cathepsin A is the major hydrolase catalyzing the intracellular hydrolysis of the antiretroviral nucleotide phosphonoamidate prodrugs GS-7340 and GS-9131. Antimicrobial agents and chemotherapy. 2007;51(2):543-50.
21. Ray AS, Fordyce MW, Hitchcock MJ. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus. Antiviral research. 2016;125:63-70.
22. Birkus G, Bam RA, Willkom M, Frey CR, Tsai L, Stray KM, et al. Intracellular Activation of Tenofovir Alafenamide and the Effect of Viral and Host Protease Inhibitors. Antimicrobial agents and chemotherapy. 2015;60(1):316-22.
23. De Clercq E. Role of tenofovir alafenamide (TAF) in the treatment and prophylaxis of HIV and HBV infections. Biochem Pharmacol. 2018;153:2-11.
24. Abbasi J. Long-acting Cabotegravir Shot Prevents HIV Among Women. JAMA. 2020;324(22):2247.
25. Mayer KH, Molina JM, Thompson MA, Anderson PL, Mounzer KC, De Wet JJ, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet. 2020;396(10246):239-54.
26. Gunawardana M, Remedios-Chan M, Miller CS, Fanter R, Yang F, Marzinke MA, et al. Pharmacokinetics of Long-Acting Tenofovir Alafenamide (GS-7340) Subdermal Implant for HIV Prophylaxis. Antimicrobial agents and chemotherapy. 2015;59(7):3913-9.
27. Su JT, Simpson SM, Sung S, Tfaily EB, Veazey R, Marzinke M, et al. A Subcutaneous Implant of Tenofovir Alafenamide Fumarate Causes Local Inflammation and Tissue Necrosis in Rabbits and Macaques. Antimicrobial agents and chemotherapy. 2020;64(3).
28. Oak Crest Institute of Science. Investigators Brochure: OCIS-001 Tenofovir alafenamide (TAF) implant. Second edition. 29 July 2019. 2019.
29. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med. 2012;4(151):151ra25.
30. Rajoli RKR, Demkovich ZR, Flexner C, Owen A, Siccardi M. Predicting pharmacokinetics of a tenofovir alafenamide subcutaneous implant using PBPK modelling. Antimicrobial agents and chemotherapy. 2020.
31. Li L, Johnson LM, Krovi SA, Demkovich ZR, van der Straten A. Performance and Stability of Tenofovir Alafenamide Formulations within Subcutaneous Biodegradable Implants for HIV Pre-Exposure Prophylaxis (PrEP). Pharmaceutics. 2020;12(11).
32. Diedrich JT, Klein DA, Peipert JF. Long-acting reversible contraception in adolescents: a systematic review and meta-analysis. Am J Obstet Gynecol. 2017;216(4):364 e1- e12.
33. Pillay D, Chersich M, Morroni C, Pleaner M, Adeagbo OA, Naidoo N, et al. User perspectives on Implanon NXT in South Africa: A survey of 12 public-sector facilities. S Afr Med J. 2017;107(10):815-21.
34. O'Neill E, Tang J, Garrett J, Hubacher D. Characteristics of Kenyan women in a prospective cohort study who continue using subdermal contraceptive implants at 12 months. Contraception. 2014;89(3):204-8.
35. Babusis D, Phan TK, Lee WA, Watkins WJ, Ray AS. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. Mol Pharm. 2013;10(2):459-66.

36. Power J, French R, Cowan F. Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods of preventing pregnancy. Cochrane Database Syst Rev. 2007(3):CD001326.
37. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606-15.
38. UNAIDS. Good participatory practice: Guidelines for biomedical HIV prevention trials, https://www.unaids.org/en/resources/documents/2011/20110629_JC1853_GPP_Guidelines_2011%20OK. 2011.

Figure 1: CAPRISA 018, phase I/II trial design summary graphic (extracted from the study protocol version 2.0, 12 Aug 2019)

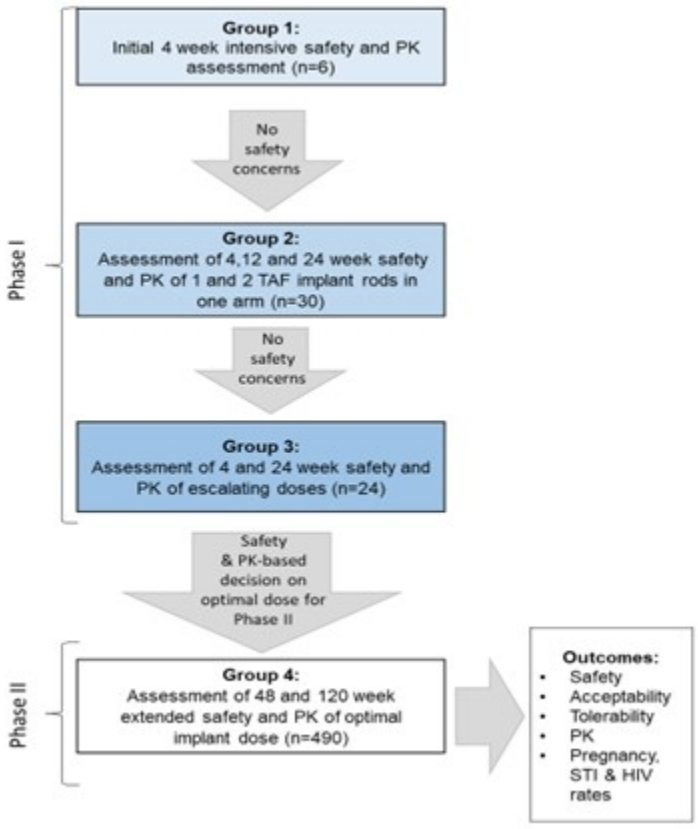

Figure 1: CAPRISA 018, phase I/II trial design summary graphic (extracted from the study protocol version 2.0, 12 Aug 2019)

30x35mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on protocol v2.0 page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	73
	2b	All items from the World Health Organization Trial Registration Data Set	1-4
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	3-4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	2-4
	5b	Name and contact information for the trial sponsor	1-2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	73,88
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	In SSP
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	15-28
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	30
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	31
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	29
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	37
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	45-55
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	31, 66
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	43
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	43
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	36

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	34,80-82
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	58
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	58
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	58
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	58
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	58
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	64
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	64
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	64
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	72
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	64
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	57
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	61
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	62
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	69
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	69

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	66-68
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	73
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	69
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	69
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	69
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	69
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	71
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	72
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	73
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	70
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	73

	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	73
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	84-85
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	80-82

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license