PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Gengiah, Tanuja; Karim, Quarraisha Abdool; Harkoo, Ishana; Mansoor, Leila; Zuma, Nonhlanhla; Radebe, Precious; Samsunder, Natasha; Baxter, Cheryl; Maharaj, B.; Baum, Marc M.; Moss, John; Pozzetto, Bruno; Hankins, Catherine; Abdool Karim, Salim

VERSION 1 – REVIEW

REVIEWER	Ivan Marbaniang McGill University, Epidemiology
REVIEW RETURNED	07-Jun-2021

GENERAL COMMENTS	Please find some comments attached. I look forward to seeing the results from the trial. Introduction: Could the authors talk in brief about the acceptability of subdermal implants in general in the source population from where they will be deriving their study population? Trial population: 1. Could the authors qualify “low risk” for HIV? What risk assessment tool is being used? 2. A minor point: Why is the target for enrollment 56 days from the day they provide informed consent? It seems like an oddly specific number of days. Why not 2 months or 60 days? 3. Shouldn’t the inclusion criteria also include being sexually active within a specific time period? 4. Would having a sexually transmitted blood borne infection other than HBsAg positivity (since different STIs are proposed to be tested in the study) be an exclusion criterion? Could the authors otherwise justify why they only included HBsAg positivity as an exclusion criterion? 5. For the inclusion criteria: “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)” What non-barrier contraceptive do the authors suggest, and will women be assessed if they are actually using any contraceptive method? The secondary objective “To assess pregnancy rates and outcomes”

	seems counterintuitive after the inclusion criteria above. Do the investigators believe that there will be low compliance with the use of non-barrier contraception? Following from the point above: Do the investigators have guidelines in place for unintentional pregnancies in the event of the contraceptive barrier failing/ reportedly being used but not actually used, especially since their first exclusion criteria is “intention of pregnancy”? Trial design 1. Could the investigators include the dimensions of the implant in the trial design? It would be informative for readers to understand how big the implant is, especially if there are going to be three and four implants in one arm. Will the implant(s) be visible externally? 2. Phase II: Could the investigators provide follow-up details that are only listed in the statistical analysis plan later in the manuscript? Trial objectives “To evaluate the safety and tolerability of sustained-release TAF 110mg sub-dermal implant/s in HIV uninfected young women.” This primary objective from what I can understand is specifically in comparison to the TDF 300mg/ FTC + 200mg oral tablet. I wonder if the investigators could talk a little about why they did not choose the comparator to be 25 mg TAF + 200 mg FTC? Informed consent Minor point: Will the participants provide an electronic or paper-based informed consent? Will the consenting procedure be recorded? Randomization Would the sequential enrollment in Group 3 be matched or unmatched on participant characteristics age, parity etc? Data management Will data be collected on handheld devices, paper or on a desktop computer? How will the data collection tool be secured? Trial results dissemination plan Will the investigators also post the datasets publicly at the end of the trial?

REVIEWER	Sylvia Kusemererwa Uganda Virus Research Institute
REVIEW RETURNED	04-Sep-2021

GENERAL COMMENTS	Thank for for an opportunity to review this manuscript. Finding new HIV prevention options is key especially for young women who at high risk of HIV acquisition. The overall protocol is well written and easy to follow and understand. Below are a few minor comments: Abstract Line 6-7: How about indicating that multiple HIV technologies are

	needed considering some will be available soon like vaginal rings? Line 24: Is the planned Phase 2 also in 490 low risk women? Methodology Line 47-48, eligibility can only be determined after informed consent has been obtained. In other words, consent should be the first procedure done. Objectives: Line 26: Is it subcutaneous or sub dermal? 18-24years would be young women above that is probably just women. Line 57, is it acceptability in one arm or also in two arms? Page 10 line 7, why not use the Partner's PrEP study that included women since there are differences by gender in creatinine and clearance calculation includes gender? Page 11, line 53-54: Please clarify what the sentence refers to. Is it the assessment will include a review of… Page 13, Line 12. Efficacy was not included as part of the study objectives.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 queries:

Introduction:

Comment: Could the authors talk in brief about the acceptability of subdermal implants in general in the source population from where they will be deriving their study population?

Response: The source population in Durban, South Africa are young African women between 18 - 40 years of age. The closest suitable comparator to the TAF implant is the contraceptive implant. There have been several studies indicating that the contraceptive implant is acceptable to young African women with high continuation rates. For women who requested early contraceptive implant removal this was for the most part, due to systemic side-effects of hormonal contraception like irregular or persistent menstrual bleeding. The following sentence has been included in the Introduction on pg. 5 to address this query.

"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 (1), with continuation rates of ~80% after 1 year, including in studies from sub-Saharan Africa (2-3)".

References added to support the additional sentence:

1. 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):e1-e12. https://doi.org/10.1016/j.ajog.2016.12.024 [Links]
2. O'Neill E, Tang J, Garrett JHD. Characteristics of Kenyan women in a prospective cohort study who continue using subdermal contraceptive implants at 12 months. Contraception 2014;89(3):204-208. https://doi.org/10.1016/j.contraception.2013.11.016
3. 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.

Trial population:

1. Could the authors qualify "low risk" for HIV? What risk assessment tool is being used?

Response: The investigators have designed an ethics committee approved HIV risk assessment

tool that is completed in discussion with the potential participant early during screening visit. The HIV risk assessment tool used in the trial is included in the revision submission. Participants are generally deemed to be at low risk if a 'No' response is given to all assessment criteria for the Phase I component of the trial. The Principal Investigator may provide additional input in cases where the response to risk criteria is not straightforward and signs off on all assessments. For the Phase II component, 'at risk participants' will be enrolled and the same risk assessment tool is completed. However, in this instance, the risk assessment will be used to better understand the individuals risk profile and discuss whether trial participation is suitable for them.

2. A minor point: Why is the target for enrollment 56 days from the day they provide informed consent? It seems like an oddly specific number of days. Why not 2 months or 60 days?

Response: The 56-day (8 week) screening window is meant to be as specific as possible and corresponds with the data management programming of the study schedule of evaluations. If we used 2 months as an example some months have 5 weeks and the screening window could possibly vary between participants.

3. Shouldn't the inclusion criteria also include being sexually active within a specific time period?

Response: The main focus of both the Phase I and II trials is not efficacy at this stage rather safety (local and systemic), acceptability, tolerability and pharmacokinetics. Therefore, being sexual active is not a requirement for enrolment.

4. Would having a sexually transmitted blood borne infection other than HBsAg positivity (since different STIs are proposed to be tested in the study) be an exclusion criterion? Could the authors otherwise justify why they only included HBsAg positivity as an exclusion criterion?

Response: While not specifically listed as an exclusion criterion, having an STI at screening would preclude a Phase I study participant from enrolling when the HIV risk assessment tool is completed. For Phase II study participants the study clinician would use their discretion for identified 'high risk' participants. The specific HBsAg positivity exclusion criteria is related to the potential but small risk for Hepatitis B associate 'hepatic flares linked withdrawal of tenofovir containing treatment.

5. For the inclusion criteria: "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)" What non-barrier contraceptive do the authors suggest, and will women be assessed if they are actually using any contraceptive method?

Response: Family planning is discussed at length with participants and adherence to participant preferred methods is monitored at each study visit. At the clinical trial sites non- barrier form of contraception are also provided to study participants and may include intrauterine contraceptive devices (IUCD), oral or injectable hormonal contraception and contraceptive implants (although not preferred because of the TAF implant use).

The secondary objective "To assess pregnancy rates and outcomes" seems counterintuitive after the inclusion criteria above. Do the investigators believe that there will be low compliance with the use of non-barrier contraception?

Response: Compliance is quite high for non-barrier contraception, but we have experience with unintended pregnancies especially with oral contraceptive users, while drug interactions when oral antibiotic use could alter contraceptive effectiveness. We anticipate pregnancies to be rare but should they occur will be followed up to ascertain safety outcomes in the mother and infant.

Following from the point above:

Do the investigators have guidelines in place for unintentional pregnancies in the event of the contraceptive barrier failing/ reportedly being used but not actually used, especially since their first exclusion criteria is “intention of pregnancy”?

Response: Yes, the study specific procedures for unintentional pregnancy would outline the detailed procedures to be followed and include the urgent removal of the implant/s and the implementation of an amended schedule of evaluations suitable for pregnant participants who are off study product.

Trial design

1. Could the investigators include the dimensions of the implant in the trial design? It would be informative for readers to understand how big the implant is, especially if there are going to be three and four implants in one arm. Will the implant(s) be visible externally?

Response: The implant dimensions are approximately 40-45mm with an inner diameter of 2mm and a wall thickness of 0.19mm. This information has been included on page 5 of the manuscript. It is unlikely to be visible to the naked eye unless there is development of post inflammatory hyperpigmentation. It is however easily palpable.

2. Phase II: Could the investigators provide follow-up details that are only listed in the statistical analysis plan later in the manuscript?

Response: For the Phase I part of the trial follow up details are contained on pgs. 7-8 and are highlighted in yellow. In addition to information provided in Figure 1: CAPRISA 018 phase I/II trial design summary graphic gives some idea of when safety during follow up is assessed. For the Phase II part of the trial the following follow up information has seen included on pg. 8. “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

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

This primary objective from what I can understand is specifically in comparison to the TDF 300mg/ FTC + 200mg oral tablet. I wonder if the investigators could talk a little about why they did not choose the comparator to be 25 mg TAF + 200 mg FTC?

Response: At present 25 mg TAF + 200 mg FTC is not registered for the HIV prevention indication in cis-gender women in any country. Studies are underway and these data are waited. The comparator arm reflects the current South African medicines regulator approved standard of care for HIV PrEP.

Informed consent

Minor point: Will the participants provide an electronic or paper-based informed consent? Will

the consenting procedure be recorded?

Response: Paper based informed consent process is used. The consenting procedure is not audio recorded. However detailed notes and other source documentation is used to ensure that the process itself and clarifications provide to the participant is adequately documented. The original signed informed consent form is maintained in the site regulatory files, while a copy is housed in the participant binder and one copy is offered to the participant.

Randomization

Would the sequential enrollment in Group 3 be matched or unmatched on participant characteristics age, parity etc?

Response: No – Group 3 will follow the standard inclusion criteria and no stratification will be applied at enrolment.

Data management

Will data be collected on handheld devices, paper or on a desktop computer? How will the data collection tool be secured?

Response: Data is collected on paper- based case report forms (CRFs). The words 'paper- based' have been included in the data management section on pg. 12. The study has secure, double-locked rooms for the storage of study forms, with a high capacity fire-proof walk-in safe at the central CAPRISA data management department. All access is electronically or key controlled and only authorized staff has access to these areas (e.g. data management staff and specified study staff). Logs are maintained for monitoring access to the facilities and for tracking the removal and return of study forms from the storage area.

The PDF CRFs are strictly version controlled and their use and distribution is managed by the study data manager. If data entered on the CRFs are taken from an external source (e.g., laboratory reports, patient records), the source documents will be maintained in the participant's medical chart or study file at the site and will be available for review. The CRFs will be faxed into the database management system which is DataFax Discover which has optical character recognition, which will read the check boxes and numerical fields on the CRFs and store them in the study database. The systems also maintain audit trails which track and record any changes made to the data after capture, the type of change made, the date and time of the change as well as the person who changed the data. The data management systems used in CAPRISA are all hosted on the secure CAPRISA network, which is firewalled and access controlled, with the servers backed up on a daily basis to a secure off-site facility. CAPRISA backup and restorations are done in line with the CAPRISA IT Disaster Recovery and Business Continuity.

Trial results dissemination plan

Will the investigators also post the datasets publicly at the end of the trial?

Response: Yes. Summary results of the trial will be made publicly available through the clinical trial registry as de-identified data. Any datasets used for analysis in publications can be requested by via an online request process to the sponsor organisation (CAPRISA). Any additional data may certainly be made available upon request to the corresponding author.

Reviewer: 2 queries

Abstract

Line 6-7: How about indicating that multiple HIV technologies are needed considering some will be available soon like vaginal rings?

Response: Agreed. However, this text is now included in the Introduction section rather than the word constrained abstract. The following referenced text has been added to the Introduction on pg.

4: “Other novel long-acting PrEP agents and innovative delivery systems such as ARV containing intravaginal rings (IVRs), viz. the Dapivirine ring and possibly long- acting injectable ARVs, are poised to be accessible soon. These formulations along with the implant under study offer specific adherence advantages over daily oral PrEP”

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Line 24: Is the planned Phase 2 also in 490 low risk women?

Response: No. The Phase II trial will not be restricted to low-risk women. The ‘at risk’ description has been added to the abstract on pg.2 to clarify this. The eligibility criteria listed in Table 1 also refer to Groups 1, 2 and 3 only as low HIV risk.

Methodology

Line 47-48, eligibility can only be determined after informed consent has been obtained. In other words, consent should be the first procedure done.

Response: We concur. Consent for screening procedures and consent for enrolment procedures are separate in this protocol. The text has been edited for added clarity. The sentence now reads as follows: “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”

Objectives:

Line 26: Is it subcutaneous or sub dermal? 18-24years would be young women above that is probably just women.

Response: Corrected to ‘sub-dermal’ on pg. 7and ‘young’ removed from the descriptor on pg. 8.

Line 57, is it acceptability in one arm or also in two arms?

Response: Acceptability assessments are conducted across all dose ranges and for the multiple insertion site group.

Page 10 line 7, why not use the Partner’s PrEP study that included women since there are differences by gender in creatinine and clearance calculation includes gender?

Response:.At the time the protocol was being prepared this data (mean decline in creatinine clearance over time) was not available from the Partners PrEP main study publication. Subsequent publications by the Partners PreP investigators (Mugwanya et al, 2018 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5762271/) only considered declines in creatinine clearance <60 mL/min but not other significant decline from normal that could be considered clinically relevant. However, as the reviewer indicated, the Cockcroft Gault equation used to estimate creatinine clearance adjusts for gender and we will monitor the literature to see if the estimated decline used in the statistical calculation requires modification.

Page 11, line 53-54: Please clarify what the sentence refers to. Is it the assessment will include a review of…

Response: Sentence grammar on pg. 11 was corrected and now reads as: “Each safety assessment will include a review of adverse events (AEs) at grade 2 or higher for local site reactions and serum chemistry”.

Page 13, Line 12. Efficacy was not included as part of the study objectives.

Response: The secondary objective to assess incidence of HIV infection is included and thos would provide a signal for efficacy in the Phase II component of the trial where a comparison between active and placebo arms would be possible if incident HIV infections are experienced.

VERSION 2 – REVIEW

REVIEWER	Ivan Marbaniang McGill University, Epidemiology
REVIEW RETURNED	23-Nov-2021

GENERAL COMMENTS	Thank you for addressing the previous comments that had been raise. I wish all the investigators all the best for the study.

REVIEWER	Sylvia Kusemererwa Uganda Virus Research Institute
REVIEW RETURNED	04-Nov-2021

GENERAL COMMENTS	The authors have responded to queries satisfactorily and revised the manuscript accordingly.