CLINICAL STUDY PROTOCOL

SPONSOR:
GlaxoSmithKline Biologicals SA (GSK)

Primary study intervention(s)	GSK *Neisseria gonorrhoeae* GMMA (NgG) investigational vaccine (GSK4348413A)
Other study intervention(s)	Placebo (Saline)
eTrack study number and abbreviated title	216156 (NGG-001)
EU CT number	2022-500883-37-00
EudraCT number	2022-001060-10
Approval date	03 Dec 2024
Title	A Phase 1/2, observer-blind, randomized, placebo-controlled multi-country study to assess safety and efficacy of GSK *Neisseria gonorrhoeae* GMMA (NgG) investigational vaccine when administered to healthy adults 18 to 50 years of age
Brief title	Safety and efficacy of GSK *Neisseria gonorrhoeae* GMMA (NgG) investigational vaccine when administered to healthy adults 18 to 50 years of age
Sponsor signatory	Ilaria Galgani (Clinical Project Lead)

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.3

PROTOCOL AMENDMENT 7 INVESTIGATOR AGREEMENT

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the participant.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the investigational intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

eTrack study number and abbreviated title	216156 (NGG-001)
EudraCT number	2022-001060-10
EU CT number	2022-500883-37-00
Title	A Phase 1/2, observer-blind, randomized, placebo-controlled multi-country study to assess safety and efficacy of GSK *Neisseria gonorrhoeae* GMMA (NgG) investigational vaccine when administered to healthy adults 18 to 50 years of age
Investigator name	_____
Signature	_____
Date	_____
PPD **name, function and title**	_____
Signature	_____
Date of signature	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document.

4. Sponsor study contact for reporting of Serious Adverse Events (SAEs)

GSK central back up study contact for reporting SAEs: refer to Section 8.3.3.1.

Study contact for reporting SAEs: refer to the local study contact information document.

5. GSK Helpdesk for emergency unblinding

Refer to Section 6.3.5.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 7	03 Dec 2024
Amendment 6	05 June 2024
Amendment 5	28 November 2023
Amendment 4	27 April 2023
Amendment 3	10 March 2023
Amendment 2	20 January 2023
Amendment 1	19 October 2022
Original Protocol	12 July 2022

Amendment 7 (03 Dec 2024)

Overall Rationale for the current Amendment: During the efficacy PoC part of the ongoing NGG-001 study, an Interim Analysis was performed as outlined in Section 9.5. Out of the 984 randomized participants in the PoC part of the study, 978 were included in the Interim Analysis.

The results of the Interim Analys did not reveal safety concerns but revealed lack of efficacy of both tested formulations in the PoC part to prevent gonorrhea cases.

Based on this, the protocol is amended to interrupt unnecessary procedures/visit; the trial will anyhow continue until the completion of the planned 12 month follow up starting from 1 month post Dose 2.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE

Section # and title	Description of change	Brief rationale
1.3. Schedule of activities	New Schedule of activities (SoA) for protocol amendment 7 was added as Table 3. The following changes were introduced compared to the previous SoA: • Removed sexual behaviour questionnaire at Visits 8, 9 and 10 • Removed unscheduled visits and ad-hoc NAAT visits. • Removed swab collection (urogenital, anorectal and pharyngeal) at Visits 8,9 and 10. • Removed urine sample collection from Visits 8,9 and 10	Revised to remove procedures/visits based on the results of the Interim Analysis where both tested formulations revealed lack of efficacy to prevent gonorrhea cases.

Section # and title	Description of change	Brief rationale
	• Removed collection of blood sample for immunogenicity assessment and assay development at Visit 10. • Removed recording of test of cure for Visits 8, 9 and 10	
2.3. Benefit/Risk assessment	Added significant information to this section after Interim Analysis results were received.	To align with updated Investigator's Brochure information. Revised to reflect the overall change in the Benefit-Risk assessment after Interim Analysis results.
3. Objectives, Endpoints, and Estimands 9.3.2. Secondary endpoint(s)/estimand(s) analyses	• Removed secondary objective ('To evaluate the efficacy of the NgG vaccine in preventing complicated gonococcal infections') and corresponding endpoint • For the teriary objective 'To explore the molecular epidemiology of Ng and Ct', added the following endpoint : 'Bacterial load as assessed by semiquantitative PCR of samples that results positive for Ng and Ct at NAAT)'	• The occurrence of complicated gonorrhea was rare and this analysis will not be informative of the candidate vaccine efficacy • To clarify that when exploring the molecular epidemiology, also a quantitative evaluation of the Ng bacterial load will be done for Ng and Ct.
Throughout the protocol: 4.1.2 Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea (including Figure 3 and footnote) 8.Study assessment and procedures 8.1.1. Biological samples (includingTable 9 footnote) 8.1.2. Read-out for efficacy assessment 8.2.1.3. General physical examination 8.2.1.4. History or symptoms directed physical examination 8.2.1.5. Sexual behaviour recommendations, sexual behaviour questionnaire and safe sex advice	Clarification added for study procedures and assessments planned at Visits 8, 9, 10, unscheduled visits and ad-hoc visits.	To align with SoA for protocol amendment 7.
9.3.1. Primary endpoint(s)/estimand(s) analyses	Clarification added for 'Within groups assessment' (deleted 'exact 95% confidence intervals').	Due to the descriptive nature of the safety analysis, presenting confidence intervals is of limited value and was removed.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale: *Neisseria gonorrhoeae* (Ng) is a strictly human bacterial pathogen causing gonorrhea, the second most prevalent bacterial sexually transmitted infection (STI) worldwide, with 87 million new cases of infections estimated globally in 2016 [Rowley, 2019]. Ng is transmitted through genital, oral and anal sexual contact infecting mucosal surfaces at these sites and, if not detected and/or appropriately treated, it can progress from a less severe condition and result in serious complications and sequelae for both sexes.

Standard of care relies on the use of antibiotics and there are relevant concerns with the increasing antibiotic resistance. There are presently no existing or available preventative therapies therefore a vaccine would contribute significantly to the current management of the disease.

GSK Biologicals' *Neisseria gonorrhoeae* GMMA (NgG) investigational vaccine is an intramuscular (IM) injectable vaccine that can be presented as 1 vial or 2 vials to be mixed immediately before the injection, depending on the antigen dose. CCI [redacted] CCI [redacted] In both cases the proposed regimen is 2 vaccine doses of 0.5 mL each, to be administered 2 months apart.

The proposed early clinical development plan consists of a Phase 1/2 study in participants 18 to 50 years of age, to assess the safety and efficacy of the NgG investigational vaccine when administered at different dosage (50, 25, and 12.5 µg of vaccine antigen per dose) according to a 2-dose schedule, with 2 months interval between the injections compared to placebo. An Interim Analysis of the Phase 2 part data has been performed as planned, at accrual of approximately 180 days of follow-up in the total study population, starting from 1 month post Dose 2.

This first time in human – proof of concept (FTiH-PoC) study aims to provide an early evaluation of the efficacy of the investigational vaccine as there are no established immunogenicity correlates of protection against infections caused by Ng.

Objectives, endpoints and estimands: Refer to Table 5 for the study objectives and endpoints.

1.2. Schema

This is a Phase 1/2, placebo-controlled, observer-blind, randomized, multi-centric study. Figure 1 presents an overview of the whole study design. The study will include the following parts: Phase 1 Dose-escalation safety lead-in in healthy participants (Figure 2) and Phase 2 Efficacy PoC in healthy participants considered at risk for gonorrhea (Figure 3).

1.3. Schedule of Activities (SoA)

Table 1 Schedule of activities of dose-escalation safety lead-in

Type of contact Group 1a/b: low dose/placebo Group 2a/b: medium dose/placebo Group 3a/b: high dose/placebo	**Screening**	**V1**	**V2**	**V3 phone call**	**V4**[3]	**V5**	**V6 phone call**	**V7 phone call**	**V8 phone call**
Time points	**Day – 1**	**Day 1**	**Day 8**	**Day 31 (M 1)**	**Day 61 (M 2)**	**Day 68**	**Day 91 (M 3)**	**Day 151 (M 5)**	**Day 241 (M 8)**
Informed consent	●								
Check inclusion/exclusion criteria	●	●							
Collect demographic data	●								
Medical and vaccination history	●								
Physical examination/vital signs[1]	O	●							
History or symptom directed physical examination		O	O		O	O			
Urine pregnancy test		●			●				
Blood sampling for hematology/biochemical analysis (~6 ml)	●		●		●	●			
Blood sample for assay development (~50 ml)	●					●			
Check contraindications and warnings and precautions to vaccination	O	O			O				
Check criteria for temporary delay for enrolment and study intervention administration	O	O			O				
Study group and intervention number allocation		O							
Treatment number allocation for subsequent doses					O				
Body temperature before study intervention administration (Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature will be oral. If any other route is used for measuring temperature, this needs to be recorded in the eCRF.)		●			●				
Vaccine or placebo administration		●			●				
Recording of administered intervention number		●			●				
Record any concomitant medication/vaccination		●	●	●	●	●	●	●	●

Type of contact Group 1a/b: low dose/placebo Group 2a/b: medium dose/placebo Group 3a/b: high dose/placebo	**Screening**	**V1**	**V2**	**V3 phone call**	**V4**[3]	**V5**	**V6 phone call**	**V7 phone call**	**V8 phone call**
Time points	**Day – 1**	**Day 1**	**Day 8**	**Day 31 (M 1)**	**Day 61 (M 2)**	**Day 68**	**Day 91 (M 3)**	**Day 151 (M 5)**	**Day 241 (M 8)**
Phone contact for safety follow-up				●			●	●	●
Recording of solicited AEs at the investigator's site within 60 minutes post-vaccination observation		●			●				
Recording of solicited adverse events (days 1 – 7 post-Dose 1 and 2			O			O			
Distribution of eDiaries/install eDiary app and training		O			O				
Return of eDiaries to the sites[2]/uninstall eDiary app				O			O		
Recording of solicited adverse events ongoing on day 7 after post-Dose 1 and 2			●			●			
Recording of non-serious adverse events within 30 days post-Dose 1 and 2		●	●	●	●	●	●		
Reporting of SAEs, AEs leading to withdrawal and pregnancies		●	●	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●
Study Conclusion									●

Note: Screening and visit 1 can happen the same day provided that all procedures can be completed.

[1]Vital signs are recorded in eCRF only on Visit 1

[2]If a device is given it should be returned by Day 241, Visit 8

[3]All study activities except recording of administered intervention number and recording of AEs post-vaccination, will be performed before the administration of vaccine or placebo.

● is used to indicate a study procedure that requires documentation in the individual eCRF; O is used to indicate a study procedure that does not require documentation in the individual eCRF.

a/b = vaccine/placebo

SAE = Serious adverse event

M = Month

V = Visit

Table 2 Schedule of activities of efficacy PoC

Type of contact	Group 4a HTD Group 4b below HTD Group 4c Placebo	**Screening**	**V1**	**V2[4]**	**V3**	**V4[8]**	**V5[4]**	**V6**	**V7[10]**	**V8[10]**	**V9[10]**	**V10**	**Unscheduled visit**	***Ad-hoc NAAT visit[9]***
Time points		**Day –14**	**Day 1**	**Day 8 (Safety)**	**Day 31 (M 1)**	**Day 61 (M 2)**	**Day 68**	**Day 91 (M 3)**	**Day 181 (M 6)**	**Day 271 (M 9)**	**Day 361 (M 12)**	**Day 451 (M 15)**		
Informed consent		●												
Check inclusion/exclusion criteria		●	●											
Collect demographic data		●												
Medical and vaccination history		●												
Sexual behavior questionnaire		●			●	●		●	●	●	●	●	●	
Physical examination/vital signs [1]		O	●										O	
History or symptom directed physical examination			O	O	O	O	O	O	O	O	O	O	O	
Urine pregnancy test			●			●								
Check contraindications and warnings and precautions to vaccination		O	O			O								
Check criteria for temporary delay for enrolment and study intervention administration		O	O			O								
Study group and intervention number allocation			O											
Treatment number allocation for subsequent doses						O								
Body temperature before study intervention administration (Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature will be oral. If any other route is used for measuring temperature, this needs to be recorded in the eCRF.)			●			●								
Blood sampling for immunogenicity (~20 ml)[5]			●		●	●		●				●	●	
Blood sample for assay development (~30 ml)[6]			●		●	●		●				●		
Blood sampling for haematology/biochemical analysis (6 ml)[2]		●		●		●	●							
Vaccine or placebo administration			●			●								
Recording of administered intervention number			●			●								
Swab collection (urogenital, anorectal and pharyngeal)		●			●	●		●	●	●	●	●	●	
Urine sample 20-30 mL (first-catch)[3]		●			●	●		●	●	●	●	●	●	

Type of contact	Group 4a HTD Group 4b below HTD Group 4c Placebo	**Screening**	**V1**	**V2[4]**	**V3**	**V4[8]**	**V5[4]**	**V6**	**V7[10]**	**V8[10]**	**V9[10]**	**V10**	**Unscheduled visit**	***Ad-hoc NAAT visit[9]***
Time points		**Day –14**	**Day 1**	**Day 8 (Safety)**	**Day 31 (M 1)**	**Day 61 (M 2)**	**Day 68**	**Day 91 (M 3)**	**Day 181 (M 6)**	**Day 271 (M 9)**	**Day 361 (M 12)**	**Day 451 (M 15)**		
Ad-hoc swab/urine sample[3] collection prior to antibiotic treatment, only from the anatomical site(s) confirmed by NAAT as positive for Ng by central laboratory.														●
Record information on occurrence of any gonorrhea-specific symptom and Disease-Related- Events (DREs).					●	●		●	●	●	●	●	●	
Record if a test of cure is performed only if the treatment administered is considered "alternative"		●	●	●	●	●	●	●	●	●	●	●	●	
Record any concomitant medication/vaccination			●	●	●	●	●	●	●	●	●	●	●	●
Record healthcare utilization (hospitalization, emergency room, and accident & emergency visits)			●	●	●	●	●	●	●	●	●	●	●	●
Record antibiotic use			●	●	●	●	●	●	●	●	●	●	●	●
Recording of solicited AEs at the investigator's site within 60 minutes post-vaccination observation			●			●								
Recording of solicited adverse events (Days 1 – 7 post-Dose 1 and 2)			O			O								
Distribution of eDiaries to the sites/install eDiary app			O			O								
Return of eDiaries to the sites[7]/uninstall eDiary app					O			O						
Recording of non-serious adverse events within 30 days post-Dose 1 and 2			●	●	●	●	●	●						
Reporting of SAEs, AEs leading to withdrawal and pregnancies			●	●	●	●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine		●	●	●	●	●	●	●	●	●	●	●	●	●
Study Conclusion												●		

[1]Vital signs are recorded in eCRF only on visit 1.

[2]Only for participants in subset for safety monitoring (Refer to Section 4.1.2 Safety monitoring for details). Additional blood samples may be obtained during the unscheduled visit at the discretion of the investigator, to assess any perceived safety issues.

[3]Urine sample obtained as follows: for male participants (or any participant with a penis), first catch urine (first part of the urine stream passed), can be collected at any time of the day with participant holding urine for at least 1 hour prior to the collection.

[4]For participants in the safety subset, a clinic visit will apply at Visit 2 (Day 8) and Visit 5 (Day 68), for all other study participants a phone call will apply. If, at Visit 2 or Visit 5, a study participant shows signs and/or symptoms suggestive of gonococcal infection, tested positive for Ng outside of the study schedule and has not yet received treatment, or had a recent sexual contact with a partner with a confirmed diagnosis of gonococcal infection, the investigator will collect samples from the 3 anatomical sites (urogenital, anorectal and pharyngeal), double samples of affected sites in case of symptoms, and blood samples for immunogenicity as described in Section 8.1.1. Additionally, the investigator will record information on occurrence of any gonorrhea-specific symptom and Disease-Related- Events (DREs) as described in Section 8.3.1, and the study participant will be required to complete a sexual behaviour questionnaire as described in Section 8.2.1.5.

[5]Blood sampling for immunogenicity from all participants. The testing strategy is described in Section 8.1.1.

[6]Blood sampling for assay development from all participants.

[7]If a device is given it should be returned by Day 451, Visit 10.

[8]All study activities except recording of administered intervention number and recording of AEs post-vaccination, will be performed before the administration of vaccine or placebo.

[9] Ad-hoc NAAT visits may be performed for gonorrhea cases diagnosed by central laboratory (1 or more anatomical sites confirmed by NAAT as positive for Ng by central laboratory) at or beyond 1 month post-Dose 2 only. When administration of antibiotic treatment against Ng is planned following this diagnosis, efforts will be made to collect ad-hoc NAAT samples for central laboratory from the anatomical sites that previously tested positive for Ng prior to antibiotic treatment administration. If treatment was already administered before central laboratory NAAT results became available, no ad-hoc NAAT visit will take place.

[10] If, at Visit 7, Visit 8 or Visit 9, a study participant shows signs and/or symptoms suggestive of gonococcal infection, tested positive for Ng outside of the study schedule and has not yet received treatment or had a recent sexual contact with a partner with a confirmed diagnosis of gonococcal infection, the investigator will collect blood samples for immunogenicity as described in Section 8.1.1.

● is used to indicate a study procedure that requires documentation in the individual eCRF; O is used to indicate a study procedure that does not require documentation in the individual eCRF.

SAE = Serious adverse event; Ng = Neisseria gonorrhoeae; NAAT = Nucleic Acid Amplification Test; M = Month; V = Visit

Table 3 Schedule of activities of efficacy PoC (protocol amendment 7)

Type of contact	Group 4a HTD Group 4b below HTD Group 4c Placebo	**Screening**	**V1**	**V2[4]**	**V3**	**V4[8]**	**V5[4]**	**V6**	**V7[9]**	**V8**	**V9**	**V10**
Time points		**Day –14**	**Day 1**	**Day 8 (Safety)**	**Day 31 (M 1)**	**Day 61 (M 2)**	**Day 68**	**Day 91 (M 3)**	**Day 181 (M 6)**	**Day 271 (M 9)**	**Day 361 (M 12)**	**Day 451 (M 15)**
Informed consent		●										
Check inclusion/exclusion criteria		●	●									
Collect demographic data		●										
Medical and vaccination history		●										
Sexual behavior questionnaire		●				●	●		●	●			
Physical examination/vital signs [1]		O	●									

Type of contact	Group 4a HTD Group 4b below HTD Group 4c Placebo	**Screening**	**V1**	**V2[4]**	**V3**	**V4[8]**	**V5[4]**	**V6**	**V7[9]**	**V8**	**V9**	**V10**
Time points		**Day –14**	**Day 1**	**Day 8 (Safety)**	**Day 31 (M 1)**	**Day 61 (M 2)**	**Day 68**	**Day 91 (M 3)**	**Day 181 (M 6)**	**Day 271 (M 9)**	**Day 361 (M 12)**	**Day 451 (M 15)**
History or symptom directed physical examination			O	O	O	O	O	O	O	O	O	O
Urine pregnancy test			●			●						
Check contraindications and warnings and precautions to vaccination		O	O			O						
Check criteria for temporary delay for enrolment and study intervention administration		O	O			O						
Study group and intervention number allocation			O									
Treatment number allocation for subsequent doses						O						
Body temperature before study intervention administration (Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature will be oral. If any other route is used for measuring temperature, this needs to be recorded in the eCRF.)			●			●						
Blood sampling for immunogenicity (~20 ml)[5]			●		●	●		●				
Blood sample for assay development (~30 ml)[6]			●		●	●		●				
Blood sampling for haematology/biochemical analysis (6 ml)[2]		●		●		●	●					
Vaccine or placebo administration			●			●						
Recording of administered intervention number			●			●						
Swab collection (urogenital, anorectal and pharyngeal)		●			●	●		●	●			
Urine sample 20-30 mL (first-catch)[3]		●			●	●		●	●			
Record information on occurrence of any gonorrhea-specific symptom and Disease-Related- Events (DREs).					●	●		●	●	●	●	●
Record if a test of cure is performed only if the treatment administered is considered “alternative”		●	●	●	●	●	●	●	●			
Record any concomitant medication/vaccination			●	●	●	●	●	●	●	●	●	●
Record healthcare utilization (hospitalization, emergency room, and accident & emergency visits)			●	●	●	●	●	●	●	●	●	●
Record antibiotic use			●	●	●	●	●	●	●	●	●	●
Recording of solicited AEs at the investigator’s site within 60 minutes post-vaccination observation			●			●						
Recording of solicited adverse events (Days 1 – 7 post-Dose 1 and 2)			O			O						
Distribution of eDiaries to the sites/install eDiary app			O			O						

Type of contact	Group 4a HTD Group 4b below HTD Group 4c Placebo	**Screening**	**V1**	**V2[4]**	**V3**	**V4[8]**	**V5[4]**	**V6**	**V7[9]**	**V8**	**V9**	**V10**
Time points		**Day –14**	**Day 1**	**Day 8 (Safety)**	**Day 31 (M 1)**	**Day 61 (M 2)**	**Day 68**	**Day 91 (M 3)**	**Day 181 (M 6)**	**Day 271 (M 9)**	**Day 361 (M 12)**	**Day 451 (M 15)**
Return of eDiaries to the sites[7]/uninstall eDiary app					O			O				
Recording of non-serious adverse events within 30 days post-Dose 1 and 2			●	●	●	●	●	●				
Reporting of SAEs, AEs leading to withdrawal and pregnancies			●	●	●	●	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine		●	●	●	●	●	●	●	●	●	●	●
Study Conclusion												●

[1]Vital signs are recorded in eCRF only on visit 1.

[2]Only for participants in subset for safety monitoring (Refer to Section 4.1.2 Safety monitoring for details).

[3]Urine sample obtained as follows: for male participants (or any participant with a penis), first catch urine (first part of the urine stream passed), can be collected at any time of the day with participant holding urine for at least 1 hour prior to the collection.

[4]For participants in the safety subset, a clinic visit will apply at Visit 2 (Day 8) and Visit 5 (Day 68), for all other study participants a phone call will apply. If, at Visit 2 or Visit 5, a study participant shows signs and/or symptoms suggestive of gonococcal infection, tested positive for Ng outside of the study schedule and has not yet received treatment, or had a recent sexual contact with a partner with a confirmed diagnosis of gonococcal infection, the investigator will collect samples from the 3 anatomical sites (urogenital, anorectal and pharyngeal), and blood samples for immunogenicity as described in Section 8.1.1. Additionally, the investigator will record information on occurrence of any gonorrhea-specific symptom and Disease-Related- Events (DREs) as described in Section 8.3.1, and the study participant will be required to complete a sexual behaviour questionnaire as described in Section 8.2.1.5.

[5]Blood sampling for immunogenicity from all participants. The testing strategy is described in Section 8.1.1.

[6]Blood sampling for assay development from all participants.

[7]If a device is given it should be returned by Day 451, Visit 10.

[8]All study activities except recording of administered intervention number and recording of AEs post-vaccination, will be performed before the administration of vaccine or placebo.

[9]If, at Visit 7 a study participant shows signs and/or symptoms suggestive of gonococcal infection, tested positive for Ng outside of the study schedule and has not yet received treatment or had a recent sexual contact with a partner with a confirmed diagnosis of gonococcal infection, the investigator will collect blood samples for immunogenicity as described in Section 8.1.1.

● is used to indicate a study procedure that requires documentation in the individual eCRF; O is used to indicate a study procedure that does not require documentation in the individual eCRF.

SAE = Serious adverse event; Ng = Neisseria gonorrhoeae; M = Month; V = Visit

Table 4 Intervals between study visits

Groups	Interval	Planned visit interval (days)	Allowed interval (days)
Group 1a/b Group 2a/b Group 3a/b	Screening → V1 (Day 1)	1	0 – 3 (-3 to 0 days)
	V1 (Day 1) → V2 (Day 8)	7	7 – 8 (0 to +1 day)
	V1 (Day 1) → V3 (Month 1, Day 31)	30	30 – 44 (0 to +14 days)
	V1 (Day 1) → V4(Month 2, Day 61)	60	53 – 74 (-7 to +14 days)
	V4 (Day 61) → V5 (Day 68)	7	7 – 8 (0 to +1 day)
	V4 (Day 61) → V6 (Month 3, Day 91)	30	30 – 44 (0 to +14 days)
	V4 (Day 61) → V7 (Month 5, Day 151)	90	83 – 104 (-7 to +14 days)
	V4 (Day 61) → V8 (Month 8, Day 241)	180	173 – 194 (-7 to +14 days)
Group 4a/b/c	Screening (Day –14) → V1 (Day 1)	14	0 – 14 (-14 to 0 days)
	V1 (Day 1) → V2 (Day 8)	7	7 – 8 (0 to +1 day)
	V1 (Day 1) → V3 (Month 1, Day 31)	30	30- 44 (0 to +14 days)
	V1 (Day 1) → V4 (Month 2, Day 61)	60	53 – 74 (-7 to +14 days)
	V4 (Day 61) → V5 (Day 68)	7	7 – 8 (0 to +1 day)
	V4 (Day 61) → V6 (Month 3, Day 91)	30	30 – 44 (0 to +14 days)
	V4 (Day 61) → V7 (Month 6, Day 181)	120	113 – 134 (-7 to +14 days)
	V4 (Day 61) → V8 (Month 9, Day 271)	210	203 – 224 (-7 to +14 days)
	V4 (Day 61) → V9 (Month 12, Day 361)	300	293 – 314 (-7 to +14 days)
	V4 (Day 61) → V10 (Month 15, Day 451)	390	383 – 404 (-7 to +14 days)

2. INTRODUCTION

2.1. Study rationale

Neisseria gonorrhoeae (Ng) is a strictly human bacterial pathogen causing gonorrhea, the second most prevalent bacterial sexually transmitted infection (STI) worldwide, with 87 million new cases of infections estimated globally in 2016 [Rowley, 2019]. Ng is transmitted through genital, oral and anal sexual contact infecting mucosal surfaces at these sites and, if not detected and/or appropriately treated, it can progress from a less severe condition and result in serious complications and sequelae for both sexes.

Standard of care relies on the use of antibiotics and there are relevant concerns with the increasing antibiotic resistance. There are presently no existing or available preventative therapies therefore a vaccine would contribute significantly to the current management of the disease.

GSK Biologicals' *Neisseria gonorrhoeae* GMMA (NgG) investigational vaccine is an intramuscular (IM) injectable vaccine that can be presented as 1 vial or 2 vials to be mixed immediately before the injection, depending on the antigen dose. CCI [redacted] CCI [redacted] In both cases the proposed regimen is 2 vaccine doses of 0.5 mL each, to be administered 2 months apart.

The proposed early clinical development plan consists of a Phase 1/2 study in participants 18 to 50 years of age, to assess the safety and efficacy of the NgG investigational vaccine when administered at different dosage (50, 25, and 12.5 µg of vaccine antigen per dose) according to a 2-dose schedule, with 2 months interval between the injections compared to placebo. An Interim Analysis of the Phase 2 part data has been performed as planned, at accrual of approximately 180 days of follow-up in the total study population, starting from 1 month post Dose 2.

This FTiH-PoC study aims to provide an early evaluation of the efficacy of the investigational vaccine as there are no established immunogenicity correlates of protection against infections caused by Ng.

2.2. Background

Ng is a strictly human bacterial pathogen causing gonorrhea. Ng is transmitted through genital, oral and anal sexual contact infecting mucosal surfaces at these sites and, if not detected and/or appropriately treated, it can progress from a less severe condition and result in serious complications and sequelae for both sexes. Clinically, it manifests differently between men and women and by anatomic site of infection.

In men, Ng is a common cause of urethritis and can lead to epididymo-orchitis, and prostatitis. In women, it causes cervicitis, which is frequently asymptomatic but can lead to pelvic inflammatory disease (PID). Up to 50% of women with an untreated infection caused by Ng and/or *Chlamydia trachomatis* (Ct) may develop PID [Llata, 2015; Ness, 2005a], but PID following gonorrhea can be more clinically severe [Reekie, 2014; Short, 2009]. PID can become recurrent leading to chronic pelvic pain, and if left untreated, to serious long-term sequelae including tubo-ovarian abscess, tubal factor infertility (in up to 20% of cases) and ectopic pregnancy (up to 9%) [Westrom, 1992; Haggarty, 2010; Ness, 2005b]. It is estimated that 4.4% of sexually active women in the United States (US) aged 18-44 years (2.5 million women) will be treated for PID during their lifetime [Kreisel, 2017]. There are also consequences for infants born to Ng-infected mothers, including small size for gestational age and low birth weight, conjunctivitis and related blindness [Butali, 2016; Kreisel, 2017].

Recurrent gonococcal infections are common among both men and women and repeated gonococcal infections increase the risk of PID. The frequency of recurrence and the time between 2 infections varies widely between genders and is dependent on sexual behavior and frequency of sexual contacts [Hosenfeld, 2009; Fung, 2007]. It is likely that rates of recurrent disease are routinely underestimated, as adherence to post-infection retesting guidelines is generally low [Carlson, 2017; Hoover, 2010]. Where it has been studied [Rose, 2017], retesting and repeat positivity shows marked gender and ethnic disparities suggesting a further social gradient in gonorrhea diagnosis and control in population subgroups with the highest disease burden.

Epidemiology and burden of disease:

Gonorrhea is the second most prevalent bacterial STI worldwide with 87 million new cases of gonococcal infections occurring globally in 2016 [Unemo, 2019]. Effective STI control relies on access to healthcare, appropriate diagnostic tools and treatment, and routine reporting from STI surveillance system that enables the national health authorities to effectively monitor epidemic trends and identify severe or emerging epidemic outbreaks. However, widespread differences in syndromic and etiological reporting, as well as a lack of standardization of case definitions lead to substantial underestimates of the burden of disease, even in industrialized countries where surveillance systems are well established and validated [Unemo, 2019].

In recent years, Ng has been rising substantially in the US with an increase of 83% in reported cases during the last 10 years [Kreisel, 2021]. In England, reported gonorrhea diagnosis increased significantly during 2010 to 2019 by an estimated 421%, with 70 936 reported diagnosis in total in 2019 [PHE, 2020a]. Ng is a common infection especially among young women, with rates of reported Ng cases in 2018 in the US for females age 15 to 19 years and age 20 to 24 years of 548 and 703 per 100 000, respectively. This compares to the overall rate of reported Ng cases among females in the US of 174.5 per 100 000 in 2020 [CDC, 2020]. Despite the high rates of reported Ng infections in young women, the highest rates of Ng infection are observed in high-risk groups such as men having sex with men (MSM) or sex workers [Stenger, 2017; PHE, 2020b]. Higher risk is also reported in both men and women with a history of previous STI infections [Bautista, 2017; Hughes, 2012; Montaño, 2019] and HIV [Li, 2020].

Overall, the economic burden of Ng is significant. Complications, co-infections and long-term health problems were estimated to contribute for more than 70% of all total direct medical cost. Here, reproductive complications and sequelae among females such as PID, ectopic pregnancy and infertility account for the majority of the cost [Arnold, 2020], though the estimated economic burden associated with HIV attributable to gonorrhea in MSM is also significant. Antimicrobial resistance (AMR) and future emergence of Ng strains resistant to the current antibiotic therapies might lead to a concomitant rise of AMR prevalence and Ng infections associated with an estimated additional economic burden of US Dollars (USD) 378.2 million over 10 years in the US [Chesson, 2018].

Unmet medical need:

There is a substantial burden of undetected and/or untreated asymptomatic Ng infection among men and women, and half of cases that occur in the US are undiagnosed or unreported [Satterwhite, 2010].

If not promptly identified and treated, gonococcal infections not only can progress to severe complications but can constitute a reservoir of Ng and facilitate spread and transmission to contact partners and enhance the transmission and acquisition of HIV by a factor of seven [Mavedzenge, 2011]. An important unmet medical need especially among MSM is the increase in the risk of acquiring and transmitting HIV infection due to Ng infection [Fleming, 1999; Bernstein, 2010]. Jones et al. [Jones, 2019] and Beck et al. [Beck, 2015] estimated the percentage of HIV infections among MSM in the US attributable to Ng and *C. trachomatis* to range from 10.2 to 14.6%, supported by findings of a longitudinal cohort study of MSM in Atlanta (US) that estimated that 14.6% of incidence HIV could be attributable to rectal chlamydia, gonorrhea and syphilis [Kelley, 2015].

There are presently no existing or available preventive therapies and the standard of care relies on the use of antibiotics. Since antibiotics were first used to treat gonorrhea, the organism has evolved or acquired resistance to multiple classes of antibiotics through nearly all known molecular, biochemical, metabolic, and physiological AMR mechanisms [Reygaert, 2018], including the ability to rapidly and efficiently exchange genes with many commensal Neisseria species. The emergence of resistant strains forced many changes in the therapeutic guidelines, and the switching between agents to newer generations and classes of antimicrobials first every 20 years then every 10 or less. The growing concern on the rate of switching therapies has prompted prominent global health organizations to consider this bacterium as a very serious health challenge globally and in 2012 the World Health Organization (WHO) and CDC formally designed Ng as a "superbug" [WHO, 2017].

Current WHO guidelines for treating uncomplicated Ng infections recommend dual therapy by combining third generation cephalosporine (ceftriaxone or cefixime) and azithromycin. Although the dual use of antibiotics is highly successful in the symptomatic diagnosed population, recently emerging resistance to azithromycin has been observed [CDC, 2019] making ceftriaxone both the first-line treatment and the last remaining single-drug option.

In the US, treatment guidelines were updated in December 2020 and dual therapy is no longer recommended. Instead, uncomplicated gonorrhea should be treated with just one injection of ceftriaxone (500 mg) [St. Cyr, 2020]. Globally however, ceftriaxone susceptibility is diminishing rapidly, 7 countries in western Pacific and Southeast Asian Regions reported more than 5% of isolates with decreased susceptibility or resistance to ceftriaxone [Unemo, 2019; Whittles, 2018]. Dual therapy treatment failure has been recently documented. At least 2 new antibiotics for gonorrhea are under development and currently in clinical trials, but it is still unclear by when a candidate will become widely available for global use. Given the propensity of Ng to develop or acquire resistance to multiple classes of antibiotics, AMR will likely continue to be a serious concern for current and future antibiotics used to treat gonorrhea [Unemo, 2014].

Experts have described the rapid rise of Ng AMR as worrying, acknowledging that the development of new antimicrobials indeed faces more challenges rather than give hope for a solution [Spellberg, 2015]. Estimates are that emerging resistance against ceftriaxone could lead to 1.2 million additional Ng infections within 10 years [Chesson, 2018].

For the above reasons, CDC has classified Ng antimicrobial resistance as an urgent threat among the most worrying AMR problems [CDC, 2019].

Existing (or available) preventive therapies:

There are presently no existing or available preventive therapies (here, vaccines) with the same indication (prevention of gonococcal infections).

Currently, the standard of care (SoC) for preventive gonococcal infections includes behavior changes and enhanced screening. Specifically, for those at risk, annual screening is recommended especially those with inconsistent condom use who are not in mutually monogamous relationships or exchanging sex for money or drugs [LeFevre, 2014]. Upon confirmation of microbiologic diagnosis, the typical treatment consists in antibiotics as mentioned above. Of note, although, the dual use of antibiotics is highly successful (99.2% of uncomplicated urogenital) in the symptomatic diagnosed population, re-infection often occurs [Newman, 2007]. Combined with the fact that the vast majority of gonococcal infections are asymptomatic, a preventive vaccine therapy would represent a substantial improvement in the SOC.

Please refer to the current Investigator's Brochure (IB) for information regarding pre-clinical studies and clinical studies of NgG investigational vaccine**.**

2.3. Benefit/Risk assessment

Detailed information about the known and expected benefits and risks and expected adverse events (AEs) of NgG investigational vaccine can be found in the IB.

Benefit considerations for participants may include the following:

- Potential benefit of developing protection against infection caused by Ng.
- Medical evaluations/assessments associated with study procedures (e.g., physical examination) and frequent testing for Ct and Ng associated with the study conduct.

As with all injectable vaccines, immediate systemic allergic reactions to vaccination can occur. In order to be able to treat participants with an immediate systemic allergic reaction to vaccination, all participants will need to remain under close observation for at least 60 minutes after each study intervention.

As with any randomized study, participants will have the risk of local reactions due to an injection without the benefit of efficacy. Participants will be required to enter information of solicited local reactions in the eDiary and will have to grade if their local reactions are mild, moderate or severe and if severe will be advised to seek medical attention. Placebo (saline) cannot be expected to have any effect on gonorrhea cases.

In terms of study procedures planned before the Interim Analysis outcome:

- Blood sampling is associated with a risk of syncope, dizziness, local reactions, and infection after or during puncture. For this reason, blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the Informed Consent Form (ICF). The amount of blood to be taken for sampling will not be harmful to the subject's health.
- Swabbing and collection of urine samples are routine procedures performed to diagnose STIs. Swabbing must be performed by qualified healthcare professionals. Self-swabbing is only allowed to collect vaginal swabs. Participants must be trained on how to perform self-sampling if this is going to occur. Potential risks associated with swabbing are irritation and bleeding of the interested anatomical site after the procedure.

Overall Benefit: Risk conclusion

For protocol amendment 7:

[redacted]

[redacted]

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 5 Study objectives, endpoints and estimands

Objectives	Endpoint(s) and estimand(s)
Phase 1 – Dose-escalation safety lead-in **Primary**	
To evaluate safety and reactogenicity following administration of the NgG vaccine administered at 3 different doses (12.5 µg, 25 µg and 50 µg)	• Number and percentage of participants reporting each solicited administration site event during the 7-day follow-up period after each dose (Day 1 and Day 61). • Number and percentage of participants reporting each solicited systemic event during the 7-day follow-up period after each dose (Day 1 and Day 61). • Number and percentage of participants reporting unsolicited AEs during the 30-day follow-up period after each dose (Day 1 and Day 61). • Number and percentage of participants reporting SAEs from Day 1 after the first dose up to study end (Day 241). • Number and percentage of participants reporting AEs leading to withdrawal from Day 1 after the first dose up to study end (Day 241). • Number and percentage of participants with haematological and biochemical laboratory abnormalities, compared to baseline values (Screening/Day 1 and Day 61), at Day 8 and Day 68, respectively.
Phase 2 – Efficacy PoC **Primary**	
To demonstrate the efficacy of the NgG vaccine in preventing gonorrhea cases[1]	• Incidence rates of confirmed gonorrhea cases from 1 month (Day 91) to 13 months post-Dose 2 (Day 451).
To evaluate safety and reactogenicity following administration of the NgG vaccine.[2.]	• Number and percentage of participants reporting each solicited administration site event during the 7-day follow-up period after each dose (Day 1 and Day 61). • Number and percentage of participants reporting each solicited systemic event during the 7-day follow-up period after each dose (Day 1 and Day 61). • Number and percentage of participants reporting unsolicited AEs during the 30-day follow-up period after each dose (Day 1 and Day 61). • Number and percentage of participants reporting SAEs from Day 1 after the first dose up to study end (Day 451). • Number and percentage of participants reporting AEs leading to withdrawal from Day 1 after the first dose up to study end (Day 451). • Number and percentage of participants with haematological and biochemical laboratory abnormalities, compared to baseline values (Screening and Day 61), at Day 8 and Day 68, respectively.[3]

Objectives	Endpoint(s) and estimand(s)
Phase 2 – Efficacy PoC **Secondary**	
To evaluate the efficacy of the NgG vaccine in preventing gonorrhea cases with and without Ct co-infection	• Incidence rates of confirmed gonorrhea cases with and without Ct co-infection from 1 month (Day 91) to 13 months post-Dose 2 (Day 451).
To evaluate the efficacy of the NgG vaccine in preventing symptomatic gonorrhea cases	• Incidence rates of symptomatic and confirmed gonorrhea cases from 1 month (Day 91) to 13 months post-Dose 2 (Day 451).
Tertiary	
CCI [redacted]	

Objectives	Endpoint(s) and estimand(s)
CCI [redacted]	
To evaluate the humoral immune responses to the NgG vaccine.	• Anti-NgG IgG antibodies Geometric mean concentrations (GMCs) at Day 1, Day 31, Day 61, Day 91, and Day 451. • hSBA Geometric mean titres (GMTs) against Ng strain at Day 1, Day 31, Day 61, Day 91, and Day 451.[8]
To explore the association between humoral immune response and vaccine efficacy.	• All endpoints of PoC efficacy (primary, secondary and tertiary objectives) and immune response (tertiary objectives) may apply to this endpoint.

A&E = Accident & Emergency; *Ct* = *Chlamydia trachomatis*; ER = emergency room; PoC = Proof of Concept, HTD = highest tolerated dose

[1]A gonorrhea case is defined as a participant with at least 1 sample collected during the defined period confirmed by FDA-approved (nucleic acid amplification test) NAAT as positive for Ng by central laboratory, regardless of the presence or absence of symptoms and irrespective of participant history of gonococcal infection. For the efficacy primary objective, only cases from urogenital and/or anorectal sites will be considered. For the secondary and tertiary efficacy objectives, cases from urogenital, anorectal and/or pharyngeal sites will be considered unless otherwise specified. For the purpose of the case definition only the first confirmed gonococcal infection will contribute.

[2]In case more than one dose will show tolerability in the safety lead-in part, the highest tolerated dose (HTD) and the dose below the highest tolerated will be tested in the PoC (text and figures in the protocol reflect this scenario). In case only the lowest dose shows adequate tolerability, this will be the only dose tested in the PoC

[3]The evaluation of the endpoint will be assessed in the subsets for intensive safety monitoring.

CCI [redacted]

CCI

Details related to attributes of estimand covering intercurrent events, population and treatment definition are provided in the Section 9.

4. STUDY DESIGN

4.1. Overall design

This is a Phase 1/2, placebo-controlled, observer-blind, randomized, multi-centric study.

Figure 1 presents an overview of the whole study design.

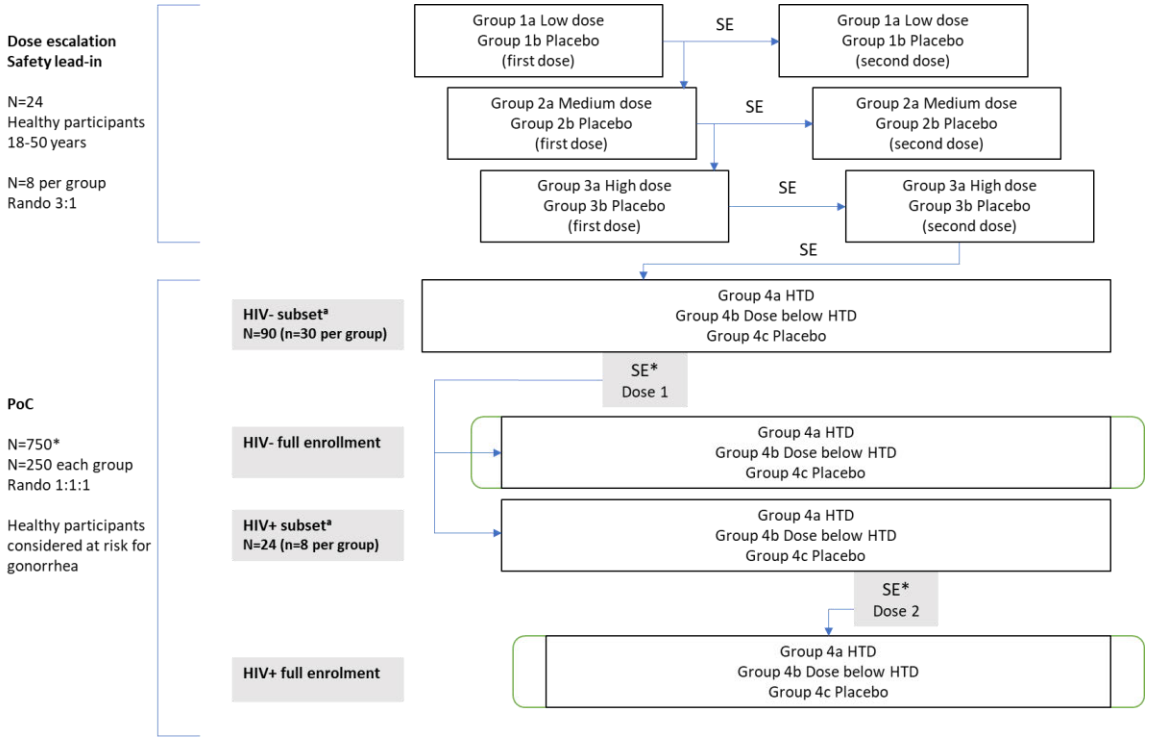
The study will include the following parts:

- Phase 1 – Dose-escalation safety lead-in in healthy participants (Figure 2).
- Phase 2 – Efficacy PoC in healthy participants considered at risk for gonorrhea (Figure 3).

The doses to be tested for efficacy will be selected based on the safety evaluation performed during the dose-escalation safety lead-in: in case more than one dose will show tolerability, the highest tolerated dose (HTD) and the dose below the highest tolerated (i.e., 2 doses) will be advanced in the efficacy PoC part of the study and compared versus placebo. In case only the lowest dose shows adequate tolerability, this will be the only dose tested in the PoC versus placebo.

For more detailed information on study groups and treatments administered, refer to Figure 1, developed considering 2 doses are selected from the dose-escalation safety lead-in.

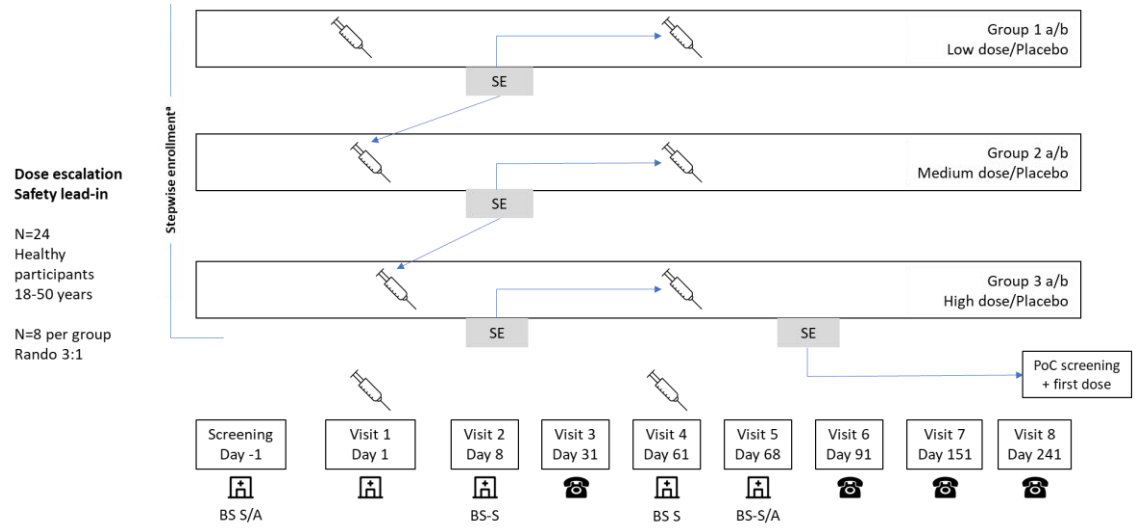
Figure 1 Overall design



Rando = Randomization; SE = Safety evaluation by Safety Review Team (SRT)/ iSRC chair (blinded review) or iSRC (unblinded review); SE* = Safety evaluation by Safety Review Team (SRT) and unblinded safety evaluation by iSRC; PoC = Proof of Concept; HTD = highest tolerated dose; HIV - = HIV negative; HIV + = HIV positive

4.1.1. Phase 1: study design of dose-escalation safety lead-in part in healthy participants

Figure 2 Study design overview of dose-escalation safety lead-in in healthy participants



Grp = Group; a/b = vaccine/placebo; Rando = Randomization; SE = Safety evaluation by SRT/ iSRC chair (blinded review) or iSRC (unblinded review); PoC = Proof of Concept; BS-S = Blood Sample for Safety evaluation; BS-S/A = Blood Sample for Safety evaluation and assay development.

[a]The administration of Dose 2 in the concerned group and the administration of dose 1 for the next group will not be permitted until receipt of the favorable outcome of the safety assessment committees' evaluation (SRT/iSRC).Refer to Section 4.1.1, Safety monitoring for more information

Vaccine/Placebo administration ☎ Phone contact. Clinic visit.

- **Type of study:** self-contained
- **Experimental design:** Phase 1, observer-blind, randomized, placebo controlled, single center study with staggered enrolment of participants in 3 groups receiving different vaccine formulations in the dose-escalation safety lead-in epochs.
- **Duration of the study:** The total duration of the study, per participant, will be approximately 8 months. Participants will have to attend/perform 5 visits and 4 phone calls.
- **Study groups:** Table 6

Table 6 Study groups, intervention and blinding in dose-escalation safety lead-in

Study groups	Number of participants	Age (Min-Max)	Treatment name	Blinding
Group 1a Low dose	6	18 - 50 years	NgG 12.5 µg	Observer-blind
Group 1b Placebo	2		Placebo	
Group 2a Medium dose	6		NgG 25 µg	
Group 2b Placebo	2		Placebo	
Group 3a High dose	6		NgG 50 µg	
Group 3b Placebo	2		Placebo	

- **Control:** placebo control.
- **Vaccination schedule(s):**
  - **Group 1 Low dose** (first group), 2 parallel groups:
    - **Group 1a Low dose**: 2 doses of NgG investigational vaccine 12.5 µg at Day 1 and Day 61
    - **Group 1b Placebo**: 2 doses of placebo (saline) at Day 1 and Day 61
  - **Group 2 Medium dose** (second group), 2 parallel groups:
    - **Group 2a Medium dose**: 2 doses of NgG investigational vaccine 25 µg at Day 1 and Day 61
    - **Group 2b Placebo**: 2 doses of placebo (saline) at Day 1 and Day 61
  - **Group 3 High dose** (third group), 2 parallel groups:
    - **Group 3a High dose**: 2 doses of NgG investigational vaccine 50 µg at Day 1 and Day 61
    - **Group 3b Placebo**: 2 doses of placebo (saline) at Day 1 and Day 61.

  For each group, the enrolment of 8 participants with an overall randomization of a 3:1 ratio either to the NgG investigational vaccine or to the placebo is planned (details are given below in bullet "Safety monitoring").
- **Treatment allocation:** randomized, subjects will be allocated to a study group using an automated, electronic System Built for Internet Randomization (SBIR).
- **Blinding:** The study will be observer blind (Table 6).
- **Sampling schedule:** Blood samples for laboratory safety evaluation and assay development will be drawn from all participants. Blood samples will be collected at the timepoints as detailed in Table 1.
- **Data collection:** standardised Electronic Case Report Form (eCRF). Solicited AEs will be collected using a participant Diary (electronic Diary [eDiary])

- **Safety monitoring:**

For each group in the dose-escalation safety lead-in, all the available safety data collected up to the Day 8 post-Dose 1 visit from the participants (including laboratory assessments at Day 8) will be evaluated. The Safety Review Team (SRT) and the internal Safety Review Committee (iSRC) Chair will evaluate all available cumulative blinded safety data and will confirm the administration of the second dose in the concerned group and the start of enrolment in the subsequent group. In case blinded data are of concern for SRT and iSRC Chair, unblinded data may be evaluated by iSRC (conditional iSRC) and only after positive opinion by iSRC the next step can start.

The administration of dose 2 for the concerned group and the administration of dose 1 for the next group will not be permitted until receipt of the favorable outcome of the safety assessment committees' evaluation (SRT/iSRC).

All the blinded data collected for all groups up to Day 68 post-Dose 2 visit of the third group (3 a/b) will be cumulatively reviewed by the SRT and, conditionally by iSRC.

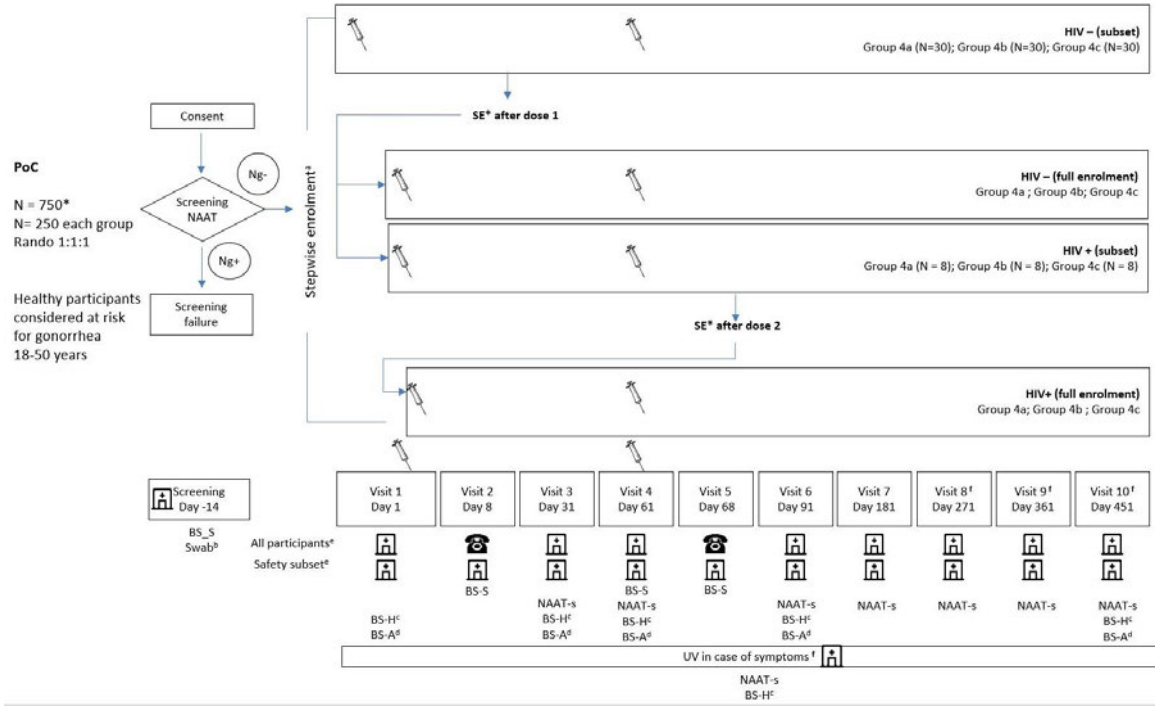
After the SRT/iSRC data review of all cumulative data collected for Group 1, Group 2 and Group 3 after dose 2 of the third group of the dose-escalation safety lead-in, the enrolment of the PoC participants (Groups 4a/b/c) in the vaccine target population can start.

For the dose-escalation safety lead-in, the doses administration must be sequential, only 1 participant will receive the product dose per day (and per site if applicable). Avoiding parallel doses administration and leaving at least 24 hours between 2 consecutive participants will ensure that, in the event of an acute adverse reaction, the site will provide the required medical attention for the individual concerned and enough time to evaluate whether other participants can be exposed to the dose administration will be secured.

All participants in the study will be closely monitored for at least 60 minutes post-administration for safety surveillance.

4.1.2. Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea

Figure 3 Study design overview of efficacy PoC in participants considered at risk for gonorrhea



NAAT = nucleic acid amplification test; NAAT-s = NAAT samples include swabs (urogenital, anorectal, and pharyngeal sites) or first-catch urine sample (male participants and those with a penis); Rando = Randomization; PoC = Proof of Concept¸ BS-A = Blood Sample for Assay Development; BS-H = Blood Sample for Humoral immune response; BS-S = Blood Sample for Safety evaluation (subset onlye); UV = Unscheduled visit; HIV - = HIV negative; HIV + = HIV positive; SE* = Safety evaluation by Safety Review Team (SRT) and unblinded safety evaluation by iSRC

*Initial target sample size. See Section 9.6 for sample size determination.

[a]The enrolment in the PoC part will proceed stepwise with HIV negative individuals to be enrolled first and then opening the recruitment to HIV positive participants. Refer to Safety monitoring for more information

[b]Screening for gonorrhea can be done as per local standard practice

[c]BS-H: Blood sample for humoral immune response from all participants: testing strategy is described in Section 8.1.1

[d]BS-A: Blood sample for assay development from all participants

[e]For participants in the safety subset, a clinic visit will apply at Visit 2 (Day 8) and Visit 5 (Day 68), for all other study participants a phone call will apply.

[f]After protocol amendment 7 is effective, the following activites are not performed: NAAT-s (Visits 8, 9, 10); BS-H and BS-A (Visit 10); NAAT-s and BS-H during UV.

Vaccine/Placebo administration ☎ Phone contact. Clinic visit.

- **Type of study:** self-contained
- **Experimental design:** Phase 2, observer-blind, randomized, placebo controlled, multi-centric study with 3 parallel groups (or 2 parallel groups in case only the lowest dose shows adequate tolerability in the Phase 1 part) in the PoC vaccination epoch.
- **Duration of the study:** The total duration of the study, per participant, will be approximately 15 months. All participants will have to attend a screening visit; participants in the safety subset will have to attend/perform 10 visits, all other participants will have to attend/perform 8 visits and 2 phone calls.

  Unscheduled visit will be arranged in case of suspicion of possible gonococcal infection (after protocol amendment 7 is effective, unscheduled visits will not be conducted; participants will be followed as appropriate, according to the local medical practice).
- **Primary Completion Date (PCD):** Visit 10 (Day 451)

  Refer to glossary of terms for the definition of PCD.
- **End of Study (EoS):** Last subject last visit (LSLV) (Visit 10).

  Refer to Section 4.4 for the definition of EoS.
- **Study groups:** Table 7

Table 7 Study groups, intervention and blinding in efficacy PoC

Study groups	Number of participants*	Age (Min-Max)	Treatment name	Blinding
Group 4a HTD	250	18 - 50 years	NgG HTD	Observer-blind
Group 4b dose below HTD	250		NgG below HTD	
Group 4c Placebo	250		Placebo	

HTD = highest tolerated dose
*initial target sample size. See Section 9.6 for sample size determination.

- **Control:** placebo control
- **Vaccination schedule(s):**
  - **Group 4a Vaccine:** A series of 2 doses of NgG highest tolerated dose* given approximately 2 months apart (Days 1 and 61)
  - **Group 4b Vaccine:** A series of 2 doses of NgG dose below highest tolerated dose* given approximately 2 months apart (Days 1 and 61)

    * The doses to be tested for efficacy will be selected based on the safety evaluation performed during the dose-escalation safety lead-in: in case more than one dose will show tolerability, the highest tolerated dose (HTD) and the dose below the HTD will be advanced in the efficacy PoC and tested versus placebo. In the case that only the lowest dose from the dose-escalation safety lead-in part shows adequate tolerability, only this dose will be advanced to the efficacy PoC part and tested versus the placebo
- **Group 4c Placebo:** A series of 2 doses of placebo (saline) given approximately 2 months apart (Days 1 and 61)
- **Treatment allocation:** randomized, subjects will be allocated to a study group using an automated, electronic system (SBIR).
- **Blinding:** Observer-blind (Table 7).
- **Vaccination visits:** Visit 1 (Day 1) and Visit 4 (Day 61) will happen at the clinic site.
- **Sampling schedule:**
- Blood samples for laboratory safety evaluation will be drawn from all participants in the two intensive safety monitoring subsets (as defined here below) at Screening, Visit 2 (Day 8), Visit 4 (Day 61), and Visit 5 (Day 68).

  Blood samples for humoral immunogenicity will be drawn from all participants at Visit 1 (Day 1), Visit 3 (Day 31), Visit 4 (Day 61), Visit 6 (Day 91), Visit 10 (Day 451), and at unscheduled visit(s) when performed. Note: after protocol amendment 7 is effective, planned blood samples at Visit 10 (Day 451) will not be drawn. ELISA like immunoassay will be performed in all participants. Approximately, the first 100 participants enrolled in each arm (n=300 total), and all participants with confirmed gonococcal infections will be tested for human serum bactericidal assay (hSBA).
  - Blood samples for assay development will be drawn from all participants at Visit 1 (Day 1), Visit 3 (Day 31), Visit 4 (Day 61), Visit 6 (Day 91), and Visit 10 (Day 451). Note: after protocol amendment 7 is effective, planned blood samples at Visit 10 (Day 451) will not be drawn.

- NAAT samples* including swabs (urogenital, anorectal, and pharyngeal sites) and/or first-catch urine samples for male participants and those with a penis, will be collected from all participants at Screening, Visit 3 (Day 31), Visit 4 (Day 61), Visit 6 (Day 91), Visit 7 (Day 181), Visit 8 (Day 271), Visit 9 (Day 361), Visit 10 (Day 451), and at unscheduled visit(s) when performed
  Note: after protocol amendment 7 is effective, NAAT samples at Visit 8 (Day 271), Visit 9 (Day 361), Visit 10 (Day 451), will not be collected nor at unscheduled visit(s) because they will no longer be conducted

  ** Sampling for Ct/Ng must be performed by qualified healthcare professionals. Self-swabbing is only allowed to collect vaginal swab. Participants must be trained on how to perform self-sampling if this is going to occur. All participants will be tested from all 3 anatomical sites (urogenital, rectal, and pharyngeal). A first-catch urine sample will be collected instead of a swab for the detection of genital infection in male participants (and those with a penis),, a vulvo/vaginal or cervical swab will be collected for the detection of genital infection in female participants (and those with a vagina). Use of vaginal medicinal treatments, vaginal moisturizers, vaginal wash/hygiene products, containing carbomer should be avoided in the 7 days before planned visits when vaginal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test. Similarly, use of anorectal medicinal treatments, anorectal lubricants and anorectal wash/hygiene products containing carbomer, should be avoided in the 7 days before planned visits when anorectal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test.*

- **Unscheduled visits** (after protocol amendment 7 is effective, unscheduled visits will not be conducted; participants will be followed as appropriate, according to the local medical practice): participants will be offered an unscheduled visit in any of the following circumstances:
  - Participant presents with symptoms suggestive of possible gonococcal infection, except pharyngitis.
  - Participant tested positive for Ng outside of the study schedule and has not yet received treatment.
  - Participant is a recent sexual contact of a partner with a confirmed diagnosis of gonococcal infection.

  An unscheduled visit should be booked only outside the time allowance for scheduled visits unless the scheduled visit has already occurred. All reasonable efforts should be made to ensure that participants attend the clinic site if they are in need for an urgent unscheduled appointment (i.e., setting up a walk-in or fast track appointment service).

Should a study participant show signs and/or symptoms suggestive of gonococcal infection either at a scheduled or unscheduled visit, a double sampling at the affected anatomical site will be executed: one will be processed by the local laboratory of reference, the other one will be processed by the GSK designated laboratory. Test execution at local laboratory will ensure results availability in shorter timeframe and a timely treatment of confirmed positive cases. In case of discrepant results between the local and the GSK designated laboratory, only the result from the GSK designated lab will be considered for the study endpoints. Note: after protocol amendment 7 is effective in case participant shows signs and/or symptoms suggestive of gonococcal infection the sampling for the GSK designated laboratory will not be performed; the participant will be managed according to the local medical practice.

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If a participant was diagnosed by any positive Ng test other than protocol mandated Ng tests (outside of the study schedule) and already received anti gonococcal treatment, there is little chance to detect bacterial genetic material and the repetition of NAAT may not be needed. The investigator should obtain records of the test results that confirm the gonococcal infection, including but not limited to NAAT positivity for Ng, or positive culture and/or microbiological isolation of Ng. In case the test results confirming the gonococcal infection cannot be obtained, the investigator will have the possibility to document the gonococcal infection based on participant report of positive Ng test only.

- Ad-hoc NAAT visit (after protocol amendment 7 is effective, ad-hoc NAAT visits will not be conducted): when a Ng diagnosis is made by central laboratory (1 or more anatomical sites confirmed by NAAT as positive for Ng by central laboratory) at or beyond 1 month post-Dose 2 and administration of antibiotic treatment against Ng is planned at the study site, efforts will be made to collect ad-hoc NAAT sample(s) for central laboratory prior to antibiotic treatment administration. Ad-hoc NAAT samples may only be collected for anatomical sites that previously tested positive for Ng by NAAT, to explore the Ng infection status at the time of antibiotic treatment in participants with a confirmed gonorrhea case. If antibiotic treatment was already administered before central laboratory NAAT results became available, no ad-hoc NAAT visit will take place.
  An ad-hoc NAAT visit should be booked only outside the time allowance for scheduled visits unless the scheduled visit has already occurred, otherwise a scheduled visit will take place.
- **Data collection:** standardised eCRF. Solicited AEs will be collected using a subject eDiary.

- **Safety monitoring:**

Subsets for intensive safety monitoring in the efficacy PoC part:

The enrolment in the PoC part will proceed stepwise with HIV negative individuals to be enrolled first and then opening the recruitment to HIV positive participants.

For both HIV positive and HIV negative participants an intensive safety monitoring will be applied to a subset composed of the first subjects enrolled as detailed below:

After positive outcome of the dose escalation safety lead-in part of the study (blinded SRT/iSRC chair review post-Dose 2) a safety subset of 30 HIV negative participants per group **(HIV negative safety subset)** will be enrolled and administered with first and second dose. A blood sample will be taken from these participants specifically for hematology/biochemical analysis at screening and pre-dose 2 (screening and Day 61) as baseline values and 7 days post each dose.

All cumulative safety data collected up to 7 days **post-Dose 1** of the last participant belonging to the HIV negative safety subset (along with available safety data collected after the second dose administered to the HIV negative safety subset, if applicable) will undergo an unblinded analysis by the iSRC. Only in case of a positive outcome of the unblinded iSRC evaluation, the administration of dose 1 and dose 2 can proceed in all HIV negative participants and enrolment can be opened to people living with HIV matching with the inclusion/exclusion criteria depicted below. The first 8 HIV positive participants per group will constitute the **HIV positive safety subset*)*** from whom blood sample for safety evaluation will be taken at screening and pre-dose 2 (screening and Day 61) as baseline values and 7 days post each dose, similarly to what is described above.

The safety data 7 days **post-Dose 2** administered to last participant belonging to the HIV positive safety subset will undergo an unblinded analysis by the iSRC and will determine whether the enrolment can progress to further HIV positive participants. The administration of the first doses in HIV positive participants will be allowed in more than 1 participant per day but vaccination of 2 participants simultaneously will not be possible**,** i.e., minimum 2 hours apart and 4 participants per day per study center at maximum, to ensure that, in the event of an acute adverse reaction, the site can provide the required medical attention for the individual concerned.

Of note, the iSRC in charge for the safety evaluation in the PoC part (i.e. for HIV positive and HIV negative safety subsets) will include a member who is expert in the area of concern and who is external to GSK.

Overall, HIV infected participants meeting the eligibility criteria for study participation will account for, at most, 20% of the entire study population enrolled in the PoC part of the study.

After completion of the above-mentioned intensive safety monitoring evaluations, for the whole study duration, in case ≥1 participant in the PoC part experiences a death or life-threatening serious adverse event (SAE) that is at least possibly related to the study product, the study will be paused (Section 8.2.3.3, Table 13). Study activities may proceed if review of safety data does not demonstrate safety concerns.

4.2. Scientific rationale for study design

The purpose of this Phase 1/2 first time in human – proof of concept (FTiH-PoC) study is to evaluate safety and reactogenicity, to demonstrate efficacy and to explore immunogenicity of GSK Biologicals' NgG investigational vaccine compared to placebo (saline), both administered in a 2-dose schedule (0-2 month).

This FTiH-PoC study aims to provide an early evaluation of the efficacy of the investigational vaccine as there are no established immunogenicity correlates of protection against *Ng* infections.

Ng is a strictly human bacterial pathogen causing gonorrhea, the second most prevalent bacterial sexually transmitted infection (STI) worldwide, with 87 million new cases of infections estimated globally in 2016 [Rowley, 2019]. *Ng* is transmitted through genital, oral and anal sexual contact infecting mucosal surfaces at these sites and, if not detected and/or appropriately treated, it can progress from a less severe condition and result in serious complications and sequelae for both sexes.

Standard of care relies on the use of antibiotics and there are relevant concerns with the increasing antibiotic resistance. There are presently no existing or available preventative therapies therefore a vaccine would contribute significantly to the current management of the disease.

Despite decades of vaccine research, no vaccines against gonorrhea have been successful in preventing the infection. However, N. meningitidis serogroup B vaccination has shown modest but clinically relevant effectiveness in preventing Ng infections: 3 case control studies from New Zealand [Petousis-Harris, 2017] and the United States [Abara, 2022; Bruxvoort, 2022] have shown that individuals who received meningitis B vaccination were less likely to contract gonorrhea, compared to their unvaccinated peers. Notably, in the aforementioned studies, a detrimental effect on vaccine effectiveness against gonococcus was observed in case of Ng-Ct coinfection. A consensus on the factors explaining this detrimental effect is not currently reached in the scientific community. Nevertheless, the current study was designed to evaluate the efficacy of GSK Biologicals' NgG investigational vaccine against Ng infections with and without Ct coinfection as a secondary objective.

[redacted] Finally, the humoral immune response to the NgG vaccine will be evaluated, and attempts will be made to identify an immune correlate of protection against gonorrhea infection.

4.2.1. Participant input into design

Participants were not involved in the design of the study as the study plans to recruit healthy adults at risk for gonorrhea.

4.2.2. Case definition

A gonorrhea case is defined as a participant with at least 1 sample collected during the defined period that is confirmed at the central lab by NAAT as positive for Ng, regardless of the presence or absence of symptoms and irrespective of participant history of gonococcal infection. For the purpose of the case definition only the first confirmed gonococcal infection will contribute.

- **For the primary objective**, only cases from **urogenital or anorectal** samples occurring from 1 month after the second vaccination (Visit 6, Day 91) until Visit 10, (Day 451) will be considered.
- **For the secondary and tertiary objectives**, overall cases (**urogenital, anorectal or pharyngeal**), and by each anatomical site (urogenital/anorectal/pharyngeal) will be considered unless otherwise specified, in accordance with the timepoints defined in Table 2 and **Table** 3.

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- A participant with positive samples at multiple anatomical sites will be counted as 1 overall case. Cases with 1 or more positive sample(s) from pharyngeal site(s), but negative sample(s) from the urogenital and anorectal sites will not be counted for the primary endpoint but will contribute to the secondary and tertiary endpoints.
- In case a highly effective antibiotic treatment is administered, the gonorrhea case will be considered as resolved 7 days after the completion of antibiotic treatment, or alternatively, at the date of a subsequent NAAT negative for Ng by central lab at the affected anatomical location, whichever comes first. In case an alternative antibiotic treatment is administered, the gonorrhea case will be considered as resolved at the date of subsequent test of cure (TOC, see Section 8) negative for Ng at the affected anatomical location, or at the date of a subsequent NAAT negative for Ng by central lab at the affected anatomical location, whichever comes first. In case no antibiotic treatment is administered, the gonorrhea case will only be considered as resolved if a subsequent NAAT negative for Ng by central lab at the affected anatomical location is obtained.. In case of early gonococcal infection prior to 1 month post-Dose 2, a **subsequent** gonorrhea case may be considered for the primary endpoint only if **the** previous gonococcal infection is considered as resolved as described above. For further details on the case definition for primary and secondary endpoints, please refer to the statistical analysis plan (SAP).

- CCI [redacted]
- CCI [redacted]

The primary endpoint will be independent of the presence or absence of co-infection with Ct (i.e., NAAT confirmed gonococcal and Ct infections identified at the same visit). Co-infection will be assessed in the corresponding secondary endpoint and positivity for Ct during the study execution, will not exclude the participant from the study.

Symptomatic gonorrhea cases are defined as positive Ng NAAT test in the presence of symptoms suggestive of gonorrhea at the infected anatomical site. [redacted] for which the NAAT is not validated, a positive [redacted] or microbiological isolation of Ng [redacted], as explained below.

Symptoms associated with gonococcal infection must be recorded in the electronic Case Report Form (eCRF). Investigator's clinical judgement should apply in case of uncertain symptoms or other possible diagnosis (e.g., urinary tract infection, sexually acquired reactive arthritis).

<u>For male participants:</u>

- Urethritis*: purulent discharge, burning pain in the urethra, dysuria, haematuria, frequency in urination.
- Epididymo-orchitis: testicular pain, tenderness, and oedema, erythema of the scrotum. CCI [redacted]
  CCI [redacted]

<u>For female participants:</u>

- Vulvovaginitis*/ cervicitis: purulent discharge, discomfort, lower abdominal pain, dyspareunia, metrorrhagia, dysuria. CCI [redacted]
  CCI [redacted]
  CCI [redacted]
  CCI [redacted]

- PID: dyspareunia, metrorrhagia, lower abdominal pain, fever. Adnexal tenderness during bi-manual examination and or cervical excitation tenderness. Diagnosis of PID should follow local guidelines (i.e., microscopic findings of neutrophils in the cervical exudate). CCI [redacted]

  *Urethritis and vulvovaginitis may develop in participants who have undergone gender affirming surgery of their genitals, according to their opposite sex at birth.

<u>For both:</u>

- Proctitis: mucopurulent anal discharge, anorectal bleeding, anorectal pain, anorectal itch, constipation, sensation of rectal fullness or incomplete defecation, and tenesmus.
- Proctocolitis: purulent discharge, pain passing stool, blood in stool, pain during receptive anal intercourse. CCI [redacted]
- Pharyngeal infections due to gonococcus are mostly asymptomatic unless a positive NAAT for gonorrhea from CCI [redacted]; even in the presence of pharyngitis it is not always possible to ascertain the aetiology. Also, individuals with pharyngitis do not attend the STI clinics but rather seek for medical attention from their general practitioner or family doctor. CCI [redacted]
- Conjunctivitis: conjunctivitis due to *Ng* is uncommon and usually associated with simultaneous positivity of the urogenital tract. Patients with gonococcal conjunctivitis do not normally attend the STI clinic, unless they are also experiencing genital symptoms. For this reason, if a participant is diagnosed with gonococcal conjunctivitis by an ophthalmologist or general practitioner, in the absence of positive urogenital, pharyngeal or anorectal NAAT, the investigator should obtain medical records and clinically validate the diagnosis. CCI [redacted]
- Perihepatitis: also known as “Fitz -Hugh -Curtis Syndrome”, it is an inflammation of the liver capsule with adhesion formation resulting in right upper quadrant pain. It is an uncommon chronic manifestation of PID affecting women of child-bearing age, though, cases have been described in men also. Given the severity of the clinical picture, participants with suspected gonococcal perihepatitis will most likely attend the emergency department or hospitalized to perform diagnostic test, including laparoscopy, which remains the gold standard for diagnosis. Etiological diagnosis is made through cultures or NAAT from genital secretions. CCI [redacted]

- Disseminated gonococcal infection (DGI): it usually comprises 2 major clinical syndromes: (1) arthritis-dermatitis syndrome; and, (2) localized purulent arthritis without associated skin lesions. There are, however, patients who present with symptoms that overlap between these 2 classic presentations. Although localized infection of the genitourinary tract, rectum, or pharynx by Ng is a prerequisite for dissemination, patients with clinical manifestations of DGI often do not manifest symptoms of localized gonococcal infection.
  - Arthritis-dermatitis syndrome: this is a form of DGI that usually comprises a triad of manifestations which include tenosynovitis, dermatitis, and polyarthralgia. It is also often associated with constitutional symptoms such as fever, chills, and body malaise. Tenosynovitis is a unique finding in gonococcal arthritis and is usually not seen in other forms of septic arthritis. It is demonstrated by tenderness along the flexor sheath and pain on a passive extension during a physical examination. It usually affects multiple tendons, more commonly the fingers, wrists, toes, and ankles. Polyarthralgia is typically asymmetric and may affect both large and small joints. Skin lesions occur in up to 75% of cases and are frequently seen in the trunk and extremities and usually spares the face. Although a large variety of skin lesions have been observed, DGI is most commonly associated with pustular or vesicular lesions. Other skin manifestations that occur less frequently include macules, papules, bullae, or nodules. Skin lesions are characteristically transient and may disappear after several days even without treatment.
  - Localized septic arthritis: this syndrome usually presents as a mono-arthritis or asymmetric oligo- or polyarthritis with pain and swelling of one or more joints. Most patients do not present with systemic symptoms such as fever or chills. Joints that are commonly affected include knees, ankles, wrist, and elbow.

Definitive diagnosis of DGI or gonococcal arthritis is made through the identification of the etiologic pathogen in a specimen taken from a non-mucosal site (such as blood, synovial fluid, or skin lesions). Microbiologic tests, however, are not always positive and in such cases, diagnosis is made clinically. A clinical diagnosis may be supported by evidence of Ng infection from specimens obtained from mucosal sites.

Because participants with suspected DGI or perihepatitis do not usually attend the STI clinic, given the severity of their symptoms, the diagnosis may be made by a physician not involved in the study. The investigator should obtain the medical records of the participant and confirm the diagnosis. CCI [redacted] CCI [redacted]

- "Other extragenital CCI [redacted] infection": Ng may be responsible of several other uncommon extra genital manifestations, secondary to dissemination from the blood stream. If a participant is diagnosed with any such condition, which is not listed above in this section, it will be classified as "other extragenital CCI [redacted] infection". As for DGI and perihepatitis, if the diagnosis is made by a physician not involved in the study, the investigator should obtain all medical records and confirm the diagnosis.

According to the study design and the study objectives, gonococcal infections (either (asymptomatic or symptomatic) will not be captured not managed as an AE/SAEs, but instead will be considered Disease-Related- Events (DREs). Accordingly, these infections will be reported in the eCRF and analyzed as secondary objectives.

Participants with a diagnosis of gonococcal infection will be treated with the standard of care and assessed for recovery in the healthcare facility where they were evaluated.

4.3. Justification for dose

[redacted]

4.4. End of Study definition

A participant is considered to have completed the study if the participant returns for the last visit or is available for the last visit as described in the protocol as described below:

- Dose-escalation safety lead-in: Groups 1a to 3b: Visit 8
- Efficacy PoC: Groups 4a to 4c: Visit 10

End of study: Last subject last visit (LSLV) (Visit 10).

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardise the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion criteria

All participants must satisfy ALL the following criteria at study entry:

5.1.1. Inclusion criteria for the dose-escalation safety lead-in part

- Participants, who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the eDiary, return for follow-up visits).
- Written or witnessed/thumb printed informed consent obtained from the participant prior to performance of any study-specific procedure.
- Healthy participants as established by medical history, clinical examination and laboratory assessment.
- A participant between and including 18 and 50 years of age at the time of informed consent.
- Female participants of non-childbearing potential may be enrolled in the study (refer to Section 10.4.1 for definition of women of non-childbearing potential).
- Female participants of childbearing potential (refer to Section 10.4.1 for definition of women of childbearing potential) may be enrolled in the study if the participant:
  - has practiced adequate contraception for 1 month prior to study intervention administration, and
  - has a negative pregnancy test on the day of study intervention administration, and
  - has agreed to continue adequate contraception during the entire treatment period and for 1 month after completion of the study intervention administration series.

5.1.2. Inclusion criteria for the efficacy PoC part

- Participants, who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the eDiary, return for follow-up visits).
- Written or witnessed/thumb printed informed consent obtained from the participant prior to performance of any study-specific procedure.

- Healthy participants as established by:
  - **For the 2 intensive safety monitoring subsets (i.e., first 30 HIV negative subjects per group followed by first 8 HIV positive subjects per group):** medical history, clinical examination, and laboratory assessment.
  - **For all the remaining participants**: medical history, clinical examination.
- At risk for gonococcus infections based on sexual behavioral characteristics: this may include men having sex with men (MSM), pre-exposure prophylaxis (PrEP) for HIV users, individuals who engage in transactional sex participants with current or past STI diagnosis, participants at time of STI screening or seeking other STI services.
- A participant between and including 18 and 50 years of age at the time of informed consent. Transgender men and women, and other gender non-conforming people who identify themselves as neither men nor women may be enrolled into the study, based on their risk factors. For the purpose of this study, they will be followed up according to their biological sex (sex at birth), sexual orientation, and genital/sexual anatomy.
- Participants of non-childbearing potential may be enrolled in the study (refer to Section 10.4.1 for definition of women of non-childbearing potential). This includes *trans*men that have not undergone gender affirming surgery of their genitals.
- Participants of childbearing potential (refer to Section 10.4.1 for definition of women of childbearing potential) may be enrolled in the study if the participant:
  - has practiced adequate contraception for 1 month prior to study intervention administration, and
  - has a negative pregnancy test on the day of study intervention administration, and
  - has agreed to continue adequate contraception during the entire treatment period and for 1 month after completion of the study intervention administration series.

A list of highly effective methods of contraception acceptable for this study, including specific recommendations for contraception in *trans*men, is available in Section 10.4.2

5.2. Exclusion criteria

The following criteria should be checked at the time of study entry. The potential participant MUST NOT be included in the study if ANY exclusion criterion applies:

5.2.1. Medical conditions

5.2.1.1. Dose-escalation safety lead-in part

- Any clinically significant** hematological (hemoglobin level, white blood cell, lymphocyte, neutrophil, platelet) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen) laboratory abnormality.

  ** The investigator should use his/her clinical judgment to decide which abnormalities are clinically significant.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention(s).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Hypersensitivity to latex.
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory tests.
- Recurrent history or uncontrolled neurological disorders or seizures.
- History of invasive meningococcal disease.

5.2.1.2. Efficacy PoC part: HIV negative intensive safety monitoring subset (i.e. first 30 HIV negative subjects per group)

- Persons under guardianship or trusteeship.
- Persons deprived of liberty.
- Gonococcal infection identified by a positive NAAT within 14 days prior to randomization.*

  *Participants that are confirmed as positive for Ng by NAAT will be invited to participate in a re-screen visit after receiving appropriate antibiotic treatment.
- Any clinically significant** hematological (hemoglobin level, white blood cell, lymphocyte, neutrophil, platelet) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen) laboratory abnormality.

  ** The investigator should use his/her clinical judgment to decide which abnormalities are clinically significant.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.

- History of severe allergic reactions and/or anaphylaxis, or any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention(s).
- Bleeding diathesis or any other condition that would contraindicate intramuscular administration.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Known seropositivity for HIV infection, regardless of viremia and CD4 cell count.
- Hypersensitivity to latex.
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory tests.
- Recurrent history or uncontrolled neurological disorders or seizures.
- History of invasive meningococcal disease.

5.2.1.3. Efficacy PoC part: HIV positive intensive safety monitoring subset (first 8 HIV positive subjects per group, enrolled in case of a positive safety outcome from the previous subset)

- Persons under guardianship or trusteeship.
- Persons deprived of liberty.
- Gonococcal infection identified by a positive NAAT within 14 days prior to randomization.*

  * Participants that are confirmed as positive for Ng by NAAT will be invited to participate in a re-screen visit after receiving appropriate antibiotic treatment.
- Any clinically significant** hematological (hemoglobin level, white blood cell, lymphocyte, neutrophil, platelet) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen) laboratory abnormality.

  ** The investigator should use his/her clinical judgment to decide which abnormalities are clinically significant.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.
- History of severe allergic reactions and/or anaphylaxis, or any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention(s).
- Bleeding diathesis or any other condition that would contraindicate intramuscular administration.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).

- Seropositivity for HIV infection if:
  - CD4 cell count < 350 cells/mm³ in the last 6 months
  - viral load > 50 cp/ml in the last 6 months
  - participant is not on antiretroviral therapy (ART) for > 3 months or has switched from a different ART in the last 3 months.
- Hypersensitivity to latex.
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory tests.
- Recurrent history or uncontrolled neurological disorders or seizures.
- History of invasive meningococcal disease.

5.2.1.4. All remaining participants

- Persons under guardianship or trusteeship.
- Persons deprived of liberty.
- Gonococcal infection identified by a positive NAAT within 14 days prior to randomization.*

  * Participants that are confirmed as positive for Ng by NAAT will be invited to participate in a re-screen visit after receiving appropriate antibiotic treatment.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.
- History of severe allergic reactions and/or anaphylaxis, or any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention(s).
- Bleeding diathesis or any other condition that would contraindicate intramuscular administration.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- except for HIV infection which is exclusion criterion only if:
  - CD4 cell count < 350 cells/mm^3 in the last 6 months
  - viral load > 50 cp/ml in the last 6 months
  - not under antiretroviral therapy (ART) for > 3 months or switch from a different ART in the last 3 months.
- Hypersensitivity to latex.
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory tests.
- Recurrent history or uncontrolled neurological disorders or seizures.

- History of invasive meningococcal disease.

Of note, should any safety concerns be identified within the HIV positive safety subset, the enrolment will progress with the inclusion of HIV negative individuals only. For them, the medical conditions listed in this section, apart from those related to the HIV positivity condition, will determine exclusion from the study.

5.2.2. Prior/Concomitant therapy

The following exclusion criteria apply for both the dose-escalation safety lead-in part and the PoC part

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study intervention(s) during the period beginning 30 days before the first dose (Day 1), or their planned use during the study period.
- Previous and planned vaccination with an OMV based *Neisseria meningitidis* group B vaccine (e.g., *Bexsero,* its predecessor *MeNZB* vaccine or *MenBvac*) at any time prior to first dose and during the entire study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 15 days before the first dose and ending 15 days after the last dose of vaccine administration*.

  *In case emergency mass vaccination for an unforeseen public health threat (e.g. a pandemic) is organized by public health authorities outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine, provided it is licensed and used according to its Product Information.
- Administration of long-acting immune-modifying drugs (e.g. infliximab) during the period starting 6 months prior to the first dose of study intervention or planned administration at any time during the study period.
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the administration of the first dose of study intervention or planned administration during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first study intervention dose(s). For long-acting immune-modifying drugs, see above. For corticosteroids, this will mean prednisone equivalent ≥20 mg/day for adult participants/ ≥0.5 mg/kg/day. Inhaled and topical steroids are allowed.

The following exclusion criterion applies only for the PoC part:

- Chronic or long-term use of systemic antibiotics (i.e., doxycycline for acne) with an activity against *Neisseria gonorrhoeae.*

5.2.3. Prior/Concurrent clinical study experience applicable for both dose-escalation safety lead-in part and the PoC part

Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational intervention (drug or invasive medical device).

5.2.4. Other exclusions applicable for both dose-escalation safety lead-in part and the PoC part

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions before 1 month after completion of the study intervention administration series.
- Any study personnel or their immediate dependents, family, or household members.
- Lifestyle consideration which may interfere with the conduct of the study or pose additional risks to the rights and wellbeing of participants are described in Section 5.3.

5.3. Lifestyle considerations

Vulnerable individuals

Gonorrhea infection can be found in vulnerable individuals, such as homeless people, exploited sex workers, victims of domestic violence, and marginalized immigrants. The ability of such individuals to comply with study procedures must be carefully assessed before considering them suitable for this study.

Drugs and alcohol abuse

Gonorrhea and other STIs are associated with the use of recreational drugs during sexual intercourse, known as “chemsex”, particularly in the MSM community. The use of recreational drugs and/or alcohol is not exclusionary *per se,* however the investigator must carefully evaluate the impact of recreational drugs and/or alcohol abuse on the ability to comply with the study procedures.

In general, when facing vulnerable individuals and those who regularly use recreational drugs or abuse alcohol, the investigator must evaluate if the participation in the study poses any additional risk to the safety, rights, and wellbeing of these participants, and assess the capacity of the participant to understand and comply with the requirements. Vulnerable individuals and those who regularly use recreational drugs or abuse alcohol should not be enrolled in the intensive safety monitoring subsets. Only in case of a positive outcome of the unblinded iSRC evaluation of the cumulative safety data collected in the intensive safety monitoring subsets, can enrolment be opened to vulnerable individuals and those who regularly use recreational drugs or abuse alcohol.

5.4. Screening failures

A screening failure is an individual who consents to participate in this study but is not randomized to a study intervention because he/she doesn't meet inclusion/exclusion criteria. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at the discretion of the investigator if the reason for screening failure no longer applies.

Participants that are confirmed as positive for Ng by NAAT at the screening visit are considered screening failure, but they will be invited to participate in a re-screen visit after receiving appropriate antibiotic treatment.

5.5. Criteria for temporarily delaying study intervention administration

Study intervention administration may be postponed within the permitted time interval until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of enrolment and/or study intervention administration. Refer to the SoA (Section 1.3) for definition of fever and preferred location for measuring temperature in this study.
- Presence of uncomplicated symptoms of gonorrhea or other STIs (e.g., urethritis or vulvo-vaginitis, syphilitic rash with no fever) is not a reason for delaying the administration of the second dose of study intervention.
- Participants with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Significant acute illness within the previous 7 days of study intervention administration.
- A positive test for COVID-19 infection prior to intervention administration. The testing should have been done using a molecular (polymerase chain reaction [PCR]) or antigenic test approved by the country regulatory authorities.
- Participants with known COVID-19 positive contacts and considered at risk of having contracted a COVID-19 infection according to local regulations.

- Administration of any other vaccines within 7 days (for inactivated vaccines) or 14 days (for live vaccines) prior to and following each vaccination*.

  * In case an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by the public health authorities, outside the routine immunization programme, the time period described above can be reduced, if necessary, for that vaccine provided it is licensed and used according to the local governmental recommendations and that the sponsor is notified accordingly.

  In case of seasonal influenza vaccination, the time period described above can be reduced, if necessary, for that vaccine, provided it is licensed and used according to its Prescribing Information and according to the local governmental recommendations.

  Under such circumstances, a participant may be considered eligible for study enrolment and/or vaccination after the appropriate window for delay described above, or as defined by local health authorities, has passed and inclusion/exclusion criteria have been re-checked, and if the participant is confirmed to be eligible.

- Participants living with HIV who experience a deterioration of their immunological parameters may not be administered further doses of study intervention until such parameters return to immunological stable levels (i.e., CD4 cell count >350 cells/mm³, viral load < 50 cp/ml). Any significant delay in receiving further doses of the study vaccine will result in their exclusion from the Per Protocol (PP) analysis Set.

- Participants who acquire HIV during the study may not receive further doses of study intervention until a positive outcome of the unblinded iSRC evaluation of the HIV positive safety subset has been obtained and the immunological parameters of the participants are at stable levels (i.e., CD4 cell count >350 cells/mm³, viral load < 50 cp/ml) while under stable antiretroviral therapy (ART) for > 3 months**.**

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention.

6.1. Study intervention(s) administered

Table 8 Study intervention(s) administered

Study intervention name:	**NgG 12.5 µg**		**NgG 25 µg**		**NgG 50 µg**	**Placebo**
Study intervention formulation:	GSKVx000000032576 (12.5 µg GSKVx000000032575); Excipients; Water for injections	Excipients; Water for injections	GSKVx000000032576 (25 µg GSKVx000000032575); Excipients; Water for injections	Excipients; Water for injections	GSKVx000000032576 (50 µg GSKVx000000032575); Excipients; Water for injections	Sodium chloride (NaCl) (0.9%); Water for injections
Presentation:	Suspension for injection/Vial		Suspension for injection/Vial		Suspension for injection/Vial	Solution for injection/Syringe
Type:	Investigational		Investigational		Investigational	Comparator
Product category:	Biologic		Biologic		Biologic	Combination product
Route of administration:	IM		IM		IM	IM
Administration site:						
Location	Deltoid		Deltoid		Deltoid	Deltoid
Directionality	Upper		Upper		Upper	Upper
Laterality *	Non-dominant		Non-dominant		Non-dominant	Non-dominant
Number of doses to be administered:	2		2		2	2
Volume to be administered ** by dose****	0.5 ml		0.5 ml		0.5 ml	At least 0.5 ml***
Packaging and labelling:	Refer to the Study Procedures Manual (SPM) for more details		Refer to the Study Procedures Manual (SPM) for more details		Refer to the Study Procedures Manual (SPM) for more details	Refer to the Study Procedures Manual (SPM) for more details
Manufacturer:	GSK		GSK		GSK	Catalent

*The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed

**Refer to the SPM for the volume after reconstitution

***The volume of the saline pre-filled syringe may be between 0.6 and 0.8 mL. The full volume is to be injected

****GSK Biologicals' NgG investigational vaccine is an intramuscular (IM) injectable vaccine that can be presented as 1 vial or 2 vials to be mixed immediately before the injection, depending on the antigen dose. CCI [redacted] CCI [redacted]

Study participants must be observed closely for at least 60 minutes after the administration of the study intervention(s). Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope.

6.2. Preparation, handling, storage, and accountability

The study intervention(s) be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorized study personnel should be allowed access to the study intervention(s) Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the Study Procedures Manual (SPM) for more details on storage and handling of the study intervention(s)

6.3. Measures to minimise bias: randomization and blinding

6.3.1. Participant identification

Participant identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study center.

6.3.2. Randomization to study intervention

Dose-escalation safety lead-in:

For each group, the enrolment of 8 participants is planned. The dose administration will be sequential, only 1 participant will receive the product dose per day and per site (as applicable). Therefore, avoiding administration of parallel doses and leaving at least 24 hours between 2 consecutive participants will ensure that, in the event of an acute adverse reaction, the site will provide the required medical attention for the individual concerned and allow enough time to evaluate whether other participants can be exposed to the dose administration. Refer to Section 4.1.1 "Safety monitoring".

Efficacy PoC:

The target enrolment for the efficacy PoC will be about 750 participants (refer to Section 9.6 for details about sample size assessment and re-assessment). The enrolment in the PoC part will proceed stepwise with HIV negative individuals to be enrolled first and administered the first dose. Following unblinded iSRC evaluation, enrolment can be opened to HIV positive subjects. Refer to Section 4.1.2, "Safety monitoring".

In the PoC part of the study, HIV infected participants will account for, at most, 20% of the entire enrolled study population.

6.3.3. Intervention allocation to the participant

The randomization algorithm during the dose-escalation safety lead-in will use Group 1, Group 2 and Group 3 as strata. Study ID will be added as a minimization factor by default.

The randomization algorithm during the efficacy PoC will use a minimization procedure accounting for sex, site, age group (18–30 years of age, 31–50 years of age), race (black, white, other), belonging to specific risk group (i.e. men having sex with men under pre-exposure prophylaxis for HIV vs others). Minimization factors will have equal weight in the minimization algorithm. HIV – (subset), HIV – (full enrolment), HIV + (subset) and HIV + (full enrolment) will be used as strata in the randomization algorithm.

Once a participant identification number is allocated, the randomization system will determine study group and will provide the study intervention number to be used for the first dose. The study intervention number(s) to be used for subsequent dosing will be provided by the same automated Internet-based system SBIR.

When an automated, Internet-based system SBIR is not available, please refer to the SBIR user guide or SPM for specific instructions.

Refer to the SPM for additional information about the study intervention number allocation.

6.3.4. Allocation of participants to assay subsets

Approximately, the first 100 participants enrolled in each arm (n=300 total), and all participants with confirmed gonococcal infections will be tested for human serum bactericidal assay (hSBA).

6.3.5. Blinding and unblinding

Data will be collected in an observer-blind manner. The participant, the site personnel involved in the clinical evaluation of the participants and the sponsor personnel involved in data analysis, are blinded. Other study personnel that do not perform study activities related to data collection, data evaluation or data review, may be aware of the treatment assignment. Study intervention(s) will be prepared and administered by a limited number of qualified unblinded site personnel who will not participate in any data collection, data evaluation, data review or the entry of any study endpoint (i.e. reactogenicity, safety, efficacy).

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant. As the last participant completes the last study visit (from the safety lead in phase) the safety lead-in phase will be unblinded.

6.3.5.1. Emergency unblinding

Unblinding a participant's individual study intervention number should occur ONLY in case of a medical emergency when this information is essential for the clinical management or welfare of the participant.

In case of emergency, the investigator can have unrestricted, immediate and direct access to the participant's study intervention information via an automated Internet-based system (e.g. SBIR). The investigator may contact a GSK Helpdesk (refer to Table 9) if help is needed to access participant's study intervention information (i.e. if the investigator is unable to access SBIR).

A physician other than the investigator (e.g. an emergency room physician) or participant/participant's caregiver or family member may also request emergency access to the participant's study intervention information either via the investigator or investigator's back up (preferred option) or via the GSK Helpdesk (back up option). The participant card provides contact information for the investigator(s), their back up and GSK Helpdesk.

Table 9 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Phone: +32 2 656 68 04 Fax: +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com

6.3.5.2. Unblinding prior to regulatory reporting of SAEs

GSK Global Safety staff may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction (SUSAR). GSK Global Safety is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to Section 10.3.10.1). For SAEs requiring expedited reporting to 1 or more regulatory agencies, a copy of the report containing participant's intervention assignment may be sent to investigators in accordance with local regulations and/or GSK policy. GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study intervention(s), prior to regulatory reporting.

6.4. Study intervention compliance

When the study intervention is administered at the site, participants will receive it directly from the investigator or designee, under medical supervision. The date of administration of each study intervention dose in the clinic will be recorded in the source documents.

6.5. Dose modification

Not applicable.

6.6. Continued access to study intervention after the end of the study

During the study conclusion visit, the investigator will ask each participant if they are interested in participating in a long-term evaluation study. If a participant is not interested in joining the long-term evaluation study the reason for refusal will be documented, when available, in the participant's eCRF.

6.7. Treatment of overdose

There is no specific treatment for an overdose, the treatment is symptom specific.

An overdose of study intervention (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in 1 dose of study vaccine. An overdose would also occur if 2 doses of the study vaccine are administered within 2 weeks.

Overdose in itself is not to be reported as an AE, however, any AEs associated with the overdose are to be reported in the relevant AE/SAE sections of the eCRF.

Overdose must be reported in the study intervention administration form of the eCRF.

6.8. Concomitant therapy

At each study visit, the investigator(s) or their delegate(s) should question the participant about all medications/products taken, and vaccinations received by the participant.

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF/CRF:

- All concomitant medication associated with an adverse event, including vaccines/products, administered after the first dose of study intervention.
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines. Please refer to Section 5.2.2 and Section 9.2.1 for further details.
- All concomitant medication which may explain/cause/be used to treat an SAE including vaccines/products, as defined in Section 8.3.1 and Section 10.3.8. These must also be recorded in the Expedited Adverse Event report.
- The use of antipyretic and/or other medications to prevent (prophylactic use) and/or treat fever during the first 7 days after vaccination to be recorded in the eCRF.

- The use of analgesics or any other medication to prevent (prophylactic use) and/or treat pain or other site administration or systemic reaction during the first 7 days after vaccination to be recorded in the eCRF.
- Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present. An anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring (refer to Table 21).
- The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications eCRF.
- Medications taken for HIV treatment or pre-exposure prophylaxis.
- Contraceptives (including intrauterine devices or systems).
- Gender affirming hormonal therapy.
- Medications taken to treat gonorrhea and other STIs.
- Medications taken as post-exposure prophylaxis following sexual contact to prevent gonorrhea and other STIs (e.g. doxycycline).

The GSK local and/or medical contacts should be used if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of the study intervention. A participant who discontinued the study intervention may continue other study procedures (e.g. safety or NAAT), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

- Adverse event requiring expedited reporting to GSK
- Unsolicited non-serious adverse event
- Solicited adverse event
- Not willing to be vaccinated
- Other (specify).

7.1.1. Contraindications to subsequent study intervention(s) administration

The eligibility for subsequent study intervention administration must be confirmed before administering any additional dose.

Participants who meet any of the criteria listed below or criteria listed in sections 5.2.1 and 5.2.2 should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigator's discretion (Section 10.3.8.2). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participants if they continue to participate in the study.
- Any occurrence of an event listed in the exclusion criteria which must be always reassessed by the investigator before administration of the next dose of study intervention.
- Anaphylaxis following the administration of study intervention(s).
- Any condition that in the judgement of the investigator would make intramuscular injection unsafe.
- Pregnancy (refer to Section 10.3.7.1).
- Breastfeeding.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for them since the date of withdrawal/last contact.

From an analysis perspective, a study 'withdrawal' refers to any participant who did not return for the concluding visit planned in the protocol.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses.

The primary reason for study withdrawal will be documented in the eCRF, based on the list below:

- Adverse events requiring expedited reporting to GSK (please refer to Section 10.3.10.1 for the details)
- Unsolicited non-serious adverse events
- Solicited adverse event
- Withdrawal by participant, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

  *If a participant is withdrawn from the study because the participant has withdrawn consent and the reason for withdrawal was provided, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.8.2).

7.3. Lost to follow-up

Participants will be considered 'lost to follow-up' if they repeatedly fail to return for scheduled visits and cannot be contacted by the study site.

Please refer to the SPM for a description of actions to be taken before considering the participant lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team becomes aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

Study procedures and their timing are summarised in the SoA (Section 1.3).

All screening evaluations must be completed and the results reviewed before confirming that potential participants meet all eligibility criteria.

The investigator will maintain a log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

Procedures conducted as part of routine clinical management (e.g. hematologic profiles), and obtained before the participant signed the Informed Consent Form (ICF), may be used for screening and/or for establishing a clinical baseline [provided the procedure met protocol specified criteria and was performed within the time frame defined in the SoA (Section 1.3)].

The SPM provides the investigator and site personnel with detailed administrative and technical information that does not impact participant safety.

Burden of the study, degree of strain and risk threshold in Dose-escalation safety lead-in part

Participants are required to undergo blood sampling as screening procedure. Participants are required to attend 4 clinic visits and complete 4 phone calls during the course of the study, to receive the study intervention, to complete the eDiary to collect solicited adverse events in the 7 days following administration of study vaccine and undergo blood samplings. A basic, routine medical assessment, including interview on past and current medical history will also be performed by the investigator or designated person. On study Day 1 and Day 61 a urine pregnancy test for female participants of childbearing potential will be required.

Burden of the study, degree of strain and risk threshold in Efficacy PoC Part

Participants are required to undergo swab sampling and/or urine tests as screening procedure. Participants are required to attend or perform at least 8 visits during the duration of the study, to receive the study intervention, to complete the eDiary to collect solicited adverse events in the 7 days following administration of study vaccine, to perform multiple swabs and/or urine tests and undergo blood samplings. A basic, routine medical assessment, including interview on past and current medical history and sexual history of last 30 days will also be performed by the investigator or designated person. On study Day 1 and Day 61 a urine pregnancy test for female participants (including *trans*men that have not undergone gender affirming surgery of their genitals) of child-bearing potential will be required. Swab sampling will be performed by qualified healthcare professionals. Self-swabbing is only allowed to collect vaginal swab. Participants must be trained on how to perform self-sampling if this is going to occur.

Treatment of positive gonorrhea cases:

Treatment of positive gonorrhea cases should follow local or international guidelines. First or second line recommended antibiotic treatments are preferred. Antibiotics used to treat gonorrhea must be recorded in the eCRF with clear indication of use.

Evaluation of treatment efficacy and test of cure (after protocol amendment 7 is effective, evaluation of treatment efficacy and test of cure will not be conducted)**:**

A test of cure (TOC) after treatment of gonococcal infection is recommended in certain countries. This has the scope of identifying early treatment failures due to antimicrobial resistance. For this clinical trial, TOC may be conducted according to local guidelines, however, if a TOC is not conducted, we consider all gonococcal infections treated successfully if the antibiotic regimen administered is highly effective (i.e., first- or second-line guideline recommended with >95% efficacy). A TOC performed at least 14 days post treatment will be required by this protocol only if the treatment administered is considered "alternative" (for instance, participants who are allergic to cephalosporins and received high dose azithromycin). In this specific case, the TOC will be documented in a dedicated section of the participant eCRF.

In case of positive Ng at TOC, the investigator will need to adjudicate whether this represents a treatment failure or a new episode / reinfection, after collecting all relevant information (sexual history, symptomatology, and sensitivity at the antibiogram, if available).

Management of concurrent STIs

The population enrolled in the efficacy PoC part of this clinical trial is exposed to the risk of contracting other STIs (chlamydia, HIV, syphilis, hepatitis C virus [HCV], hepatitis B virus [HBV], mycoplasma, trichomonas, lymphogranuloma venereum and other infections). These STIs are not considered end points and will be reported as AEs only. Their management will follow the standard of care and it is left to the investigators who will need to provide appropriate care and follow up. This is particularly relevant for new cases of HIV, HBV and HCV diagnosed during the trial, that may require referrals to other specialists.

Repetition of inconclusive Ct/Ng NAATs (after protocol amendment 7 is effective, repetition of inconclusive Ct/Ng NAATs will not be conducted).

Participants with an "invalid", "equivocal" or otherwise inconclusive result at NAAT are invited to repeat the test within a reasonable time frame. If they received anti gonococcal treatment meanwhile, there is little chance to detect bacterial genetic material and the repetition of NAAT may not be needed. All inconclusive test results will be documented in the eCRF.

Study procedures in special circumstances:

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied.

For this trial, special circumstances may also include objective inability for the participants to perform the visit at the study site (e.g., inability to travel). The study site remains the mandatory location for the screening visit(s) and the preferable location for the study visits nevertheless, for the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Study visits may be performed at a different location** other than the study site (e.g., at participant's home). Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- The dose of study intervention should be delivered within the interval predefined in the protocol (Table 4).

  ** It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets International Council on Harmonisation (ICH) Good Clinical Practice (GCP) requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site.

  ** In case of home visits, the study procedures should be carried out by a qualified person/s as delegated by the principal investigator, provided that the compliance with protocol procedures are ensured. Refer to SoA for the schedule of visits (Table 2 and **Table** 3).

  Refer to local regulations on the conduct of clinical trials during the COVID-19 pandemic for more details.

8.1. Efficacy and/or immunogenicity assessments

8.1.1. Biological samples

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. Additionally, biological samples may also be used to further investigate and characterize the immune response elicited by the study vaccine, and to explore the development of additional laboratory assays to evaluate the immune response elicited against the study vaccine.

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. All participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior IEC/IRB approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

Sample testing will be done in accordance with the recorded consent of the individual participant.

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

Samples from 3 anatomical sites (urogenital, anorectal and pharyngeal) will be collected from all participants at specific timepoints during the PoC and blood samples will be collected from participants as described in Table 10.

Table 10 Collection of biological samples

Sample Type	Quantity	Subset Name
Blood sampling for any hematological/biochemical laboratory abnormality	Approximately 6 mL	Phase 1 All participants Phase 2 Subset of participants
Swab: Urogenital, anorectal and pharyngeal sites	1 per anatomical site[2]	Phase 2 All participants
Urine: First-catch urine[1]	-	Phase 2 All male participants and those with a penis
Blood sampling for antibody determination	Approximately 20 ml	Phase 2 All participants
Blood sampling for assay development	Approximately 50 ml Approximately 30 ml	Phase 1 All participants Phase 2 All participants

[1]First-catch urine will be collected instead of an urogenital swab from male participants and those with a penis
[2]Should a study participant show signs and/or symptoms suggestive of gonococcal infection either at a scheduled or unscheduled visit, a double sampling will be executed (refer to Section 8.1.2). Not applicable after protocol amendment 7 is effective.

All laboratory testing for efficacy endpoint and humoral immune responses will be performed at GSK laboratory or in a laboratory designated by GSK. The testing of blood samples for safety evaluation and NAAT* testing for screening or when double sampling is performed in case of symptoms suggestive of possible gonococcal infection~~,~~ will be performed by the local laboratory at the investigator's site. Note: after protocol amendment 7 is effective, in case participant shows signs and/or symptoms suggestive of gonococcal infection, the NAAT sampling for the GSK designated laboratory will not be performed (the paricipant will be managed according to the local medical practice).

*Store NAAT in accordance with laboratory and manufacturer recommended conditions.

Table 11 Laboratory assays

Test Classification	System	Component	Challenge	Method
Molecular Biology[2]	Swab: Urogenital sites	Ng Ct	[redacted]	NAAT
	Swab: anorectal sites	Ng Ct		NAAT
	Swab: pharyngeal sites	Ng Ct		NAAT
	Urine: First-catch urine[1]	Ng Ct		NAAT
Humoral Immunity (Antibody determination)	Serum	Anti-Gono GMMA Ab IgG	[redacted]	ELISA-like
	Serum	Ng FA1090 hSBA		hSBA

Ct: *Chlamydia trachomatis*; NAAT: Nucleic Acid Amplification Test; Ab: antibodies; IgG: Immunoglobulin G; ELISA: Enzyme Linked ImmunoSorbent Assay; hSBA: Human complement Serum Bactericidal Assay; Ng, *Neisseria gonorrhoeae*

[1]First-catch urine will be collected instead of an urogenital swab from male participants and those with a penis [redacted]

Further laboratory testing related to NgG investigational vaccines and/or gonorrhea disease, CCI [redacted] CCI [redacted] NAAT, may be performed if deemed necessary or if assay(s) become available.

Please refer to Section 10.2 for a brief description of the assays performed in the study.

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

GSK clinical laboratories have established a Quality System supported by procedures. The activities of GSK clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

8.1.2. Read-out for efficacy assessment

NAAT samples include swabs (urogenital, anorectal, and pharyngeal sites) and/or first-catch urine samples for male participants and those with a penis. They will be collected at specific time points during the study as illustrated in Figure 3. Diagnostic tests (NAAT) for the detection of Ng and Ct nucleic acids will be used. Use of vaginal medicinal treatments, vaginal moisturizers, vaginal wash/hygiene products containing carbomer should be avoided in the 7 days before planned visits when vaginal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test. Similarly, use of anorectal medicinal treatments, anorectal lubricants and anorectal wash/hygiene products containing carbomer, should be avoided in the 7 days before planned visits when anorectal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test.

All laboratory procedures for sampling and the detection of gonococcal infection will follow the standard of care at the study centers. The respective testing for gonorrhea (NAAT) in scope for the primary and secondary endpoints will be conducted in a central laboratory designated by GSK, using FDA-approved NAAT method.

Should a study participant show signs and/or symptoms suggestive of gonococcal infection either at a scheduled or unscheduled visit, a double sampling at the affected anatomical site will be executed: one will be processed by the local laboratory of reference, the other one will be processed by the GSK designated laboratory. Test execution at local laboratory will ensure results availability in shorter timeframe and a timely treatment of confirmed positive cases. In case of discrepant results between the local laboratory and the GSK designated laboratory, only the result from the GSK designated lab will be considered for the study endpoints. Note: after protocol amendment 7 is effective, in case participant shows signs and/or symptoms suggestive of gonococcal infection, the sampling for the GSK designated laboratory will not be performed: the participant will be managed according to the local medical practice.

CCI [redacted]

CCI [redacted]

8.1.3. Immunological read-outs

To explore the immunogenicity of the candidate vaccine in human, blood samples from all participants of the PoC study part will be collected and analyzed using an Enzyme-Linked Immunosorbent Assay (ELISA)-like immunoassay for measuring specific Immunoglobulin G (IgG) against NgG vaccine antigen at specific time points during the study as illustrated in Figure 3.

To further characterize the immune response, serum samples of a subset of the PoC participants will also be analyzed using a hSBA to assess the functionality of antibodies generated by the candidate vaccine to induce complement mediated killing of Ng homologous strain at the same timepoints. The subset will represent approximately the first 100 participants enrolled in each arm (n=300 total). Evaluation of the humoral immune responses (tertiary objective) is subject to the assay availability and the respective blood samples will also be used to the assay's development.

8.1.4. Cytology

Not applicable.

8.1.5. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far for Ng. Attempts will be made to identify an immunological correlate of protection in the efficacy PoC study.

8.2. Safety assessments

The investigator(s) and their designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up all AEs.

In the safety lead-in part, safety follow-up calls are calls made to the participant by a qualified healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information.

8.2.1. Pre-intervention administration procedures

8.2.1.1. Collection of demographic data

Dose escalation safety lead-in: At Screening record demographic data such as date of birth (month and year), sex at birth, race and ethnic origin*, weight, and height in the participant's eCRF. More detailed information on sex, gender and sexual orientation are in the Glossary of terms.

Efficacy PoC: At Screening record demographic data such as year of birth, sex at birth, gender, sexual orientation, race and ethnic origin*, weight, and height in the participant's eCRF. More detailed information on sex, gender and sexual orientation are in the Glossary of terms.

* Differences in the safety and efficacy of certain medical products, including vaccines [Haralambieva, 2013; Pérez Losada, 2009; Kollmann, 2013], have been observed in racially and ethnically distinct subgroups. These differences may be attributable to intrinsic factors (e.g. genetics, metabolism, elimination), extrinsic factors (e.g. diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both race and ethnicity will be collected for all participants in this study. Furthermore, collection of sex, race, and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.2.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention in the eCRF. Vaccination history must also be collected up to 6 months prior to enrolment.

8.2.1.3. General physical examination

A complete physical examination will be performed for all participants at the following visits (Table 1, Table 2 and **Table** 3):

- Dose escalation safety lead-in: Screening visit and Visit 1.
- Efficacy PoC: Screening visit, Visit 1, and unscheduled visits. After protocol amendment 7 is effective, unscheduled visits (thus complete physical examination) will not be conducted.

A general physical examination is to be performed by a qualified healthcare practitioner. "Qualified health care practitioner" refers to any licensed or certified healthcare professional who is permitted by institutional policy to perform protocol required procedures, and who is identified within the Delegation of Responsibility Log. The physical examination will include examination of organ systems that are relevant to the investigator based on medical history and review of systems (e.g., measurement of body temperature, heart rate, blood pressure).

Collected information at Visit 1 needs to be recorded in the eCRF. Should the physical assessment reveal any abnormal values or events, these must be documented in the eCRF AEs Form.

If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled within the allowed time interval for this visit (see Table 4). Refer to the Section 5.5 for the list of criteria for temporary delay of study intervention administration.

Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

Physical examination at each study visit after the first study intervention administration visit will be performed only if the participant indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

For participants with suspected proctitis/proctocolitis: perform examination with a proctoscope and collect the swab directly from the rectal mucosa.

8.2.1.4. History or symptoms directed physical examination

History or symptom directed physical examination at:

- **Dose escalation safety lead-in:** Visits 1, 2, 4 and 5

  Efficacy PoC: Visits 1 to 10 and unscheduled visits (after protocol amendment 7 is effective, unscheduled visits - thus history or symptom directed physical examination - will not be conducted).

will be performed only if the participant indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

Collected information does not need to be recorded in the eCRF (Table 1, Table 2 and **Table** 3).

Genital examination and sample collection in participants with symptoms in the Efficacy PoC Part (after protocol amendment 7 is effective, genital examination and sample collection in participants with symptoms will not be required for the remaining clinic visits).

In general, a physical examination of the genito-urinary tract is required only if participants attend with symptoms of possible gonococcal infection.

For male participants (and those with a penis) with suspected urethritis: first catch urine, with the participant having held urine for at least 1 hour, may be collected instead of the collection of exudates with a swab. Microscopy and cultures of the exudate are not required by this protocol but may be performed to support the diagnosis and isolation of other infective agents as per routine practice.

For female participants (and those with a vagina) with suspected vulvo-vaginitis, cervicitis or PID: perform examination with the speculum and collect the swab from the cervix and/or the vaginal walls. Microscopy and cultures are not required by this protocol but may be performed to support the diagnosis and isolation of other infective agents as per routine practice.

For participants with suspected proctitis: perform examination with a proctoscope and collect the swab directly from the rectal mucosa.

8.2.1.5. Sexual behaviour recommendations, sexual behaviour questionnaire and safe sex advice

For the efficacy PoC phase, information about sexual history and practices are needed to identify the risks of participants to contract an STI and to establish the correct study procedures that a participant must undergo. For this reason, participants will be required to complete a sexual behaviour questionnaire at Screening and at Visits 3, 4, 6, 7, 8, 9, 10 and unscheduled visits to collect the following data:

- Occurrence of sexual intercourse (including oral sex, vaginal sex, and anal sex) without a condom (female or male condom) within 24 hours of swab execution/first catch urine collection.

- Number of sexual partners with whom the participant has had sexual intercourse (including oral sex, vaginal sex, and anal sex) within the 30 days prior to screening, and since the last visit at the time of swab execution/first catch urine collection.
- Number of times a participant has had sexual intercourse (including oral sex, vaginal sex, and anal sex) within the 30 days prior to screening, and since the last visit at the time of swab execution/first catch urine collection.
- Proportion of sexual intercourses (including anal sex and vaginal sex) without a condom (female or male condom), given as percentage, within the 30 days prior to screening, and since the last visit at the time of swab execution/first catch urine collection.

Collected information will be recorded in the eCRF.

Note: after protocol amendment 7 is effective, participants will not be required to complete a sexual behaviour questionnaire at Visits 8, 9, 10 (nor at unscheduled visits as they will not be conducted). Recording of such information in eCRF for corresponding visits will not occur.

In the efficacy PoC phase, swabs from urogenital (or first catch urine in men and those with penis), anorectal and pharyngeal sites will be collected every three months starting from one month post second injection, i.e., at scheduled Visits 6, 7, 8, 9 and 10 for primary endpoint data collection. Study participants are recommended not to engage in sexual intercourses for 7 days before these scheduled Visits.

The investigator will ask if sexual intercourse(s) occurred in the 7-day period antecedent to the above-mentioned Visits 6, 7, 8, 9 and 10 and to unscheduled visit(s) as applicable, information will be recorded in the eCRF.

Note: after protocol amendment 7 is effective, swabs from urogenital (or first catch urine in men and those with penis), anorectal and pharyngeal sites will not be collected at planned Visits 8, 9, 10 (nor at unscheduled visits as they will not be conducted). Information about sexual intercourse(s) occurring in the 7-day period antecedent to these visits will not be collected in eCRF.

Should the investigator, or their designee, ascertain an inconsistent use of condoms and a high risk of contracting STIs, they must advise to follow safer sexual practices, including but not limited to use of condoms.

It will be the responsibility of the investigator to ascertain if a participant is at increased risk of HIV and to provide for an appropriate medical intervention as per standard of care (e.g., pre- or post-exposure prophylaxis, counselling).

8.2.1.6. Pregnancy test

Female participants of childbearing potential, including *trans*men that have not undergone gender affirming surgery of their genitals, must perform a urine pregnancy test before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

Refer to Section 10.4.2.1 for the information on study continuation for participants who become pregnant during the study.

8.2.1.7. Warnings and precautions to administration of study intervention

Warnings and precautions to administration of study intervention must be checked at each visit with planned administration of study intervention as specified in SoA (Section 1.3).

8.2.2. Clinical safety laboratory tests

Refer to Section 10.2.1 for the list of clinical laboratory safety assessments required by the protocol. These assessments must be conducted according to the clinical laboratory manual and the SoA (Section 1.3).

8.2.3. Study holding rules and safety monitoring

8.2.3.1. Staggered administration of study intervention

The investigator is not permitted to begin dosing study participants in Step 2 until the receipt of favourable written documentation of iSRC safety evaluations. Screening procedures may continue to facilitate the enrolment of remaining participants.

8.2.3.2. Outcome of safety evaluation

If a safety signal is observed during the safety evaluations or if any of the holding rules 2a-c (Table 12) is met, the iSRC Chair (or his/her representative) is responsible for any urgent communication to GSK, including the rationale for the decision to put the study intervention administration on hold or not.

8.2.3.3. Study holding rules

Phase 1, dose-escalation safety lead-in part

A staggered enrolment of healthy participants for the Phase 1 dose-escalation safety lead-in part is chosen. In case blinded data are of concern for SRT and iSRC Chair, unblinded data may be evaluated by iSRC (conditional iSRC) and only after positive opinion by iSRC can the next step start. At minimum the SRT will consist of the following core members: the study safety lead (safety representative), a safety product specialist, the study clinical science lead (clinical representative), the project epidemiologist, the project biostatistician and the global regulatory affairs lead. The iSRC will include 3 core

members independent from the clinical development project to ensure an unbiased assessment: a clinician, a safety representative and a statistician and their respective delegates. The Chair is usually the safety representative.

Holding rules are defined to ensure well-controlled exposure to the investigational vaccine. Holding rules 1a-d and 2a-c will apply to all dose-escalation safety lead-in participants after first and second dose. Holding rules 1a-d will be monitored by the investigators on a continuous basis for as long as doses administration is ongoing in the study. Holding rules 2a-c will be assessed by the SRT in a blinded way. If no safety concerns are identified, SRT will confirm the administration of the second dose in the concerned group and the start of enrolment in the subsequent group. In case blinded data are of concern for SRT, then the iSRC will look at the unblinded data (conditional iSRC).

Phase 2, PoC part

Enrolment will proceed stepwise in Part II where intensive safety monitoring will be put in place for the first 30 HIV- participants per group, and then for the first 8 HIV+ participants per group. The iSRC in charge for the safety evaluation in the PoC part (i.e. for HIV positive and HIV negative safety subsets) will include a member who is expert in the area of concern and who is external to GSK.

Holding rules 1a-d will also apply to the HIV negative subset for safety monitoring (consisting in the first 30 HIV negative participants enrolled per group) after first and second dose and holding rules 1a-d and 2a-c will apply to the HIV positive subset for safety monitoring (consisting of the first 8 HIV positive participants enrolled per group) after first and second dose.

For the rest of the study participants of the PoC part, not belonging to the intensive safety monitoring subset, for the whole study duration, in case ≥1 participant experiences a death or life-threatening SAE that is at least possibly related to the study product, the study will be paused. Study activities may proceed if review of safety data does not demonstrate safety concerns.

Meeting any of these holding rules will trigger a hold of vaccination. The holding rules will hence serve as criteria to point attention to safety signals and require escalation within GSK, in order to decide whether other participants can be exposed. However, medical judgment considering all available safety data at the time of safety review should be the basis for decision to continue the study or not.

Holding rules (Table 12 and Table 13) are not designed to assess the acceptability of the reactogenicity profile of a specific candidate vaccine.

Table 12 Study holding rules for Phase 1 and of Phase 2 PoC intensive safety monitoring subset

Holding rule	Event	Number of participants needed to trigger the hold in Phase 1 part (Safety lead-in)	Number of HIV negative participants needed to trigger the hold in Phase 2 part (PoC)[1]	Number of HIV positive participants needed to trigger the hold** in Phase 2 part (Poc)[2]
1a	Death or any life-threatening SAE regardless of causality	≥ 1	≥ 1	≥ 1
1b	Any non-life-threatening SAE that cannot be reasonably attributed to a cause other than vaccination as per Investigator or Sponsor assessment	≥ 1	≥ 1	≥ 1
1c	Any withdrawal from the study (by investigator or participant request) following a Grade 3 AE	≥ 1	≥ 1	≥ 1
1d	Any local or general solicited AE leading to hospitalization, OR Necrosis at the injection site Each with an event onset within the 7-day (Day 1-7) post-vaccination period	≥ 1	≥ 1	≥ 1
2a	Any Grade 3 solicited administration site event (lasting 48h or more as Grade 3), with an event onset within the 7-day (Day 1-7) post-vaccination period	≥ 1	N/A	≥ 1
2b	Any Grade 3 solicited systemic events (lasting 48h or more as Grade 3), with an event onset within the 7-day (Day 1-7) post-vaccination period	≥ 2	N/A	≥ 2
2c	Any Grade 3 unsolicited AE that can be reasonably attributed to the vaccination as per Investigator or Sponsor assessment, with an event onset within the 7-day (Day 1-7) post-vaccination period OR Any Grade 3 or above abnormality in pre-specified haematological or biochemical laboratory parameters in an investigational group with an event onset within the 7-day (Day 1-7) post-vaccination period	≥ 1	N/A	≥ 1*

AE = Adverse event; SAE = Serious adverse event; h = hours.

[1] This applies to the subset composed of the first 30 HIV negative participants from each study group

[2] This applies to the subset composed of the first 8 HIV positive participants from each study group enrolled in case of a positive safety outcome of the unblinded analysis of the first 30 HIV negative participants

* DAIDS Guidance for grading the severity in pre-specified haematological or biochemical laboratory parameters of HIV positive subjects.

** Holding rules will trigger a temporary pause of vaccinations in all study groups, as soon as they are identified. While vaccination will be paused, the responsible safety committee(s) providing study oversight will analyze available information related to the events triggering the hold. The Sponsor will then decide to suspend, modify or continue the conduct of the study, based on available evidence. The outcome of the decision will be documented and provided in writing to the investigators.

Table 13 Study holding rules for Phase 2 PoC participants not belonging to the intensive safety monitoring subset

Holding rule (Event)	Number of participants needed to trigger the hold in Phase 2 part (PoC)
Death or any life-threatening SAE that is at least possibly related to the study product	≥ 1

If a holding rule is met, the investigator must suspend enrolment and administration of the study intervention and inform GSK immediately (e.g. holding rules 1a-d). Refer to Table 17 for contact information.

GSK will inform the investigator if holding rules 2a-c are met.

The following communication sequence must be followed:

Blinded review

Figure 4 gives the probability of not meeting holding rules 1a, b, c, d and 2a, c in all groups in the dose-escalation safety lead-in part and in the safety subsets (holding rules 2 a-c only in the HIV positive subset) in the PoC part during the blinded review (i.e., investigational and placebo groups pooled together).

Figure 4 **Blinded review: Probability of not meeting holding rules 1a, b, c, d and 2a, c (all groups, safety lead-in and safety subsets PoC, holding rules 2 only in HIV positive subset)**

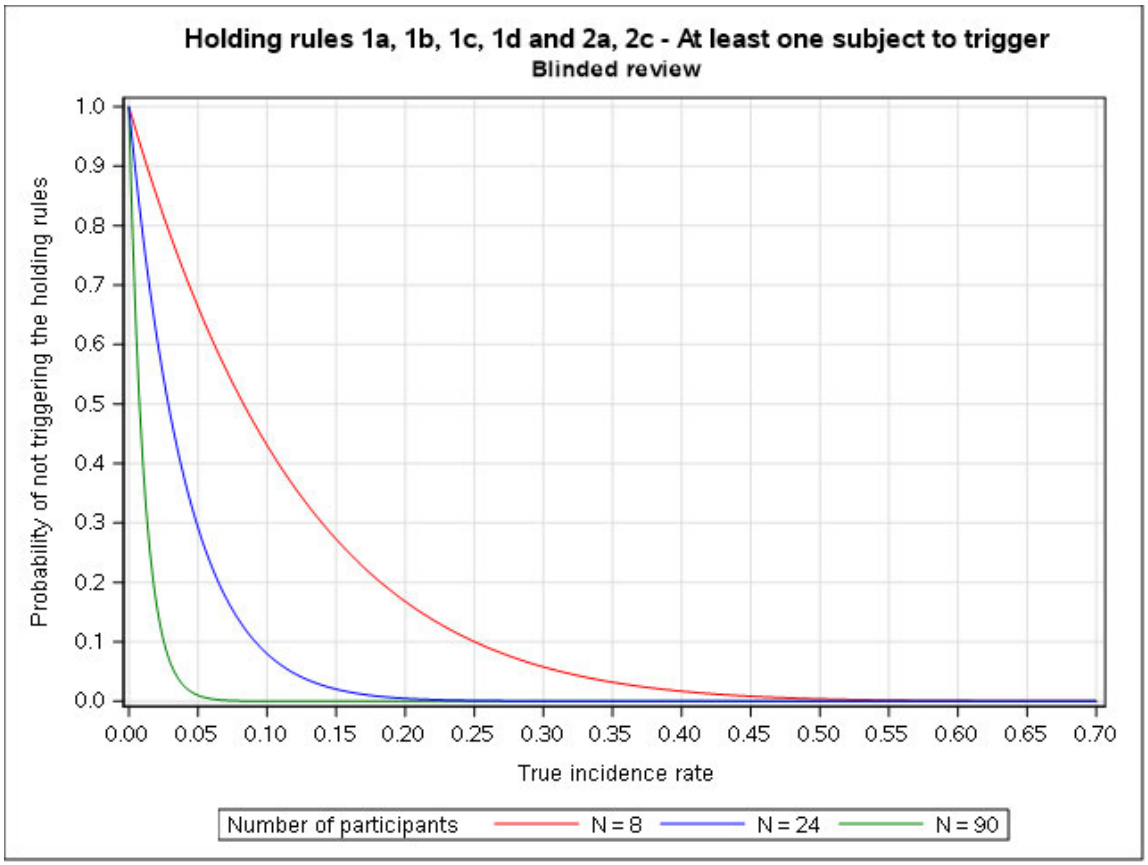

Figure 4 illustrates that:

- with 8 subjects, each holding rule (1a, b, c, d and 2a, c) has more than 80% chance of being met for vaccination with a true incidence rate above 18% and has more than 80% chance of not being met for vaccination with a true incidence rate below 2.7%;
- with 24 subjects, each holding rule (1a, b, c, d and 2a, c) has more than 80% chance of being met for vaccination with a true incidence rate above 6.5% and has more than 80% chance of not being met for vaccination with a true incidence rate below 0.95%;
- with 90 subjects, each holding rule (1a, b, c, d) has more than 80% chance of being met for vaccination with a true incidence rate above 1.75% and has more than 80% chance of not being met for vaccination with a true incidence rate below 0.25%;

Figure 5 gives the probability of not meeting holding rules 2b in all groups in the dose-escalation safety lead-in part and in the HIV positive safety subset in the PoC part during the blinded review (i.e., investigational and placebo groups pooled together).

Figure 5 Blinded review: Probability of not meeting holding rules 2b (all groups safety lead-in and HIV positive subset PoC)

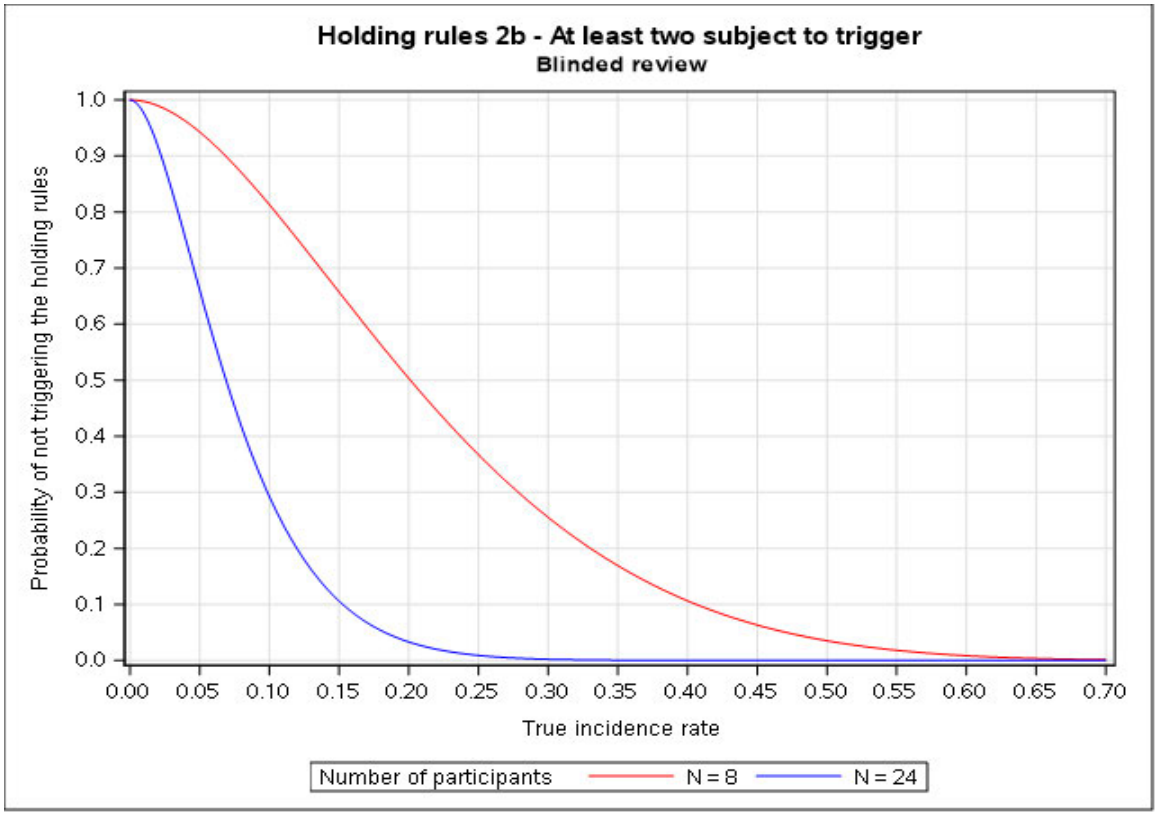

Figure 5 illustrates that:

- with 8 subjects, holding rule 2b has more than 80% chance of being met for vaccination with a true incidence rate above 33% and has more than 80% chance of not being met for vaccination with a true incidence rate below 10.5%;
- with 24 subjects, holding rule 2b has more than 80% chance of being met for vaccination with a true incidence rate above 12% and has more than 80% chance of not being met for vaccination with a true incidence rate below 3.4%;

Unblinded review

Figure 6 gives the probability of not meeting holding rules 1a, b, c, d and 2a, c in the investigational groups in the dose-escalation safety lead-in part and in the safety subsets (holding rules 2 only in the HIV positive one) in the PoC part during the unblinded review.

Figure 6 **Unblinded review: Probability of not meeting holding rules 1a, b, c, d and 2a, c (all groups, safety lead-in and safety subsets PoC, holding rules 2 only in HIV positive subset)**

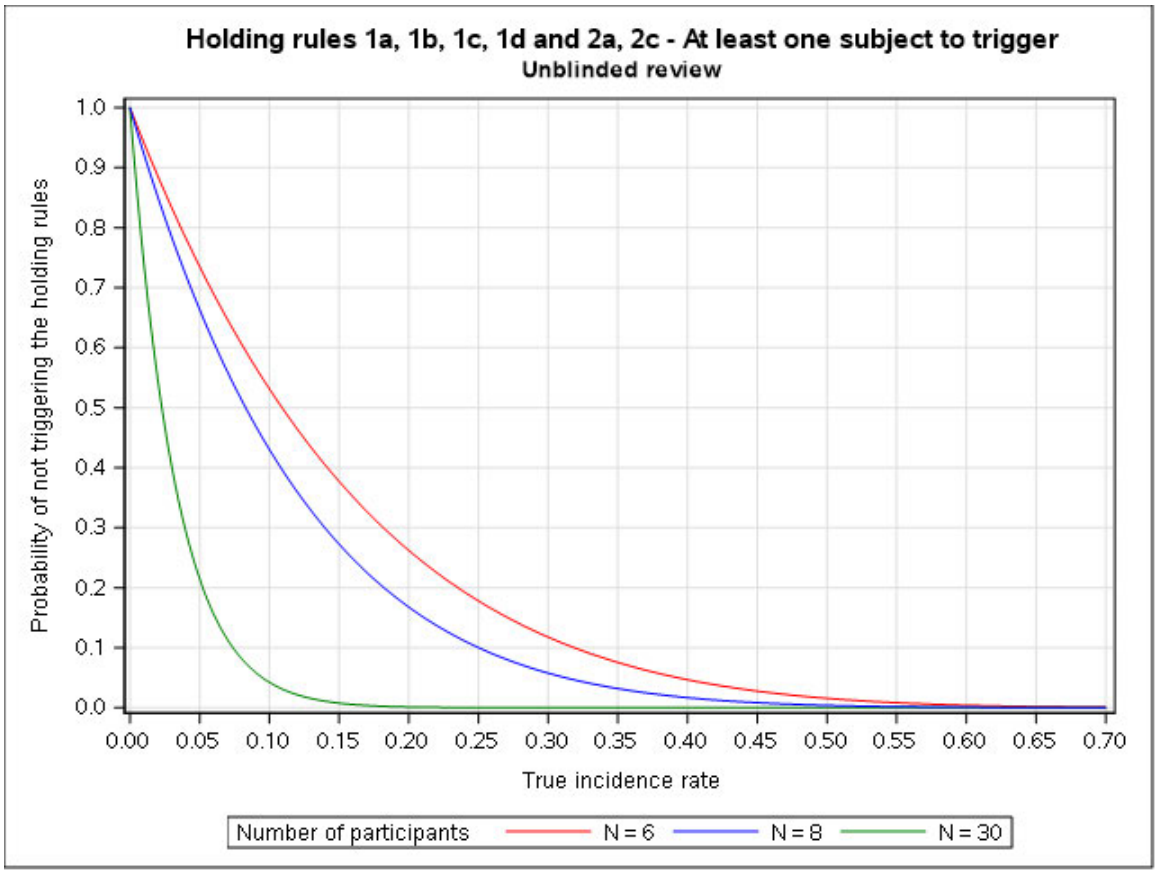

Figure 6 illustrates that:

- with 6 subjects, each holding rule (1a, b, c, d and 2a, c) has more than 80% chance of being met for vaccination with a true incidence rate above 23.5% and has more than 80% chance of not being met for vaccination with a true incidence rate below 3.7%;
- with 8 subjects, each holding rule (1a, b, c, d and 2a, c) has more than 80% chance of being met for vaccination with a true incidence rate above 18% and has more than 80% chance of not being met for vaccination with a true incidence rate below 2.7%;
- with 30 subjects, each holding rule (1a, b, c, d) has more than 80% chance of being met for vaccination with a true incidence rate above 5.2% and has more than 80% chance of not being met for vaccination with a true incidence rate below 0.75%.

Figure 7 gives the probability of not meeting holding rules 2b in the investigational groups in the dose-escalation safety lead-in part and in the HIV positive safety subset in the PoC part during the unblinded review.

Figure 7 Unblinded review: Probability of not meeting holding rules 2b (all groups safety lead-in and HIV positive subset PoC)

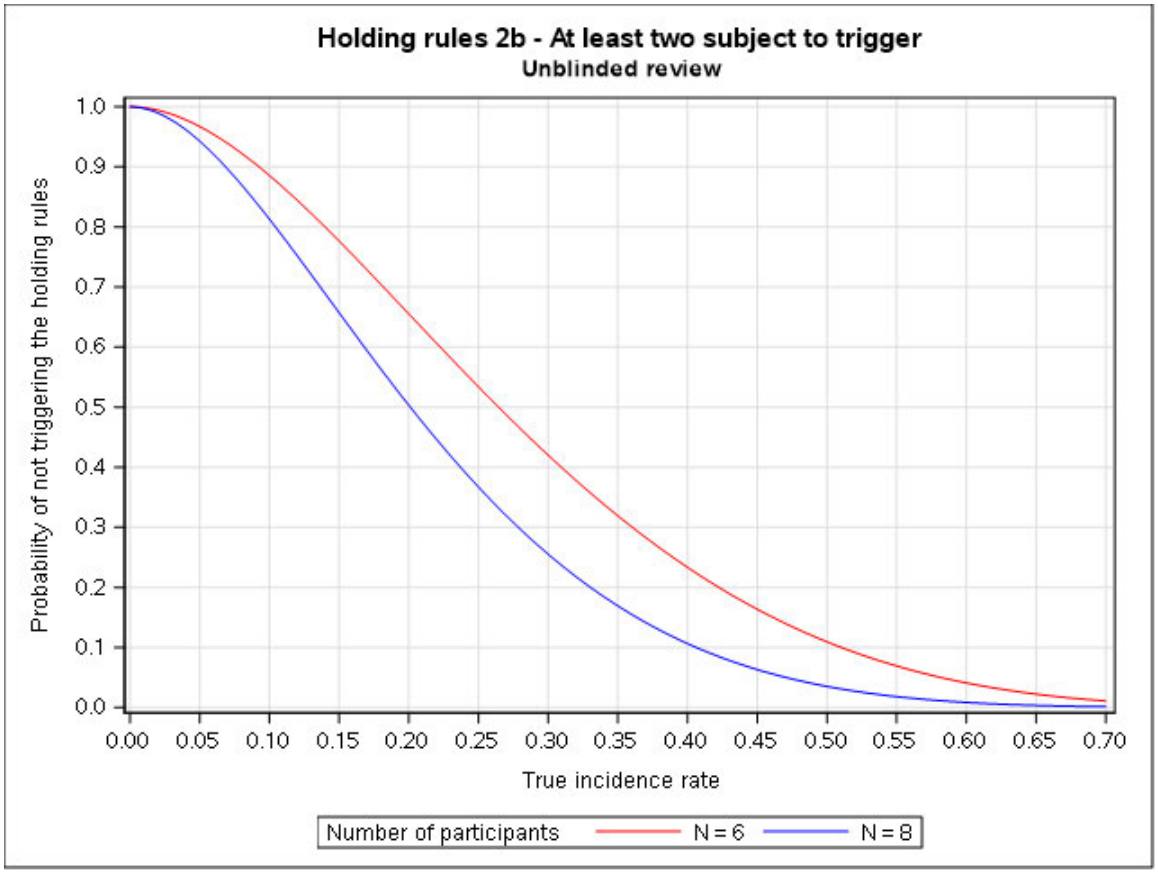

Figure 7 illustrates that:

- with 6 subjects, each holding rule 2b has more than 80% chance of being met for vaccination with a true incidence rate above 42% and has more than 80% chance of not being met for vaccination with a true incidence rate below 14%;
- with 8 subjects, each holding rule 2b has more than 80% chance of being met for vaccination with a true incidence rate above 33% and has more than 80% chance of not being met for vaccination with a true incidence rate below 10.5%.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and other safety reporting

8.3.1. Time period and frequency for collecting AE, SAE and other safety information

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 14 for dose-escalation safety lead-in and Table 15 for PoC. Refer to the Section 10.3.8.3 for details on the time period for recording safety information.

Table 14 Timeframes for collecting and reporting of safety information (dose escalation safety lead-in)

Event	Pre-Vac	Vac1			Vac2				Study Conclusion
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Day	**D–*14****	**D1**	**D8**	**D31**	**D61**	**D68**	**D91**	**D151**	**D241**
Solicited local and general AEs									
Unsolicited AEs									
AEs/SAEs leading to withdrawal from the study									
SAEs									
SAEs related to study participation* or concurrent GSK medication/vaccine									
Pregnancies									

* i.e. consent obtained.

AEs = Adverse Events; SAEs = Serious Adverse Events; Vac = Vaccination; D = Day; M = Month

*Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

Table 15 Timeframes for collecting and reporting of safety information (efficacy PoC)

Event	Pre-Vac	Vac1			Vac2						Study Conclusion
Visit	Screening	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Day	D–*14**	D1	D8	D31	D61	D68	D91	D181	D271	D361	D451
Solicited local and general AEs											
Unsolicited AEs											
AEs/SAEs leading to withdrawal from the study											
SAEs											
SAEs related to study participation* or concurrent GSK medication/vaccine											
Pregnancies											
DREs											

AEs = Adverse Events; DREs = Disease-Related Events; SAEs = Serious Adverse Events; Vac = Vaccination; D = Day
*Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

The investigator or designee will record and immediately report all SAEs in enrolled participants to the sponsor or designee via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.10. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 14.

Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and if the investigator considers the event to be reasonably related to the study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in the Table 17.

Events or outcomes not qualified as AEs/SAEs:

According to the study design and the study objectives, gonococcal infections (either asymptomatic or symptomatic) are considered Disease-related-events (DREs) and will not be captured nor managed as AEs/SAEs, but instead will be reported in the eCRF and analyzed as efficacy objectives in the POC part of the study. An overview of the protocol required reporting for DRE is given in Table 15. Refer to Section 10.3.1.2 for details on the time period for recording Safety Information.

8.3.2. Method of detecting AEs and SAEs, pregnancies and other events

Detection and recording of AE/SAE/ pregnancies are detailed in Section 10.3.8.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.9.

Care will be taken not to introduce bias when detecting AE/SAE/pregnancy. Open-ended and non-leading verbal questioning of participants is the preferred method of acquiring information related to an AE/SAE/pregnancy.

8.3.2.1. Clinically significant abnormal laboratory findings

The investigator must review the laboratory report, document that the review occurred, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All clinically significant abnormal laboratory test values reported during the study or within 8 days after the last dose of study intervention should be repeated until the values return to normal/baseline, or until they are no longer considered significantly abnormal by the investigator or GSK local and/or medical contacts. Refer to Section 10.3.6 for more information on clinically abnormal laboratory assessments that qualify as an AE or SAE.
- If such values do not return to normal/baseline after an interval judged reasonable by the investigator, the aetiology of the abnormal value should be identified, and the sponsor notified.

8.3.3. Regulatory reporting requirements for SAEs, pregnancies and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pregnancy, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 16. This is essential for GSK to meet legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.9.2.

Local regulatory requirements and sponsor policy for preparation of an investigator safety report of SUSAR must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has the legal responsibility to notify local authorities/regulatory agencies about the safety of an investigational study intervention. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC and investigators.

Please refer to Section 10.3.10 for further details regarding the reporting of SAEs/pregnancies.

Table 16 Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*,‡,‡‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	24 hours*	electronic pregnancy report	24 hours*	electronic pregnancy report

SAEs = serious adverse event

Refer to Table 2, **Table 3** and Table 15 for the timing for collection of DREs

*Timeframe allowed after receipt or awareness of the information by the investigator/site staff.

‡Paper Expedited Adverse Events Report will be dated and signed by the investigator (or designee)

‡‡ For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.3.3.1. Contact information for reporting SAEs, pregnancies and study holding rules

Table 17 Contact information for reporting SAEs, pregnancies and study holding rules

Study contact for questions regarding SAEs, pregnancies Refer to the local study contact information document	**Study contact for reporting of study holding rules** If a holding rule is met, the investigator must immediately inform the GSK local and/or medical contacts.
Back up study contact for reporting SAEs, pregnancies Available 24/24 hours and 7/7 days: **GSK Global Safety** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: ogm28723@gsk.com US sites only: Fax: 1 610 787 7053 Canadian sites only: Fax: 1 866 903 4718	**Back up study contact for escalation of holding rules** Available 24/24 hours and 7/7 days: **GSK Global Safety** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: ogm28723@gsk.com US sites only: Fax: 1 610 787 7053 Canadian sites only: Fax: 1 866 903 4718

8.3.4. Treatment of expedited adverse events (SAE)

Any medication administered for the treatment of an SAE should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to Section 10.3.10.1).

8.3.5. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

8.3.6. Medical device deficiencies

Medical devices are being provided for use to some study groups in this study as the study intervention (e.g., pre-filled syringes). To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

If the site(s) uses non-sponsor medical devices, i.e., medical devices not provided by GSK, then the investigators are obligated to report any device deficiencies to the legal manufacturer of the devices directly.

The definition of a medical device deficiency can be found in Section 10.6.

Note: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.6 of the protocol.

8.3.6.1. Detection, follow-up, and prompt reporting of medical device deficiency

The investigator is responsible for the detection, documentation and prompt reporting of any medical device deficiency occurring during the study to GSK. This applies to any medical device provided for the conduct of the study.

Device deficiencies will be reported to GSK within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. Refer to Section 10.6 for definitions and details on recording and reporting of these events.

The investigator will ensure that follow-up includes any additional investigations to elucidate the nature and/or relatedness of the device deficiency to the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and reported to GSK within 24 hours.

Medical device deficiencies and any associated AE/SAEs for associated person (i.e., spouse, caregiver, site staff) will also be collected. The associated person will be provided with a safety reporting information and authorization letter.

The sponsor will be the contact for the receipt of device deficiency reports.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

Follow-up applies to all participants, including those who discontinue study intervention or the study, and associated persons.

8.3.6.2. Regulatory reporting of medical device deficiency when used as combination product

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study to GSK. GSK has a legal responsibility to notify appropriate regulatory authorities and other entities about safety information linked to medical devices being used in clinical studies. Refer to Section 10.6.3 for details of reporting.

The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements linked to the reporting of device deficiencies to the IRB/IEC.

8.4. Pharmacokinetics

Not applicable.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity assessments

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

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9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

Statistical hypotheses are associated to the primary efficacy objective assessed in the efficacy PoC.

The global null hypothesis related to the primary efficacy objective is that the vaccine efficacy (VE) of the HTD and the dose below the HTD equal 0. This should be rejected in favor of the alternative hypothesis that VE > 0 for at least one investigational dose. The VE is defined as 1- the incidence rate (IR) ratio of gonorrhea cases (investigational over placebo). Family-wise type I error is set at 7.5% (1-sided).

9.2. Analysis sets

Table 18 Analysis sets

Analysis set	Description
Screened	All participants who were screened for eligibility
Enrolled	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). The allocation in a group will be done in function of the randomized intervention; non-randomized subjects will be part of a "Non randomized" group. Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.
Exposed	All participants who received at least 1 dose of the study intervention. Analysis per group using the exposed set is based on the administered intervention.
Full Analysis – Efficacy (Intention-To-Treat population)	All randomized participants who received at least one dose of study intervention. The allocation in a group will be done in function of the randomized intervention.
Modified Full Analysis Efficacy	All participants who received full study intervention (2 doses) and have post-vaccination efficacy data. The allocation in a group will be done in function of the randomized intervention.
Modified Full Analysis – Immunogenicity	All participants who received full study intervention (2 doses) and have post-vaccination immunogenicity data. The allocation in a group will be done in function of the randomized intervention.
Per Protocol – Efficacy	All eligible participants who received all doses as per protocol, had post-vaccination efficacy data, complied with dosing intervals, without intercurrent conditions that may interfere with immune response and without prohibited concomitant medication/vaccination. The analysis will be done according to the study intervention that participants received at dose 1.
Per Protocol – Immunogenicity	All eligible participants who received all doses as per protocol, had post-vaccination immunogenicity data, complied with dosing intervals, without intercurrent conditions that may interfere with immune response and without prohibited concomitant medication/vaccination. The analysis will be done according to the study intervention that participants received at dose 1.
Unsolicited Safety	All participants who received at least 1 dose of the study intervention (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.
Solicited Safety	All participants who received at least 1 dose of the study intervention (Exposed Set) who have solicited safety data in the period beginning 60 minutes after vaccination until 7 days after vaccination.
Solicited Safety 60m	All participants who received at least 1 dose of the study intervention (Exposed Set) who have solicited safety data during a period of 60 minutes after the vaccination.

9.2.1. Criteria for elimination from analysis

If a participant meets the criterion mentioned below or ones listed in the Section 7.1.1, he/she may be eliminated from per protocol analysis.

- Participants who acquire HIV (seroconversion) during the study will be excluded from the PP analysis.

All elimination criteria will be fully detailed in the Statistical Analysis Plan (SAP) along with rules for exclusions of subjects from analysis sets. SAP will be finalized before study start.

9.3. Statistical analyses

9.3.1. Primary endpoint(s)/estimand(s) analyses

Analysis of Safety

The analysis of primary endpoints will include descriptive analyses of safety data based on the Exposed/Unsolicited Safety/Solicited Safety set, depending on the specific endpoint under evaluation for both Phase 1 – Dose-escalation safety lead-in and Phase 2 – Efficacy PoC.

Statistical Analysis Methods
Within groups assessment The overall incidence of any solicited AE (administration site or systemic), of at least 1 solicited administration site AE and of at least 1 solicited systemic AE during the 7-day (Day 1-7) period will be tabulated per study group, for each dose and overall. The same calculations will be performed for solicited AEs rated as Grade 3. Duration for solicited AEs will be provided. The overall incidence of any unsolicited AE, by MedDRA system organ class and by preferred term during the 30-day (Day 1-30) follow-up post-vaccination period will be tabulated per study group, after each dose and overall. The same calculations will be performed for unsolicited AEs rated as Grade 3, for unsolicited AEs causally related to vaccination and for Grade 3 unsolicited AEs causally related to vaccination. The number and percentages of subjects who experienced at least one SAE during the entire study period will be reported. Analogously, the number and percentages of subjects who experienced at least one DRE during the entire study period will be reported. The percentage of subjects having hematology or biochemistry results below or above the normal laboratory ranges and graded according to FDA grading (Section 10.9) will be compared with baseline values (Screening/Day 1 and Day 61) by timepoint (Day 8 and Day 68). The verbatim reports of unsolicited symptoms will be reviewed by a GSK physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Event Terminology. Serious adverse events and withdrawal due to adverse event(s) will be described in detail.

AEs = adverse events; DRE disease-related events; FDA Food and Drug Administration; MedDRA Medical Dictionary for Reporting Adverse Events; SAE serious adverse event.

Analysis of VE

The observed IR of gonorrhea cases in the 2 investigational groups (i.e., the group administered with the HTD and the group administered with the dose below the HTD) will be sequentially compared to the IR in the placebo group to test the null hypothesis of VE = 0. Starting from the HTD, the dose below the HTD will be tested only if the HTD efficacy is demonstrated. Positive VE will be claimed for an investigational dose if the lower limit of the 2-sided 85% (1-sided $\alpha = 7.5\%$) confidence interval of the VE will be above 0. Confidence intervals for the VE will be obtained from the binomial exact method conditional on the total number of cases (i.e., sum of the number of cases in the investigational and placebo groups), assuming that the number of cases in each group is a realization from a Poisson distribution.

For this primary endpoint, only cases from urogenital and/or anorectal sites will be considered.

In case only the lowest dose from the dose-escalation safety lead-in part will show tolerability and be advanced in the efficacy PoC, no sequential testing will be needed.

The primary analysis set will be the Modified Full Analysis set, addressing intercurrent events like concomitant medications or vaccinations according to a treatment policy strategy.

9.3.2. Secondary endpoint(s)/estimand(s) analyses

The analyses of secondary endpoints will further evaluate the VE including:

- VE with and without Ct co-infection;
- VE against symptomatic gonococcal infection;

The primary analysis set will be the Modified Full Analysis set, addressing intercurrent events like concomitant medications or vaccinations according to a treatment policy strategy.

Additional details on the analyses associated to the secondary endpoints will be provided in the statistical analysis plan.

9.3.3. Additional exploratory analyses on vaccine efficacy

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[redacted]

9.3.4. Other exploratory analyses

The analyses for the evaluation of the humoral immune response will be performed on the Modified Full Analysis Set – Immunogenicity. Some analyses may additionally be performed on the Per Protocol Set – Immunogenicity.

The analysis set for these additional efficacy analyses will be the Exposed Set.

Ad-hoc central laboratory NAAT results that were collected prior to antibiotic treatment of confirmed gonorrhea cases, at or beyond 1 month post-Dose 2, will be listed.

Additional details on the analyses associated to the tertiary endpoints on immunogenicity, its association with efficacy and safety and the possible exploration of the molecular epidemiology of Ng and Ct will be provided in a dedicated statistical analysis plan for tertiary endpoints.

9.4. Handling of missing data

For the analysis of safety, missing and/or partial unsolicited AE data including start dates, end dates, severity, and relationship to study intervention, will be imputed according to GSK standard rules. All partial dates will be displayed as captured in participant listings. Other missing or unevaluable safety data, including safety laboratory measurements and eDiary data will not be imputed.

For the primary efficacy analysis, a person-time adjusted approach will be used. Missing or unobserved efficacy data will be accounted for in the calculation of person-time at risk as follows:

- For participants with an event, individual person-time at risk will be defined as the time from 1 month post-Dose 2 until the date of first confirmed gonorrhea case.
- For participants without an event, individual person-time at risk will be defined as the time from 1 month post-Dose 2 until the earliest of withdrawal date, data cut-off date or collection date of last central NAAT sample.
- In case a confirmed gonorrhea case is diagnosed prior to 1 month post-Dose 2 and is still ongoing after 1 month post-Dose 2, person-time at risk will start after this infection is considered resolved.

Both for participants with an event and participants without an event, individual person-time at risk will be calculated regardless of the number of intermittent missed/unevaluable efficacy assessments.

Any missing or inconclusive test result will not be considered in the case definition. No other imputation of efficacy data is planned.

A similar approach will be used in the analysis of other efficacy endpoints, adapting to the corresponding case definition and/or time frame under evaluation.

9.5. Interim analyses

No interim analysis is planned in the dose escalation safety lead-in part of the study.

In the PoC part, an interim futility assessment will be performed to evaluate potential significant evidence of lack of efficacy when a median observation time of approximately 180 days is reached in the total study population starting from 1 month post dose 2.

9.5.1. Sequence of analyses

In preparation for the SRT/iSRC safety evaluations during the dose-escalation safety lead-in and PoC part, analyses of available safety data will be performed by an independent data analysis center (IDAC) to maintain the study blind. Following completion of the dose-escalation safety lead-in part, all data collected in this part (up to Day 241) will be analyzed. However, a CSR will not be generated at the time of this analysis.

During the efficacy PoC part, ongoing estimates of the gonorrhea IR in the placebo group will be generated to inform the sample size adaptation plan. When a median observation time of approximately 180 days post-dose 2 is reached in the total study population, a futility assessment will be performed. The ongoing estimates of the gonorrhea IR in the placebo group as well the futility assessment will be produced by IDAC. The futility assessment results will be reviewed by an internal Data Review Committee (iDRC), including clinical, research, safety and statistics managers or representatives, independent from the study team to maintain study integrity and enable strategic vaccine development assessments. At the time of the futility assessment, key safety data will be evaluated as well by the iSRC and iDRC. The composition and responsibilities of the iSRC and iDRC will be described in a dedicated charters.

A final analysis will be performed when all data up to Day 451 are available: at this stage, primary safety endpoints will be evaluated as well as primary and secondary efficacy ones. The conclusion of vaccine efficacy will be based on the final analysis.

Tertiary endpoints will be evaluated as part of the final analysis but if the data become available at a later stage, (an) additional analysis/analyses will be performed.

9.5.2. Statistical considerations for interim analysis

The sample size adaptation based on interim estimates of the placebo IR requires no α-adjustment [FDA, 2019].

The futility assessment will be performed for the primary efficacy endpoint when a median observation time of approximately 180 days is reached in the total study population starting from 1 month post dose 2. This assessment will evaluate the VE of the HTD and bHTD at interim. Lack of benefit (futility) will be declared if the conditional power for the first efficacy analysis is <17%. The futility boundary of 17% may be subject to change to reflect subsequent program-related decisions by the sponsor and will be applied in a nonbinding way. This futility assessment requires no α-adjustment and has no major detrimental effect on the study power.

9.6. Sample size determination

The sample size for the dose-escalation safety lead-in is determined to support an adequate safety assessment of the investigational doses, including evaluation of the holding rules as detailed in Section 8.2.3. No statistical hypothesis is specified.

The initial target sample size for the efficacy PoC is 750 participants: 2 groups of 250 participants each receiving the investigational doses (i.e., the HTD and the dose below the HTD) and 1 group of 250 participants receiving placebo. Using the sequential testing procedure (see Section 9.3.1), with 627 participants (209 for each group, 47 events for each pair of investigational, HTD or below HTD, and placebo groups) there is 80% power to prove positive VE in at least one investigational dose at 1-sided $\alpha = 0.075$, assuming a 15% IR in the placebo group and a 50% true efficacy. The sequential testing procedure requires no α-adjustment. An approximate 15% drop-out rate is accounted.

The conclusion of vaccine efficacy will be based on all cases accrued at the time of the complete analysis. A number of cases higher than the required 47 cases will result in higher statistical power to prove positive vaccine efficacy.

In case only the lowest dose from the dose-escalation safety lead-in part will show tolerability and be advanced in the efficacy PoC, the initial target sample size will be 500 participants (2 groups of 250 participants each).

The sample size reassessment will be based on the results of a recurrent non comparative analysis.

Considering an initial sample size of 209 evaluable subjects in the placebo arm and a yearly IR of 15%, 31 cases are expected to be seen. The placebo IR will be monitored approximately every two months from the start of the PoC enrolment, in accordance with the enrolment rate. If there is sufficient evidence against the original assumption of 15% (based on the probability of seeing a number of cases higher than the one observed, given a Poisson distribution with a yearly rate of 15%), the sample size for each arm will be increased by a fixed number of 50 subjects per arm. Whenever a sample size increase is triggered, the assumed placebo IR will be updated to the value needed to have 31 cases in the placebo group with the new increased sample size. If, based on the observed placebo IR, the evidence to support the newly assumed placebo IR is still low, the sample size for each arm can be further increased by a fixed number of 50 subjects per arm. At every re-estimation of the placebo IR, the same computations will be performed, but the sample size can be updated no more than 3 times, when a maximum of 400 participants per group is reached. The maximum number of potential participants randomized to the study will therefore be limited to 1200 participants in total. In order to guarantee the blinding, this assessment will be performed by an independent data analysis center (IDAC); further details on the statistical methodologies and how to perform the assessment will be provided in the main statistical analysis plan (SAP).

Participants who withdraw from the study will not be replaced, since sample size computations already take into account the potential drop-out rate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3. Informed consent process

The investigator(s) or their representative(s) must fully explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary.

Freely given and written/witnessed/thumb printed informed consent must be obtained from each participant and/or each participant's witness, as appropriate, prior to participation in the study.

The content of the informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection (e.g, Health Insurance Portability and Accountability Act [HIPAA] requirements), where applicable, and the IRB/IEC or study center.

Sample testing will be done in accordance with the recorded consent of the individual participant.

The medical record must include a statement that written or witnessed/thumb printed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be re-consented if a new version of the ICF(s) or an ICF addendum is released during their participation in the study.

A copy of the ICF(s) must be provided to the participants.

Participants who are rescreened are required to sign a new ICF, only if there are changes to the original ICF. If there are no changes to the original ICF, participants should confirm that they still agree to be part of the study. This information should be captured in the participant source document.

In case of unexpected pregnancy, participant must be informed that principal investigator such as date of birth and sex of the baby will be collected as part of safety follow-up. Consent for collection of information about the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Recruitment strategy

Potential participants will be invited to participate in this clinical study by the study personnel or clinical staff (including participants' primary health physicians) in the clinic.

For Phase 2, advertisements will be placed in appropriate resources such as, but not limited to, printed media, Internet, or social media.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets transferred to the sponsor will contain only the identifier. Name and any other information which would identify the participant will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participants must be informed that:
    - Their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participants, that their data will be used as described in the informed consent.
    - Their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.6. Committees structure

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/IEC before study start. Properly constituted IRB/IEC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 [ICH, 1997]. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to GSK before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to GSK monitors, auditors, GSK Clinical Quality Assurance representatives, designated agents of GSK, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinic site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable participants within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions.
- Ensuring that appropriately trained healthcare professionals who can perform all study-related medical decisions and for ensuring appropriate medical care of participants experiencing any AE related to the study.
- If permission to do so is given by the subject and/or parent(s)/legal guardian(s), ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study participants without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- To the IRB/IEC for review and approval/favorable opinion,
- To the Sponsor for agreement and, if required,
- To the regulatory authority(ies).

10.1.7. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorisation by regulatory authorities.

Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.

GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.

GSK intends to make anonymised patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.8. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents, including source documents. The document storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential study documents may be added or removed where justified (in advance of study initiation) based on their importance and relevance to the study. When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfil the requirements for certified copies.

All participant data related to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of CRF will be provided in CRF completion guidelines.

The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants that supports information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies for such review and inspection.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data.

Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorised site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be fully explained if necessary (e.g. via an audit trail). The safety and rights of participants must be protected, and the study conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Quality tolerance limits (QTLs) will be pre-defined in the Quality Plan Quality Tolerance Limit review report to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarised in the Clinical Study Report (CSR).

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organisations).

Study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 25 years from issuance of the final CSR/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source documents

For this study, there will not be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).

Source documents provide evidence to establish the existence of the participant and substantiate the integrity of collected data. Source documents are filed at the investigator's site. The investigator should maintain a record of the location(s) of their source documents.

Data transcribed into the eCRF from source documents must be consistent with those source documents; any discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data and documents can be found in the Glossary of terms.

10.1.10. Study and site start and closure

First act of recruitment

The start of study is defined as first subject first visit (FSFV) at a country-level.

Study/Site termination

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion of GSK, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites will occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and enough notice in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

GSK aims to submit the results of the study for publication in searchable, peer reviewed scientific literature within 18 months from the Last Subject Last Visit (LSLV) for interventional studies and follows the guidance from the International Committee of Medical Journal Editors (ICMJE).

10.2. Appendix 2: Clinical laboratory test

10.2.1. Protocol required safety laboratory assessments

Table 19 Protocol required safety laboratory assessments

Laboratory assessments	Parameters	
Haematology	Platelet Count Haemoglobin	WBC count with Differential: Neutrophils Lymphocytes
Clinical chemistry	BUN	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)
	Creatinine	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)

hCG = human chorionic gonadotropin; SGOT = Serum Glutamic-Oxaloacetic Transaminase; SGPT = Serum Glutamic-Pyruvic Transaminase

Notes:

All events of ALT [or AST] ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (> 35% direct bilirubin) or ALT [or AST] ≥3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to GSK in 24 hours.

Local urine pregnancy testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

The tests detailed in Table 19 will be performed by the laboratory designated by the sponsor. Unscheduled clinical laboratory measurements may be obtained at any time during the study at the discretion of the investigator, to assess any perceived safety issues. Where tests are carried out locally, the results of each test carried must be entered in the eCRF for participants in the safety lead in part of the study and for participants in the HIV-positive and HIV-negative subset for intensive safety monitoring in the efficacy PoC part of the study.

10.2.2. Assay use for efficacy assessment

GSK plans to use the NAAT as the primary assay to demonstrate the efficacy of the NgG investigational vaccine in preventing gonococcal infection. NAAT specimens will include samples from urogenital, anorectal and oropharyngeal anatomical sites (i.e., swabs from vaginal, rectal and pharyngeal sites or first-catch urine from male participants and for those with a penis).

NAATs are designed to amplify and detect nucleic acid sequences that are specific for the organism being detected (Ng and Ct nucleic acids in this case). NAATs are the CDC-recommended assays for screening or diagnostic of Ng and Ct infections [Papp, 2014].

The performance of NAATs with respect to overall sensitivity, specificity, and convenience of specimen transport is more optimal than that of any of the other tests currently available for the diagnosis of gonococcal infections. Indeed, NAATs offer greatly expanded sensitivities of detection, usually well above 90%, while maintaining very high specificity, usually ≥99% [Papp, 2014]. The increased sensitivity of NAATs is attributable to their theoretical ability to produce a positive signal from as few as one copy of target deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). This high sensitivity has allowed for shed organisms to be detected in specimens collected through less invasive procedures, such as first-catch urine samples and vaginal swabs [Papp, 2014].

10.2.3. Immunological assessment

10.2.3.1. ELISA-*like*

To evaluate the immunogenicity of the investigational NgG investigational vaccine in humans, GSK is planning to develop an ELISA-like immunoassay. The intended use of this immunoassay will be to measure the total IgG titer against *Ng* GMMAs in blood samples.

Firstly, the assay will be optimized, and the format defined during set-up using blood samples from all the participants of the safety lead-in part (Phase 1) and from a subset of participants of the PoC part (Phase 2) of study. The optimized assay resulting from the set-up will then be used to measure all blood samples from all participants in the PoC part of the study at the 5 scheduled timepoints (plus the timepoints of confirmed gonococcal infections when applicable) as an exploratory endpoint.

For the ELISA-like immunoassay, the NgG investigational vaccine antigen will be used for the coating. The ELISA-like immunoassay will be indirect, where anti-human total IgG will be used as conjugate.

10.2.3.2. hSBA

With the aim of further characterizing the immune response of the NgG investigational vaccine, an hSBA will also be developed and adapted based on the assay used in the nonclinical phase. The assay will be set-up using blood samples from all participants included in the safety lead-in part (Phase 1) of the study and a subset of participants included in the PoC part (Phase 2) of the study, as for the ELISA-like immunoassay.

The intended use of this assay will be to assess the functionality of antibodies generated by the NgG investigational vaccine to induce complement-mediated killing of the *Ng* FA1090 vaccine strain.

The hSBA will be tested on samples collected from a subset of participants included in the PoC part of the study, as an exploratory endpoint. Approximately, the first 100 participants enrolled in each arm (n=300 total), and all participants with confirmed gonococcal infections will be tested for hSBA. This subset will be identified once the end of the study is reached and samples are unblinded in order to include all participants who tested as positive for Ng using NAAT. By then, this subset will be completed with relevant control cases. For all these participants, at least 5 scheduled timepoints (plus the timepoints of confirmed gonococcal infections when applicable) will be tested for hSBA: baseline (Visit 1), 1 month post-Dose 1 (Visit 3), pre-dose 2 (Visit 4), 1 month post-Dose 2 (Visit 6), and 13 months post-Dose 2 (Visit 10).

The hSBA assay that will be developed for the study will use human serum as the exogenous complement source.

The hSBA assay using exogenous human complement involves the following steps:

- Step 1: Serial dilutions of the heat-inactivated serum sample are prepared in a 96-well plate.
- Step 2: Bacteria are added to the sera and incubated for the appropriate time and temperature under shaking. The Ng-specific antibodies bind to the target cell surface via Ng-specific proteins or carbohydrate moieties.
- Step 3: Exogenous human complement is added to the mixture and incubated for the appropriate time and temperature under shaking.

  C1q binds the constant fragment (Fc) of the antibody and the classical complement pathway is activated, ultimately resulting in death of the bacteria.
- Step 4: The surviving bacteria will be quantified by counting either colonies or through quantification of metabolically active bacteria. The number of bacteria is inversely proportional to the presence of specific bactericidal antibodies.

CCI

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence (an unfavourable/unintended sign - including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the study intervention.

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits)
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

10.3.1.2. Events NOT Meeting the AE Definition

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

10.3.1.2. Events NOT Meeting the AE Definition

• Disease-related events (DRE), typically associated with the disease under study. These events will be recorded in the participant's eCRF and will be monitored by the Safety Review Team (SRT) on a routine basis. However, if 1 or both of the following conditions apply, then the event should be reported promptly to GSK as an SAE (see Section 10.3.8):
  • The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
  • The investigator considers that there is a reasonable possibility that the event was related to the administration of the study intervention

10.3.2. Definition of an SAE

An SAE is any untoward medical occurrence that:	
a.	Results in death
b.	Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c.	Requires hospitalisation or prolongation of existing hospitalisation Note: In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
d.	Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e.	Is a congenital anomaly/birth defect in the offspring of a study participant.
f.	Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy)
g.	Other situations

An SAE is any untoward medical occurrence that:
Medical or scientific judgement must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should be considered serious. Examples of such events are invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; and convulsions that do not result in hospitalisation.

10.3.3. Solicited events

Solicited events are predefined administration site events and systemic events for which the participant is specifically questioned, and which are noted by the participant in their eDiary.

a. Solicited administration site events

The following administration site events will be solicited:

Table 20 Solicited administration site events

Pain at administration site
Redness at administration site
Swelling at administration site

b. Solicited systemic events

The following systemic events will be solicited:

Table 21 Solicited systemic events

Fever
Headache
Myalgia (muscle pain)
Arthralgia (joint pain)
Fatigue (tiredness)

Note: Participants will be instructed to measure and record the oral temperature in the evening. If temperature is measured via routes other than oral this should be recorded in the eDiary. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the eDiary.

10.3.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited AEs must have been communicated by a participant who has signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e. symptoms or illnesses requiring a hospitalisation, or an emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended or perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

10.3.5. SAEs related to Study Participation

Any SAEs related to study participation (e.g. SAEs due to study mandated procedures, invasive tests or change in existing therapy) should be reported as per Section 8.3.3.

10.3.6. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Section 10.3.1 and Section 10.3.2).

The investigator(s) must exercise their medical and scientific judgement in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any abnormal pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an SAE. Please refer to Section 10.3.2 for definition of SAE.

10.3.8. Recording and follow-up of AEs, SAEs and pregnancies

The participants will be instructed to contact the investigator immediately should they experience any signs or symptoms they perceive as serious.

When an AE/SAE occurs, it is the investigator's responsibility to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.

The investigator will then record all relevant information regarding an AE/SAE on the eCRF.

The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers will be blinded on copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event, based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE instead of individual signs/symptoms.

An Electronic Diary (eDiary) will be used in this study to capture solicited administration site or systemic events. If the data related to the study objectives/endpoints to be collected by the participants cannot be encoded in their eDiary (e.g., unresolved technical issues), they can be reported directly to the site staff and submitted via the eCRF. The participant should be trained on how and when to complete the eDiary.

Anyone who measures administration site or systemic events and who will record the event in the eDiary should be trained on using the eDiary. This training must be documented in the participant's source record.

Collect (or uninstall app) by end of study (Visit 8 for safety lead-in and Visit 10 for PoC). and verify completed eDiary during discussions with the participant on Visit 2 and Visit 5.

Any unreturned eDiary will be sought from the participant through telephone call(s) or any other convenient procedure.

Refer to the SPM for more information regarding the use of eDiary.

10.3.8.1. Time period for collecting and recording AEs, SAEs, and pregnancies

All solicited events that occur during 7 days following administration of each dose of study intervention (Day 1 to Day 8 and Day 61 to Day 68) must be recorded into the eDiary, irrespective of intensity. An automatic reminder to complete the eDiary will be sent to the participants during this time frame. All other AEs occurring within this time frame should be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

10.3.8.2. Follow-up of AEs, SAEs, pregnancies or any other events of interest

After the initial AE/SAE/ pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up.

Other non-serious AEs must be followed until the last visit of the participant or until the participant is lost to follow-up.

10.3.8.2.1. Follow-up during the study

AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last visit of the participant.

If a participant dies during their participation in the study or during a recognised follow-up period, GSK will be provided with any available post-mortem findings, including histopathology.

10.3.8.2.2. Follow-up after the participant is discharged from the study

The investigator will provide any new or updated relevant information to GSK on a previously reported SAE using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the SAE as fully as possible.

10.3.8.2.3. Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report/electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.10.

10.3.8.3. Updating of SAE, and pregnancy information after removal of write access to the participant's eCRF

When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study contact for reporting SAEs (refer to Section 8.3.3.1 or to GSK Global Safety department within the defined reporting timeframes specified in the Table 16).

10.3.9. Assessment of intensity and causality

10.3.9.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

Table 22 Intensity scales for solicited events in adults

Event	Intensity grade	Parameter
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness at administration site		Greatest surface diameter in mm
Swelling at administration site		Greatest surface diameter in mm
Temperature*		Temperature in °C/°F
Headache	0	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue (tiredness)	0	None
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia (muscle pain)	0	None
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia (joint pain)	0	None
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

* Refer to the SoA (Section 1.3) for the definition of fever and the preferred location for temperature measurement.

The maximum intensity of injection site swelling, and redness (erythema) will be scored at GSK as follows:

0:	<25 mm
1:	25–50 mm
2:	51–100 mm
3:	>100 mm

The maximum intensity of fever will be scored at GSK as follows:

0:	<38.0°C (100.4°F)
1:	≥38.0 C but <39.0°C (≥100.4°F but <102.2°F)
2:	≥39.0°C but <40.0°C (≥102.2°F but <104.0°F)
3:	≥40.0°C (≥104.0°F)

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to 1 of the following categories:

1 (mild)	=	An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in the Section 10.3.2.

10.3.9.2. Assessment of causality

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgement. Where several different interventions were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the IB while making their assessment.

Causality should be assessed by the investigator using the following question:

Is there a reasonable possibility that the unsolicited AE may have been caused by the study intervention?

YES	:	There is a reasonable possibility that the study intervention contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study intervention. There are other, more likely causes and administration of the study intervention is not suspected to have contributed to the AE.

If an event meets the criteria to be determined 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the study intervention, if applicable.
- An error in study intervention administration.
- Other cause (specify).

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to GSK.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator(s) may change their opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.9.3. Medically attended visits

For each solicited and unsolicited AE the participant experiences, the participant will be asked if they received medical attention (defined as unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the participant's diary (for solicited AEs) and in the participant's eCRF as part of normal AE reporting (for unsolicited AEs). Medical attention received for SAEs will have to be reported using the normal AE reporting process in the eCRF.

10.3.9.4. Assessment of outcomes

The investigator will assess the outcome of all serious and non-serious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.10. Reporting of SAEs, pregnancies and other events

10.3.10.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in enrolled participant, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event.

The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The investigator will always provide an assessment of causality at the time of the initial report.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section).

If the site during the course of the study or post study becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous individual case safety reports (ICSRs).

Refer to the Table 16 for the details on timeframes for reporting of SAEs/pregnancies.

Refer to Section 10.3.10.2 for information on back-up systems in case the electronic reporting system does not work.

10.3.10.2. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designee) must fax or email a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (refer to Sponsor Information) or to GSK Global Safety department within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours after the electronic reporting system is working again. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential (WOCBP)

A *cis* woman or a *trans* man is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

10.4.1.2. Women not considered as women of childbearing potential

- **Premenarchal**

  Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

  Additional evaluation should be considered if a participant's fertility status is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention.

- **Premenopausal female with ONE of the following:**
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Transgender men taking gender affirming hormonal therapy with testosterone cannot be considered of not childbearing potential, even in the presence of amenorrhea.

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview. For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

- **Postmenopausal female**

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause (for instance testosterone treatment in *trans*men). A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

  - Females on HRT and whose menopausal status is in doubt will be required to use a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception guidance

- Female participants (*cis* women and *trans* men) of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 23).

Table 23 Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent[a] ***Failure rate of <1% per year when used consistently and correctly.***
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Injectable • Oral

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal ligation or occlusion
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. Sexual abstinence should not be considered a valid method of contraception in the PoC part of this trial, given that participants must be sexually active. If, however, changes in personal circumstances occur for which a participant is no longer sexually active, abstinence may be considered acceptable.

*Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies

10.4.2.1. Contraception advice for *trans*men

*Trans*men should be counselled for contraception if they engage in hetero-sexual activity relative to their biological sex and if they have not undergone gender affirming surgical procedures that makes them infertile [Mancini, 2021].

Some studies report cases of unintended pregnancies among *trans*gender men under masculinizing therapy, therefore testosterone treatment cannot be considered a contraceptive option.

Testosterone does not represent a contraindication to any form of contraception (hormonal or nonhormonal methods) therefore all options may be offered to *trans*men. There is no research demonstrating possible negative effects of hormonal contraceptives when combined with testosterone treatment. Each birth control method has its potential benefits and drawbacks, therefore tailored counseling should be offered in order to customize the prescription. Most considerations regarding contraception are the same as those for *cis*gender women, therefore eligibility criteria for contraceptive use should be consulted even though it should be recognized that the needs and concerns in *trans*men may be different.

Most *trans*men want to avoid all contraceptive options that may be a source of gender dysphoria: daily or weekly medications that remind them of their gender incongruency may be uncomfortable and unacceptable, estrogen-containing contraceptives are perceived as contrasting compounds to the testosterone masculinizing effect, contraceptive methods that require pelvic procedures, such as the vaginal ring or IUD , or options that may cause breast tenderness at the initiation cause concerns in this population. Subdermal implants may be a good option for *trans*men. They represent the most effective methods of birth control in cisgender women, do not require any pelvic procedure for delivery, can be used for at least 3 years without the necessity of daily or

weekly action, and are easily concealed. Implants are progestin-only options containing levonorgestrel or etonogestrel. These are compounds with androgenic activity that may act synergistically and additively with testosterone in the induction of male physical changes (hirsutism, androgenic alopecia, male fat distribution). All these benefits avoid the recurrent reminder of their birth gender and subsequent dysphoria with the assumption of these hormones perceived as counteracting the masculinizing process. Other progestin-only options, such as depot medroxyprogesterone acetate or levonorgestrel intrauterine device show potential benefits in the *trans*men population: complete menstrual suppression, reduction of abnormal vaginal bleeding, and contraceptive efficacy are some benefits of these medications without the assumption of "feminizing" hormones

10.4.2.2. Female participants who become pregnant

Refer to Section 8.3.1, Section 8.3.2, Section 10.3.8.1, Section 10.3.8.2 and Section 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study will not receive any further dose of study intervention until the pregnancy/breastfeeding is concluded.

Pregnant partners of male participants will not be followed to determine the outcome of the pregnancy, since no impact of the vaccine on spermatogenesis nor transfer via semen is anticipated, and therefore no teratogenicity is expected in pregnant partners.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Definition of medical device AE, adverse device effect (ADE), serious adverse device effect (SADE) and unanticipated SADE (USADE)

10.6.1. Definition of medical device AE and adverse device effect (ADE)

- Medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether considered related to a medical device or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is an AE related to the use of a medical device. This definition includes any AE resulting from:
  - insufficient or inadequate instructions for use (i.e., user error), or
  - any malfunction of a medical device, or
  - intentional misuse of the medical device.

10.6.2. Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term ‘life-threatening' in the definition of ‘serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • ***Chronic disease (MDR 2017/745)***
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product.

Serious Adverse Device Effect (SADE) definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, ***intervention had not occurred,*** or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the IB (see Section 2.3).

10.6.3. Definition of device deficiency

Device deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.6.4. Recording and reporting of medical device AE, ADEs, SADEs and USADE

- Any device deficiency must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- Refer to paper 'Medical device or combination product with device deficiency/incident report form' for details on transmission of this information to the sponsor.
- GSK will review all device deficiencies, determine, and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- If required or in case of any issues refer to the general safety contacts for SAE/AE reporting in Section 8.3.3.1.

10.6.5. Reporting of Medical Device Deficiencies for Associated Person

- If an Associated Person (e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the safety reporting information and authorization to contact physician letter.
- If follow up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent.

- Medical device deficiencies should be reported using the medical device deficiency report form.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for Medical Device Deficiency reporting can be found in the medical device deficiency report form.

10.7. Appendix 7: Country-specific requirements

10.7.1. Requirements for France

This appendix includes all applicable requirements of French Public Health Code/specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the "SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA"

- Subjects will be compensated for the inconvenience of participating in the study. The amount of compensation is stated in the Informed Consent Form. Subjects not completing the study for whatever reason could be compensated generally on a pro rata basis.
- According to French Public Health Code (L.1121-16 and R.1121-16), the following people must be registered in National File ("Fichier National"):
    - Healthy volunteer;
    - Subjects if the aim of the study is not linked to their disease;
    - Subjects on request of the Ethics Committee regarding study risks and constraints.

The following details will be described:

- Reference of the study
- Surname and first name
- Date and place of birth
- Gender
- Dates of beginning and termination of the study
- Exclusion period during which the subject cannot participate to another study (French Public Health Code L.1121-12)
- The total amount of compensation.

The subjects' registration in National File ("Fichier National") should be documented in the source document - subject notes and monitored by the CRA.

- The following vulnerable subject populations will be excluded of compensation for the inconvenience of participating in the study: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.
- A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code L.1124-1). It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject: is affiliated to or beneficiary of a social security category.

2. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process"**
  - Concerning **the process for informing the subject** and/or his/her legally authorized representative, the following text is added:

    French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the single scientific and ethical regulatory authorisation.
  - Concerning **the process for obtaining** subject informed consent:
    - **if the subject is minor**, the following text is added:

      The informed consent of the holders of parental authority must be obtained before the beginning of the study. The consent of the child will be also sought when he/she is old enough to express his/her opinion. His/her refusal or the revocation of his/her consent cannot be disregarded. If there is only 1 holder of parental authority, the investigator will ask the present person to file, date and sign the parental certificate indicating their situation regarding the parental authority. A copy of this parental certificate is joined to each consent form.

  If these directives are not followed, the subject inclusion could be considered as a protocol violation and the data of this case won't be taken into account.

  - When a research involving human being **is carried out on a minor / on an adult in the care of a "tutelle" guardian**, consent is given by their legal representative.
  - **Concerning the management of the Patient Informed Consent Forms**, the following text is added:

    French Patient Informed Consent Form is in duplicate (triplicate for minor subject).

The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

In accordance with Article R.1123-69 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- **INFORMATION TO THE HOSPITAL PHARMACIST**

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g., included in the CIB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

3. Concerning the " DATA MANAGEMENT " the following text is added:

- Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GlaxoSmithKline data bases by Laboratoire GlaxoSmithKline or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Data Protection French Law n° 78-17 of 6th January 1978 updated and the General Data Protection Regulation (GDPR), each of these people aforesaid has a right of access, correction, and opposition on their own data through GlaxoSmithKline Laboratory (Clinical Operations Department).

- **Ethnic Origin**

  In accordance with the Data Protection French Law n° 78-17 of 6th January 1978 updated – article 4-3°, the ethnic origin can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

  In accordance with the French Public Health Code– article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

4. Monitoring visits

The Health Institution and the Investigator agree to receive on a regular basis a Clinical Research Assistant (CRA) of GLAXOSMITHKLINE or of a service provider designated by GLAXOSMITHKLINE. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GLAXOSMITHKLINE or from a service provider designated by GLAXOSMITHKLINE. In addition, the Health Institution and the Investigator agree that the CRA or the service provider designated by GLAXOSMITHKLINE have direct access to all the data concerning the Study (test results, medical record, etc …). This consultation of the information by GLAXOSMITHKLINE is required to validate the data registered in the electronic Case Report Form (eCRF), in particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

5. Data entry into the eCRF

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's electronic Case Report Form (eCRF) use here below:

The Health Institution and the Investigator undertake:

1. That the Investigator and the staff of the investigator center make themselves available to attend the training concerning the computer system dedicated to the electronic Case Report Form (eCRF) of the Study provided by GLAXOSMITHKLINE or by a company designated by GLAXOSMITHKLINE.
2. That the Investigator and the staff of the investigator center use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
3. That the Investigator and the staff of the investigator center use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GLAXOSMITHKLINE.
4. To keep the IT Equipment and/or access codes in a safe and secure place and to authorize only the use of this IT Equipment by investigator center staff designated by the principal investigator to enter the data of the Study.
5. To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
6. To return at the end of the Study the IT Equipment and/or access codes to GLAXOSMITHKLINE or to any company designated by GLAXOSMITHKLINE and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

6. CTR publication

It is expressly specified that GLAXOSMITHKLINE and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GLAXOSMITHKLINE GROUP named Clinical Trial Registred (CTR) including the registration of all the clinical trials conducted by the GLAXOSMITHKLINE Group and this before or after the publication of such results by any other process.

7. Data Protection French Law of 6th January 1978 updated (CNIL)

In accordance with the Data Protection French Law of 6 January 1978 updated, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference (MR-001) or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GLAXOSMITHKLINE in accordance with the legal provisions.

10.7.2. Requirements for Germany

Prior to any rSDV activity a written agreement by the investigator will be obtained. The agreement include the extent and the method of rSDV activities.

Monitoring Plan and Study Specific Risk Register will be updated to include rSDV activities. CRAs will be guided for the conduct of rSDV (refer to separate document " Guidance for CRAs when conducting rSDV")

Option 1 Transfer of redacted Source Documentation

Process for transfer and review of redacted source documentation provided by the site:

The CRA instructs study site on the source data needed for the remote SDV activities.

The CRA instructs site staff they must pseudonymize the requested documentation, do a quality check that anonymized (redacted) areas cannot be read, and then delivers the documentation to the CRA in an encrypted form of communication (the site should have a documented process).

The minimum requirements regarding quality of the copies will be agreed with the site upfront:

- For the scanning of paper documents resolution will be a minimum of 300 dots per inch (dpi).
- For the scanning of photographs and images resolution will be 600 dots per inch (dpi) minimum.
- Color scanners must be able to produce copies that match the original.

- A4 format as final size without loss of information.
- Documents will be saved as portable document format (PDF).

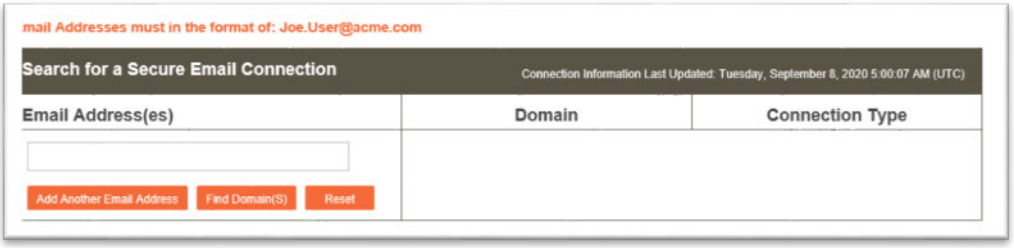
In order to maintain quality standards, a captured image will not be subjected to non-uniform scaling (i.e. sizing) or re-sampling to a lower resolution.

- Redacted source document scans will be sent to the CRA via email using one of the following secure options:
  - **(a) Transport Layer Security (TLS) connection:**

    TLS connections are intended to support significant mail flow between GSK and external partners in a secure manner.
  - **(b) GSK Secure**

    In cases where only a handful of users are communicating or the volume of emails is low, the use of GSK secure, the GSK ad-hoc message encryption solution is recommended.
  - **(c) Password protected PDF attachment**

    A password protected scan (PDF) will be attached to an email. The password to open the attachment will be send in a separate email.
- The CRA may use the secure email website to assess whether the sites email address is secure (i.e. encrypted).



- Prior to starting remote SDV the CRA ensures that the provided documents is complete and does not contain any Personal Information (PI).
  - In case the CRA detects any PI that has not been redacted, the CRA informs the study site and deletes the files (incl. the Recycle bin).
  - A Data Breach must be reported Data Breach Web Report Form.
- Use of an external PC screen is recommended. The CRA will not generate any copies from the source data received.
- Source data verification/review will be conducted according to the process outlined in the GSK Monitoring SOP.
- After completion of SDV activities, the CRA deletes all copies/images of subject data received from the site. This includes the deletion of the recycle bin and any temporary files.

- A statement confirming that all documents were destroyed will be provided by the CRA via email to the site.
- Details of what was monitored remotely will be documented in the appropriate section of the Monitoring Visit Report.

Option 2 – Review of Subject Source Documentation remotely

Process for use of Webcams, WebEx, MS Teams for viewing subject source remotely:

- The CRA ensures that the site personnel sharing information with GSK have authority to do so.
- Remote SDV activities will be performed exclusively by the assigned site monitor.
- Prior to conducting any remote SDV activities the CRA ensures that a written Informed Consent, covering the proposed SDV activities, has been signed by the study patient.
- For CRAs using GSK laptops only use GSK approved video conferencing tools (eg. MS Teams or GSK WebEx). Live image transmission is fully encrypted and protected for authorized user. By using these systems it will be assured that data will be viewed only but not transmitted/stored.
- FSP/Local CRO CRAs not using GSK laptops only MS Teams via RAA (Remote Access Application) may be used for meetings between the CRA and the site. WebEx is not permitted from non-GSK laptops. Other tools like FaceTime, WhatsApp or Zoom are not permitted since they do not have sufficient encryption features, GSK does not have an enterprise contract/privacy agreement with these providers.
- Prior to the remote monitoring visit, the CRA instructs study site on the specific data needed for the remote SDV.
- Source data verification will be conducted according to the process outlined in the Monitoring SOP.
- The use of a headset is required, do not use computer audio.
- The CRA does not capture screens or take pictures of screens to ensure we are not transferring content outside of clinical sites.
- Webex or Teams do not store or have access to any data, GSK staff is not allowed to make or store any screenshots or save any data which has been shared.
- Details of what was monitored remotely will be documented in the appropriate section of the MVR.
- In case of technical malfunctions or if the security of the transmission is no longer ensured we will pause rSDV activitities. GSK Issue Management Procedures will be initiated.

10.7.3. Requirements for Brazil

Data quality assurance

Study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for ***15*** years from issuance of the final CSR/equivalent summary. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.7.4. Requirements *for UK*

Study holding rules

Holding rules are defined to ensure well-controlled exposure to the NgG investigational vaccine and they will apply to study participants who have received investigational vaccine in the study as detailed in Section 8.2.3.3. The holding rules will hence serve as criteria to point attention to safety signals that require escalation within GSK, and meeting any of the holding rules will trigger a hold of vaccination. If any of the study holding rules in Table 12 or Table 13 of Section 8.2.3.3 are met and confirmed following unblinded review, any subsequent restart of the study in the UK will require prior approval by the Medicines and Healthcare products Regulatory Agency (MHRA) of a substantial amendment summarising the clinical data and rationale for the restart.

10.8. Appendix 8: Abbreviations and glossary of terms

10.8.1. List of abbreviations

A&E	Accident and Emergency
ADE	Adverse Device Effect
AE	Adverse Event
ALT	Alanine Transferase
AMR	Antimicrobial Resistance
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
BS	Blood Sample

BS-A	Blood Sample for Assay development
BS-H	Blood Sample for Humoral immune response
BS-S	Blood Sample for Safety evaluation
BS-S/A	Blood Sample only for Safety evaluation and Assay development
BUN	Blood Urea Nitrogen
CDC	Center for Disease Control
CI	Confidence Intervals
CIOMS	Council for International Organisations of Medical Sciences
CLS	Clinical Laboratory Sciences
COVID-19:	Novel Coronavirus disease 2019
CSR	Clinical Study Report
Ct	*Chlamydia trachomatis*
DAIDS	Division of Acquired Immunodeficiency Syndrome
DGI	Disseminated Gonococcal Infection
DNA	Deoxyribonucleic Acid
DRE	Disease-related event
eCRF	electronic Case Report Form
EoS	End of Study
ER	Emergency Room
FDA	Food and Drug Administration, United States of America
FSFV	First Subject First Visit
FSH	Follicle Stimulating Hormone
FTiH-PoC	first time in human - proof of concept
GCP	Good Clinical Practice

GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
HTD	Highest Tolerated Dose
IAF	Informed Assent Form
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IDAC	Independent Data Analysis Centre
iDRC	Internal Data Review Committee
IEC	Independent Ethics Committee
IM	Intra-Muscular
IND	Investigational New Drug
IRB	Institutional Review Board
iSRC	Internal Safety Review Committee
IUD	Intra-Uterine Device
IUS	Intra-Uterine System
IWRS	Interactive Web Response System
LLOQ	Lowe Limit of Quantitation

LOD	Limit Of Detection
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MSM	Men having Sex with Men
MSW	Men having Sex with Women
NAAT	Nucleic Acid Amplification Test
Ng	*Neisseria gonorrhoeae*
NgG	*Neisseria gonorrhoeae* GMMA
NIH	National Institutes of Health
OMV	Outer Membrane Vessicle
PCD	Primary Completion Date
PCR	Polymerase Chain Reaction
PID	Pelvic Inflammatory Disease
PoC	Proof of Concept
PP	Per Protocol
QTL	Quality Tolerance Limit
RNA	Ribonucleic Acid
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	Source data Base for Internet Randomization
SE	Safety Evaluation by Safety Review Team (SRT)/ iSRC chair (blinded review) or iSRC (unblinded review)
SE*	Safety Evaluation by Safety Review Team (SRT) and unblinded safety evaluation by iSRC
SGOT	Serum Glutamic-Oxaloacetic Transaminase

SGPT	Serum Glutamic-Pyruvic Transaminase
SI	International System of Units
SoC	Standard of Care
SPM	Study Procedures Manual
SRT	Safety Review Team
STI	Sexually Transmitted Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal
US	United States (of America)
USADE	Unanticipated Serious Adverse Device Effect
USD	United States Dollars
UV	Unscheduled Visit
VE	Vaccine Efficacy
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

10.8.2. Glossary of terms

Adverse event:

Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Blinding:

A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event

In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment.

Caregiver:

A ‘caregiver’ is someone who

- lives in the close surroundings of a participant and has a continuous caring role or
- has substantial periods of contact with a participant and is engaged in their daily health care (e.g. a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home).

In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified procedures.

Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Combination product:	Combination product comprises any combination of • drug • device • biological product Each drug, device and biological product included in a combination product is a constituent part.
Comparator:	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
eDiary	Electronically registered patient data and automated data entries on, for example, a handheld mobile device, tablet or computer.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced

eTrack:	GSK's tracking tool for clinical studies.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Gender:	Is the state of being male or female in relation to the social and cultural roles that are considered appropriate for men and women. People who identify themselves with a gender conforming to their biological sex are cisgender, whereas people who identify their gender with the opposite biological sex are transgender. if neither of these 2 apply, the term "gender nonconforming" may be used.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Investigational vaccine:	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. Synonym: Investigational Product
Investigator:	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions

Legally acceptable representative:	An individual, judicial or other body authorised under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorised representative are used in some settings.
Medical device deficiency:	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Pharmacogenomics:	The International Council on Harmonisation (ICH) E15 Guidance for Industry defines pharmacogenomics as the, "Study of variation of DNA and RNA characteristics as related to drug or treatment response." Pharmacogenetics, a subset of pharmacogenomics, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g. mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research is not pharmacogenomics.

Placebo:	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical study was concluded according to the pre-specified protocol or was terminated.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit:	This term refers to the visit conducted in the place other than the study site.
Self-contained study:	Study with objectives not linked to the data of another study.
Sex:	Is defined by a set of anatomical and biological characteristics and is either male or female. Sexual orientation is the term used to refer to a person's sexual (erotic) feelings. Terms like homosexual, heterosexual, bisexual, gay, straight, or bi, refers to that person's sexual orientation.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data

	are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical study).
Standard of Care:	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. 1. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Study monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Sub-cohort:	A group of participants for whom specific study procedures are planned as compared to other participants or a group of participants who share a common characteristic (e.g. ages, vaccination schedule, etc.) at the time of enrolment.
SUSAR:	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting.

Telemedicine:	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, patient and professional health-related education, public health and health administration.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Virtual visit:	This term refers to study visits conducted using multimedia or technological platforms.

10.9. Appendix 9: Toxicity grading scales

Table 24, derived from the NIH Guidance: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1 July 2017) [NIH, 2017], will be used to determine the toxicity grades of hematology and biochemistry results for HIV positive safety subset in the PoC part of the study.

For HIV negative participants in both safety lead-in and PoC parts of the study, Table 25, derived from the FDA Guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007) [FDA, 2007], will be used to determine the toxicity grades of hematology and biochemistry results.

Table 24 Toxicity Grading Scale for HIV positive safety subset in PoC part of the study with SI units

Parameter	Unit	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Chemistry					
Blood Urea Nitrogen BUN[1]					
Creatinine, High *Report only one		1.1 to 1.3 x ULN[4]	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
ALT/AST, High		1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Hematology					
Hemoglobin[2], Low ≥ 13 years of age (male only) Change from baseline value refer to Table 25[3]	g/dL	10.0 to 10.9	9.0 to < 10.0	7.0 to < 9.0	< 7.0
	SI unit: g/L (1 g/dL= 10 g/L)	100 to 109	90 to < 100	70 to < 90	< 70
Hemoglobin[2], Low ≥ 13 years of age (female only) Change from baseline value refer to Table 25[3]	g/dL	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5
	SI unit: g/L (1 g/dL= 10 g/L)	95 to 104	85 to < 95	65 to < 85	< 65
WBC, decreased > 7 days of age	cells/mm^3	2000 to 2499	1500 to 1999	1000 to 1499	< 1000
	SI unit: 10^9cells/L (1 10^9cells/L= 1/1000 cells/mm^3)	2.00 to 2.49	1.50 to 1.99	1.00 to 1.49	< 1.00

Parameter	Unit	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Absolute Lymphocyte Count, Low **> 5 years of age (not HIV infected)**	cells/mm^3	600 to < 650	500 to < 600	350 to < 500	< 350
	SI unit: 10^9/L (1 10^9cells/L= 1/1000 cell/mm^3)	0.60 to < 0.65	0.50 to < 0.60	0.35 to < 0.50	< 0.35
Absolute Neutrophil Count (ANC), Low **> 7 days of age**	cells/mm^3	800 to 1000	600 to 799	400 to 599	< 400
	SI unit: 10^9/L (1 10^9cells/L= 1/1000 cell/mm^3)	0.80 to 1.00	0.60 to 0.79	0.40 to 0.59	< 0.40
Platelets, Decreased	cells/mm^3	100000 to < 125000	50000 to < 100000	25000 to < 50000	< 25000
	SI unit: 10^9 cells/L (1 10^9cells/L= 1/1000 cell/mm^3)	100.00 to < 125.00	50.00 to < 100.00	25.00 to < 50.00	< 25.00

ALT = alanine aminotransferase; ANC, absolute neutrophil count; AST = aspartate aminotransferase; HIV, human immunodeficiency virus

*Reminder: Choose the method that selects for the higher grade.

[1]No Blood Urea Nitrogen (BUN) specific gradings were reported for HIV positive individuals, the values for HIV negative individuals should be used (Table 25)

[2]Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[3] No hemoglobin (Female and Male) change from baseline values were reported for HIV positive individuals, the values for HIV negative individuals should be used (refer to Table 25)

[4]ULN is the upper limit of the normal range.

Table 25 Toxicity Grading Scale for HIV negative safety subsets in safety lead-in PoC parts of the study with SI units and specific boundaries for grading categories

Parameter*	Unit	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)**
Chemistry					
Blood Urea Nitrogen BUN	mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
		23.0 to <26.5	26.5 to 31.0	>31.0	Requires dialysis
	mmol/L (1 mg/dL= 0.3571 mmol/L)	8.21 to <9.46	9.46 to 11.07	>11.07	Requires dialysis
Creatinine	mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
		1.50 to <1.75	1.75 to <2.05	2.05 to 2.50	>2.50 or requires dialysis
	µmol/L (1 mg/dL= 1/0.0113 µmol/L)	132.74 to <154.87	154.87 to <181.42	181.42 to 221.24	> 221.24 or requires dialysis
Liver Function Tests –ALT, AST increase by factor		1.1 – 2.5 x ULN[1]	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
		1.10 to <2.55 x ULN	2.55 to <5.05 x ULN	5.05 to 10.00 x ULN	> 10.00 x ULN
Hematology					
Hemoglobin (Female)	gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
		10.95 to 12.00	9.45 to <10.95	8.00 to <9.45	<8.00
	SI unit: g/L (1 g/dL= 10 g/L)	109.5 to 120.0	94.5 to<109.5	80.0 to <94.5	<80.0
Hemoglobin[3] (Male)	gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
		12.45 to 13.50	10.45 to <12.45	8.50 to <10.45	<8.50
	SI unit: g/L (1 g/dL= 10 g/L)	124.5 to 135.0	104.5 to <124.5	85.0 to <104.5	<85.0

Parameter*	Unit	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)**
Hemoglobin[3] (Female and Male) change from baseline value	gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
		0[2]< to <1.55	1.55 to <2.05	2.05 to 5.00	>5.00
	SI unit: g/L (1 g/dL= 10 g/L)	0[2]< to <15.5	15.5 to <20.5	20.5 to 50.0	>50.0
WBC Increase	cell/mm^3	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
		10800.0 to <15000.5	15000.5 to <20000.5	20000.5 to 25000.0	>25000.0
	SI unit: 10^9cells/L (1 10^9cells/L= 1/1000 cell/mm^3)	10.8 to <15.0	15.0 to <20.0	20.0 to 25.0	>25.0
WBC Decrease -	cell/mm^3	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
		2499.5 to 3500.0	1499.5 to <2499.5	1000.0 to <1499.5	<1000.0
	SI unit: 10^9cells/L (1 10^9cells/L= 1/1000 cell/mm^3)	2.499 to 3.500	1.499 to <2.499	1.000 to <1.499	<1.000
Lymphocytes Decrease	cells/mm^3	750 – 1 000	500 – 749	250 – 499	< 250
		749.5 to 1.000	499.5 to <749.5	250.0 to <499.5	<250.0
	SI unit: 10^9/L (1 10^9cells/L= 1/1000 cells/mm^3)	0.749 to 1.000	0.499 to <0.749	0.250 to <0.499	<0.250
Neutrophils Decrease	cell/mm^3	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
		1499.5 to 2000.0	999.5 to <1499.5	500.0 to <999.5	<500.0
	SI unit: 10^9/L (1 10^9cells/L= 1/1000 cells/mm^3)	1.499 to 2.000	0.999 to <1.499	0.500 to <0.999	<0.500

Parameter*	Unit	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)**
Platelets Decreased	cells/mm^3	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000
		124500 to 140000	99500 to <124500	25000.0 to <99500	<25000.0
	SI unit: 10^9/L (1 10^9cells/L= 1/1000 cells/mm^3)	124.5 to 140.0	99.5 to <124.5	25.0 to <99.5	<25.0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = Blood Urea Nitrogen; SI; International System of Units; WBC = white blood cell

*The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

**The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4).

[1]ULN is the upper limit of the normal range.

[2]Baseline result – result at visit; only decrease is graded.

[2]Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

10.10. Appendix 10: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 7	03 Dec 2024
Amendment 6	05 June 2024
Amendment 5	28 November 2023
Amendment 4	27 April 2023
Amendment 3	10 March 2023
Amendment 2	20 January 2023
Amendment 1	19 October 2022

10.10.1. Protocol Amendment 6

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC.

In the below sections (Section 10.10.1 to Section 10.10.6), added text is formatted in ***bold italics***, and deleted text is formatted as ~~strikethrough~~.

Amendment 6: 05 June 2024

Overall Rationale for the Amendment: This protocol amendment primarily aims at updating the case definition for gonorrhoea and at removing the option of performing urogenital swab sampling for male participants and others with a penis. The sequence of analysis was also updated to ensure that futility and efficacy evaluations are performed with an adequate duration of observation. The analyses are no longer triggered by a prespecified number of events, but will use all cases accrued at the time of analyses.

During blinded case accrual monitoring, a higher than anticipated attack rate of gonorrhea cases was observed. The sequence of analysis being event-driven, the number of cases required to trigger efficacy and futility assessments would be reached with limited observation time. These analyses, if conducted as originally planned, would not answer the research question of the study. Therefore, the sequence of analyses was updated and analyses are no longer triggered by reaching a predefined number of events.The primary analysis will be conducted using all cases accumulated until the end of the study. The futility interim analysis will be conducted once a median follow-up time of approximately 6 months is reached, and it will include all cases accumulated up to that point.

Also, sections are aligned to harmonise with the latest protocol template. Minor edits for clarification and correction of typographical errors have been made (see below for information) in the statistical sections.

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	Footnote 10: Added footnote to provide instructions for collection of blood samples.	To clarify that immunogencity is evaluated as well at Visits 7, 8, and 9 in case of suspicion of gonococcal infection.
Section 3 Objectives, endpoints, and estimands	Deleted the description of "at time points of confirmed gonorrhea cases where applicable" from endpoints associated with objective of humoral immune response to the NgG vaccine.	The "time points of confirmed gonorrhea cases where applicable" is valid only for the association between humoral immune response and vaccine efficacy which is covered by separate tertiary objective/endpoint.
Section 4.1.2 Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea Section 8.1.1 Biological samples Section 8.1.2 Read-out for efficacy assessments	Deleted the urogenital swab for male participants and those with a penis.	To clarify that only first-catch urine samples will be collected for the detection of genital infections in male participants and those with a penis.
Section 4.2.2 Case definition Section 9.4 Handling of missing data	Clarified the case definition for gonococcal infections.	To further clarify the different conditions under which a gonorrhea case can be considered as resolved.
Section 8.2.1.1 Collection of demographics data	Added instructional text from new protocol template.	To provide additional instructions and harmonise with the latest protocol template.
Section 8.3 Adverse Events (AEs), Serious Adverse Events (SAEs) and other safety reporting Section 8.3.2 Method of detecting AEs and SAEs, pregnancies and other events Section 8.3.6 Medical device deficiencies Section 8.3.6.1 Detection, follow-up, and prompt reporting of medical device deficiency	Added instructional text from new protocol template.	To harmonise with protocol template.
Section 9.3.4 Other explratory analyses	Deleted the 95% CI from the analyses.	To avoid assumptions on the distributions of exploratory endpoints, which are unknown. These details will be included in the SAP.

Section # and Name	Description of Change	Brief Rationale
Section 9.5 Interim analyses Section 9.5.1 Sequence of analyses Section 9.5.2 Statistical considerations for interim analysis	The sequence of analyses was updated to dissociate the futility and efficacy assessments from a predefined number of events.The primary analysis will be conducted using all cases accumulated until the end of the study. The futility interim analysis will be conducted once a median follow-up time of approximately 6 months is reached, and it will include all cases accumulated up to that point. Also, added the information on internal Data Review Committee (iDRC).	To ensure that efficacy and futility analyses are performed with an adequate duration of observation. Due to the higher than anticipated attack rate of gonnorhea cases, the number of cases required to trigger futility and efficacy assessments would be reached with limited observation time. If conducted as originally planned, these analyses would not answer the research question of the study. To clarify that the futility assessment result will be reviewed by an iDRC.
Section 9.6 Sample size determination	Updated to indicate that all cases accrued until end of study will be used in the vaccine efficacy analyses.	To clarify that the statistical power to reject the null hypothesis will be higher than 80%, if the total number of cases used for analysis exceeds 47.
Section 10.1.3 Informed consent process Section 10.1.5 Data protection Section 10.1.7 Dissemination of clinical study data Section 10.1.8 Data quality assurance Section 10.1.9 Source documents Section 10.1.10 Study and site start and closure	Added instructional text from new protocol template.	To provide additional instructions and harmonise with the latest protocol template.
Section 10.3.1.2 Events Not Meeting the AE Definition Section 10.3.3 Solicited events Section 10.3.10.1 Events requiring expedited reporting to GSK	Added instructional text from new protocol template.	To provide additional instructions and harmonise with the latest protocol template.
Section 10.6.2 Definition of medical device SAE, SADE and USADE Section 10.6.3 Definition of device deficiency	Added instructional text from new protocol template.	To provide additional instructions and harmonise with the latest protocol template.
Section 10.7.3 Requirements for Brazil	Updated the retention period from “5” to “15” years.	To align with local legislation.

In the following sections, deleted text is indicated in ~~strikethrough~~ and changed text in ***bold italics***:

In Table 3 Schedule of activities of efficacy PoC Footnote 10 is added.

[10] If, at Visit 7, Visit 8 or Visit 9, a study participant shows signs and/or symptoms suggestive of gonococcal infection, tested positive for Ng outside of the study schedule and has not yet received treatment or had a recent sexual contact with a partner with a confirmed diagnosis of gonococcal infection, the investigator will collect blood samples for immunogenicity as described in Section 8.1.1.

In Section 3 Objectives, Endpoints, and Estimands

Tertiary	
To evaluate the humoral immune responses to the NgG vaccine.	• Anti-NgG IgG antibodies Geometric mean concentrations (GMCs) at Day 1, Day 31, Day 61, Day 91, ***and*** Day 451, ~~***and at time points of confirmed gonorrhea cases***~~ where applicable. • hSBA Geometric mean titres (GMTs) against Ng strain at Day 1, Day 31, Day 61, Day 91, ***and*** Day 451, ~~and ***at time points of confirmed gonorrhea cases*** where applicable~~.[8]

In Section 4.1.2 Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea

- **Sampling schedule:**
- Blood samples for laboratory safety evaluation will be drawn from all participants in the two intensive safety monitoring subsets (as defined here below) at Screening, Visit 2 (Day 8), Visit 4 (Day 61), and Visit 5 (Day 68).
  - Blood samples for humoral immunogenicity will be drawn from all participants at Visit 1 (Day 1), Visit 3 (Day 31), Visit 4 (Day 61), Visit 6 (Day 91), Visit 10 (Day 451), and at unscheduled visit(s) when performed. ELISA-like immunoassay will be performed in all participants. ~~At least~~***Approximately,*** the first 100 participants enrolled in each arm (n=300 total), and all participants with confirmed gonococcal infections will be tested for human serum bactericidal assay (hSBA).

– NAAT samples* including swabs (urogenital, anorectal, and pharyngeal sites) and***/or*** first-catch urine ~~sample which may be collected as an alternative to the urogenital swab~~***samples*** for male participants and those with a penis, will be collected from all participants at Screening, Visit 3 (Day 31), Visit 4 (Day 61), Visit 6 (Day 91), Visit 7 (Day 181), Visit 8 (Day 271), Visit 9 (Day 361), Visit 10 (Day 451), and at unscheduled visit(s) when performed

** Sampling for Ct/Ng must be performed by qualified healthcare professionals. Self-swabbing is only allowed to collect vaginal swab. Participants must be trained on how to perform self-sampling if this is going to occur. All participants will be tested from all 3 anatomical sites (urogenital, rectal, and pharyngeal). ~~Preferably, a~~**A** first-catch urine sample will be collected instead of a swab for the detection of genital infection in male participants (and those with a penis~~) but urogenital swab is acceptable, whereas~~ a vulvo/vaginal or cervical swab will be ~~required over~~**collected for** the ~~urine sample~~**detection of genital infection** in female participants (and those with a vagina)….*

In Section 4.2.2 Case definition

- ~~***In absence of antibiotic treatment, a gonorrhea case cannot be considered as resolved. In case of persistent gonococcal infection detected by subsequent positive NAAT samples at the same anatomical site when no intercurrent treatment was given, this gonococcal infection will be counted as a single gonorrhea case, with a start date of the first positive NAAT sample, and an end date of the antibiotic treatment administration. In case of early gonococcal infection prior to 1 month post-Dose 2, a gonorrhea case may be considered for the primary endpoint only if it occurs after the initiation of antibiotic treatment for this early gonococcal infection.***~~
- ***In case a highly effective antibiotic treatment is administered, the gonorrhea case will be considered as resolved 7 days after the completion of antibiotic treatment, or alternatively, at the date of a subsequent NAAT negative for Ng by central lab at the affected anatomical location, whichever comes first. In case an alternative antibiotic treatment is administered, the gonorrhea case will be considered as resolved at the date of subsequent test of cure (TOC, see section 8) negative for Ng at the affected anatomical location, or at the date of a subsequent NAAT negative for Ng by central lab at the affected anatomical location, whichever comes first. In case no antibiotic treatment is administered, the gonorrhea case will only be considered as resolved if a subsequent NAAT negative for Ng by central lab at the affected anatomical location is obtained. In case of early gonococcal infection prior to 1 month post-Dose 2, a subsequent gonorrhea case may be considered for the primary endpoint only if the previous gonococcal infection is considered as resolved as described above. For further details on the case definition for primary and secondary endpoints, please refer to the statistical analysis plan (SAP).***

<u>For both:</u>

- ***Proctitis: mucopurulent anal discharge, anorectal bleeding, anorectal pain, anorectal itch, constipation, sensation of rectal fullness or incomplete defecation, and tenesmus.***

In Table 10 Collection of biological samples footnote update

[1]First-catch urine ~~may~~***will*** be collected ~~as~~***instead of an*** ~~alternative to the~~ urogenital swab ***from male participants and those with a penis***

In Table 11 Laboratory assays footnote updated

[1]First-catch urine ~~may~~***will*** be collected ~~as~~***instead of an*** ~~alternative to the~~ urogenital swab from male participants and those with a penis

In Section 8.1.2 Read-out for efficacy assessment

NAAT samples include swabs (urogenital, anorectal, and pharyngeal sites) and***/or*** first-catch urine ~~sample as an alternative to the urogenital swab~~***samples*** for male participants and those with a penis…..

In Section 8.2 Safety assessments

The investigator(s) and their designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up ~~AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study intervention or study~~***all AEs***.

In Section 8.2.1.1 Collection of demographic data

* Differences in the safety and efficacy of certain medical products, including vaccines [Haralambieva, 2013; Pérez Losada, 2009; Kollmann, 2013], have been observed in racially and ethnically distinct subgroups. These differences may be attributable to intrinsic factors (e.g. genetics, metabolism, elimination), extrinsic factors (e.g. diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both race and ethnicity will be collected for all participants in this study. ***Furthermore, collection of sex, race, and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.***

In Section 8.3.2 Method of detecting AEs and SAEs, pregnancies and other events

Care will be taken not to introduce bias when detecting AE/SAE/pregnancy. Open-ended and non-leading verbal questioning of participants is the preferred method of acquiring information related to an AE/SAE/pregnancy.

In Section 8.3.6 Medical device deficiencies

~~Some study groups have study interventions that is a combination product constituted of a device and biologic product (e.g., pre-filled syringes). Refer to the Glossary of terms for the definition of combination product and medical device deficiency.~~

Medical devices are being provided for use to some study groups in this study as the study intervention (e.g., pre-filled syringes). To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

If the site(s) uses non-sponsor medical devices, i.e., medical devices not provided by GSK, then the investigators are obligated to report any device deficiencies to the legal manufacturer of the devices directly.

The definition of a medical device deficiency can be found in Section 10.6.

Note: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.6 of the protocol.

In Section 8.3.6.1 Detection, follow-up, and prompt reporting of medical device deficiency

The sponsor will be the contact for the receipt of device deficiency reports.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

In Section 9.3.4 Other exploratory analyses

CCI

[redacted]

In Section 9.4 Handling of missing data

In case a confirmed gonorrhea case is diagnosed prior to 1 month post-Dose 2 and is still ongoing ~~***(no treatment administered yet)***~~ after 1 month post-Dose 2, person-time at risk will start ~~***on the day after the initiation of antibiotic treatment for***~~ this infection ***is considered resolved***.

In Section 9.5 Interim analyses

In the PoC part, an interim futility assessment will be performed to evaluate potential significant evidence of lack of efficacy. ~~An analysis of the primary and secondary endpoints will be performed when sufficient gonorrhea cases are accrued as described in Section . There will be no related clinical study report (CSR) for these analyses.~~***when a median observation time of approximately 180 days is reached in the total study population starting from 1 month post dose 2.***

In Section 9.5.1 Sequence of analyses

During the efficacy PoC part, ongoing estimates of the gonorrhea IR in the placebo group will be generated to inform the sample size adaptation plan. When ***a median observation time of*** approximately ~~65% of~~ ***180 days post-dose 2 is reached in the*** ~~expected number of gonorrhea cases in HTD vs placebo comparison (i.e., 31 cases overall, summing up the cases in the HTD and placebo groups) will be accrued~~***total study population,*** a futility assessment will be performed. The ongoing estimates of the gonorrhea IR in the placebo group as well the futility assessment will be produced by IDAC ~~and checked~~. ***The futility assessment results will be reviewed*** by an ~~unblinded statistician~~***internal Data Review Committee (iDRC), including clinical, research, safety and statistics managers or representatives,*** independent from the study team to maintain study integrity ***and enable strategic vaccine development assessments***. At the time of the ~~interim~~ futility assessment, key safety data will be evaluated as well by the iSRC and ***iDRC***. ***The composition and responsibilities of the iSRC and iDRC will be described in a dedicated charters.***

~~An analysis for the primary and secondary endpoints will be performed when 47 cases are reached for both the HTD vs placebo comparison (i.e., 47 cases overall, summing up the cases in the HTD and placebo groups) and for the below HTD vs placebo comparison (i.e., 47 cases overall, summing up the cases in the below HTD and placebo groups). In case of ties in event dates when identifying the 47th case, all eligible events will be taken into account in the analysis. If HTD efficacy is not demonstrated, then the comparison of below HTD vs placebo groups may be reported as a descriptive analysis. This analysis will be produced by IDAC and group unblinded results will be shared with a restricted group of study team members, as described in the SAP. In this analysis, by participant listings will not be shared and frequency counts below 5 participants will not be reported in summary tables.~~

A ~~complete~~ ***final*** analysis will be performed when all data up to Day 451 are available: at this stage, primary safety endpoints will be evaluated as well as primary and secondary efficacy ones. The conclusion of vaccine efficacy will be based on the ~~analysis of the first 47 cases accrued for each comparison. Additional efficacy data (beyond 47 cases per comparison) will be~~ ***analysed*** ~~for descriptive purposes.~~***final analysis.***

~~If by the end of the study, the total number of cases is below 47 in any of the comparisons, the conclusion of vaccine efficacy will be based on the complete analysis i.e., all data up to Day 451.~~

Tertiary endpoints will be evaluated as part of the ~~complete~~***final*** analysis but if the data become available at a later stage, (an) additional analysis/analyses will be performed.

In Section 9.5.2 Statistical considerations for interim analysis

The futility assessment will be performed for the primary efficacy endpoint ~~with 31 cases accrued for~~ ***when a median observation time of approximately 180 days is reached in the*** ~~HTD vs placebo comparison and~~ ***total study population starting from 1 month post dose 2. This assessment*** will evaluate the VE of the HTD~~, in accordance with the sequential testing procedure~~ ***and bHTD at interim***. Lack of benefit (futility) will be declared if the conditional power for the first efficacy analysis is <17%. The futility boundary of 17% may be subject to change to reflect subsequent program-related decisions by the sponsor and will be applied in a nonbinding way. This futility assessment requires no α-adjustment and has no major detrimental effect on the study power.

In Section 9.6 Sample size determination

The conclusion of vaccine efficacy will be based on all cases accrued at the time of the complete analysis. A number of cases higher than the required 47 cases will result in higher statistical power to prove positive vaccine efficacy.

In Section 10.1.3 Informed consent process

The investigator(s) or their representative(s) must fully explain the nature of the study***,*** ***including the risks and benefits,*** to the participant and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary

The content of the informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, ***privacy and data protection (e.g,*** Health Insurance Portability and Accountability Act [HIPAA] requirements), where applicable, and the IRB/IEC or study center.

Sample testing will be done in accordance with the recorded consent of the individual participant.

In case of unexpected pregnancy, participant must be informed that principal investigator such as date of birth and sex of the baby will be collected as part of safety follow-up. Consent for collection of information about the baby may be obtained from the participant and/or their partner as per local regulations.

In Section 10.1.5 Data protection

- Their personal study-related data will be used by the sponsor in accordance with local data protection law***. The level of disclosure must also be explained to the participants, that their data will be used as described in the informed consent.***
- ***GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws***.

In Section 10.1.7 Dissemination of clinical study data

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate. ***The full study report will be made available upon request, after decision on marketing authorisation by regulatory authorities.***

Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.

GSK will provide the investigator with the randomization codes ***and participant-level line listings*** for their site only after completion of the full statistical analysis.

GSK intends to make anonymised patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. ***Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.***

In Section 10.1.8 Data quality assurance

Guidance on completion of CRF will be provided in CRF completion guidelines.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organisations).

In Section 10.1.9 Source documents

For this study, there will not be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).

Source documents provide evidence to establish the existence of the participant and substantiate the integrity of collected data. ***Source documents are filed at the investigator's site.*** The investigator should maintain a record of the location(s) of their source documents.

In Section 10.1.10 Study and site start and closure

For study termination:

- ***Discontinuation of further study intervention development.***

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate ***or no*** recruitment ***(evaluated after a reasonable amount of time)*** of participants by the investigator
- ~~Discontinuation of further study intervention development~~

In Section 10.3.1.2 Events NOT Meeting the AE Definition

- ***Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.***

In Section 10.3.3 Solicited events

Solicited events are predefined administration site events and systemic events for which the participant is specifically questioned, and which are noted by the participant in their eDiary.

In Section 10.3.10.1 Events requiring expedited reporting to GSK

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section).

If the site during the course of the study or post study becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous individual case safety reports (ICSRs)

In Section 10.6.2 Definition of medical device SAE, SADE and USADE

A medical device SAE is any serious adverse event that:
b. Led to serious deterioration in the health of the participant, that either resulted in: • ***Chronic disease (MDR 2017/745)***
Serious Adverse Device Effect (SADE) definition
• Any device deficiency that might have led to an SAE if appropriate action had not been taken, ***intervention had not occurred,*** or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the IB (***see Section*** 2.3).

Section 10.6.3 Definition of device deficiency added

Device deficiency definition
• ***A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.***

In Section 10.7.3 Requirements for Brazil

Data quality assurance

~~In accordance with local legislation, study~~***Study*** records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for ~~5~~***15*** years from issuance of the final CSR/equivalent summary ~~unless local regulations or institutional policies require a longer retention period~~. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.10.2. Protocol Amendment 5

Amendment 5: 28 November 2023

Overall Rationale for the Amendment: This protocol amendment primarily aims at adding the collection of ad-hoc NAAT samples for gonorrhea cases diagnosed by central laboratory prior to antibiotic treatment administration. The schedule of activities for the efficacy PoC was updated to include an ad-hoc NAAT visit. Minor edits for clarification and correction of typographical errors have been made (see below for information).

Section # and Name	Description of Change	Brief Rationale
In Section 1.3 Schedule of Activities, Table 3	Addition of ad-hoc swab/urine samples during ad-hoc NAAT visit	To collect ad-hoc swab/urine samples from participants with confirmed gonococcal infection, from the anatomical sites confirmed by NAAT as positive for Ng prior to antibiotic treatment administration
In Section 3 Objectives, Endpoints, and Estimands, Table 5, Tertiary	Clarification of timepoints for evaluation of humoral immune response analysis	To evaluate the humoral immune response at time points of confirmed gonorrhea cases.
In Section 4.1.2 Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea	Addition of ad-hoc NAAT visit	To clarify that for participants with a confirmed gonoccocal infection, ad-hoc NAAT samples for central laboratory may be collected prior to antibiotic treatment administration during an ad-hoc NAAT visit, in order to explore the Ng infection status at the time of antibiotic treatment in participants with confirmed gonorrhea infections.

Section # and Name	Description of Change	Brief Rationale
In Section 4.2.2 Case definition	Clarification on gonorrhea case definition and the duration of gonorrhea cases added.	To clarify that in absence of antibiotic treatment, a gonorrhea case cannot be considered as resolved.
In Section 9.3.4 Other exploratory analyses	Ad-hoc NAAT results collected prior to Ng treatment will be listed	To describe how ad-hoc NAAT results will be reported.
In Section 9.4 Handling of missing data	Details of the calculation of time at risk when a Ng infection is diagnosed prior to 1 month post-dose 2.	To clarify the calculation of time at risk when a Ng infection is diagnosed prior to 1 month post-dose 2.
In Section 10.2.1. Protocol required safety laboratory assessments	Addition of text.	To clarify that safety laboratory results will only be documented in the eCRF for participants in the safety lead in part of the study and for participants in the HIV-positive and HIV-negative subset for intensive safety monitoring in the efficacy PoC part of the study.
In Section 10.2.3.1 ELISA-like	Addition of text to clarify timepoints	To clarify the specific timepoints for analysis for the ELISA-like immunoassay.
In Section 10.2.3.2 hSBA	Update timepoints for hSBA tests	To specify the timepoints of the hSBA test.
In Section 10.3.1.2 Events NOT Meeting the AE Definition	Deleted text	To align with the protocol template
In Section 10.3.8 Recording and follow-up of AEs, SAEs and pregnancies	Addition of text on eDiary.	To clarify that solicited AEs that cannot be recorded in the eDiary, can be reported directly to the site staff and submitted via the eCRF.
In Section 10.8.2 Glossary of terms	Addition and update of glossary terms	To align with the protocol template

In the following sections, deleted text is indicated in ~~strikethrough~~ and changed text in ***bold italics***:

In Section 1.3 Schedule of Activities (SoA), table 3

Type of contact	Group 4a HTD Group 4b below HTD Group 4c Placebo	**Screening**	**V1**	**V2[4]**	**V3**	**V4[8]**	**V5[4]**	**V6**	**V7**	**V8**	**V9**	**V10**	**Unscheduled visit**	***Ad-hoc NAAT visit[9]***
Time points		**Day –14**	**Day 1**	**Day 8 (Safety)**	**Day 31 (M 1)**	**Day 61 (M 2)**	**Day 68**	**Day 91 (M 3)**	**Day 181 (M 6)**	**Day 271 (M 9)**	**Day 361 (M 12)**	**Day 451 (M 15)**		
Ad-hoc swab/urine sample[3] collection prior to Ng treatment, only from the anatomical site(s) confirmed by NAAT as positive for Ng by central laboratory.														●
Record any concomitant medication/vaccination														●
Record healthcare utilization (hospitalization, emergency room, and accident & emergency visits)														●
Record antibiotic use														●
Reporting of SAEs, AEs leading to withdrawal and pregnancies														●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine														●

[9] Ad-hoc NAAT visits may be performed for gonorrhea cases diagnosed by central laboratory (1 or more anatomical sites confirmed by NAAT as positive for Ng by central laboratory) at or beyond 1 month post-Dose 2 only. When administration of antibiotic treatment against Ng is planned following this diagnosis, efforts will be made to collect ad-hoc NAAT samples for central laboratory from the anatomical sites that previously tested positive for Ng prior to antibiotic treatment administration. If treatment was already administered before central laboratory NAAT results became available, no ad-hoc NAAT visit will take place.

Ng = Neisseria gonorrhoeae, NAAT = Nucleic Acid Amplification Test

In Section 3 Objectives, Endpoints, and Estimands

Phase 2 – Efficacy PoC Secondary	
CCI [redacted]	
To evaluate the humoral immune responses to the NgG vaccine.	• Anti-NgG IgG antibodies Geometric mean concentrations (GMCs) at Day 1, Day 31, Day 61, Day 91 ,~~and~~ Day 451, and ~~unscheduled visits~~ ***at time points of confirmed gonorrhea cases*** where applicable. • hSBA Geometric mean titres (GMTs) against *Ng* strain at Day 1, Day 31, Day 61, Day 91, ~~and~~ Day 451, and ~~unscheduled visits~~ ***at time points of confirmed gonorrhea cases*** where applicable.[8]

In Section 4.1.2. Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea

- **Duration of the study:** The total duration of the study, per participant, will be approximately 15 months. All participants will have to attend a screening visit; participants in the safety subset will have to attend/perform 10 visits, all other participants will have to attend/perform 8 visits and 2 phone calls. Unscheduled visit will be arranged in case of ~~symptoms suggestive~~***suspicion*** of possible gonococcal infection.

- **Sampling schedule:**
  - Blood samples for humoral immunogenicity will be drawn from all participants at Visit 1 (Day 1), Visit 3 (Day 31), Visit 4 (Day 61), Visit 6 (Day 91), Visit 10 (Day 451), and at unscheduled visit(s) when performed. ELISA-like immunoassay will be performed in all participants. At least the first 100 ~~hundred~~ participants enrolled in each arm (n=300 total~~, 40% of the total study population~~), and all participants with ~~unscheduled visits~~***confirmed gonococcal infections*** will be tested for human serum bactericidal assay (hSBA).

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

- ***Ad-hoc NAAT visit: When a Ng diagnosis is made by central laboratory (1 or more anatomical sites confirmed by NAAT as positive for Ng by central laboratory) at or beyond 1 month post-Dose 2 and administration of antibiotic treatment against Ng is planned at the study site, efforts will be made to collect ad-hoc NAAT samples for central laboratory prior to antibiotic treatment administration. Ad-hoc NAAT samples may only be collected for anatomical sites that previously tested positive for Ng by NAAT, to explore the Ng infection status at the time of antibiotic treatment in participants with a confirmed gonorrhea case. If treatment was already administered before central laboratory NAAT results became available, no ad-hoc NAAT visit will take place.***
  An ad-hoc NAAT visit should be booked only outside the time allowance for scheduled visits unless the scheduled visit has already occurred, otherwise a scheduled visit will take place.

In Section 4.2.2. Case definition

- **For the primary objective**, only cases from **urogenital or anorectal** samples occurring from 1 month after the second vaccination (Visit 6, Day 91) until ~~study end (~~Visit 10, ***(***Day 451) will be considered.
- ***In absence of antibiotic treatment, a gonorrhea case cannot be considered as resolved. In case of persistent gonococcal infection detected by subsequent positive NAAT samples at the same anatomical site when no intercurrent treatment was given, this gonococcal infection will be counted as a single gonorrhea case, with a start date of the first positive NAAT sample, and an end date of the antibiotic treatment administration. In case of early gonococcal infection prior to 1 month post-Dose 2, a gonorrhea case may be considered for the primary endpoint only if it occurs after the initiation of antibiotic treatment for this early gonococcal infection.***

In Section 6.3.4. Allocation of participants to assay subsets

At least the first 100 ~~hundred~~ participants enrolled in each arm (n=300 total~~, 40% of the total study population~~), and all participants with ~~unscheduled visits~~ ***a confirmed gonococcal infection*** will be tested for human serum bactericidal assay (hSBA).

In Section 8. Study Assessments and Procedures

Burden of the study, degree of strain and risk threshold in Dose-escalation safety lead-in part

A basic, routine medical assessment, including interview on past and current medical history will also be performed by the investigator or designated person. On study Day 1 ***and Day 61*** a urine pregnancy test for female participants of childbearing potential will be required.

Burden of the study, degree of strain and risk threshold in Efficacy PoC Part

On study Day 1 ***and Day 61*** a urine pregnancy test for female participants (including *trans*men that have not undergone gender affirming surgery of their genitals) of child-bearing potential will be required.

In Section 8.1.2. Read-out for efficacy assessment

CCI [redacted]

In Section 8.1.3.Immunological read-outs

The subset will represent at least the first 100 ~~hundred~~ participants enrolled in each ***treatment*** arm (n=300 total~~, 40% of the total study population~~), and all participants with ~~unscheduled visits~~ ***confirmed gonococcal infections***.

In Section 8.3.1. Time period and frequency for collecting AE, SAE and other safety information, table 15

Event	Pre-Vac	Vac1			Vac2						Study Conclusion
Visit	Screening	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Day	~~*D–14*~~*	D1	D8	D31	D61	D68	D91	D181	D271	D361	D451
Solicited local and general AEs											
Unsolicited AEs											
AEs/SAEs leading to withdrawal from the study											
SAEs											
SAEs related to study participation* or concurrent GSK medication/vaccine											
Pregnancies											
DREs											

Events or outcomes not qualified as AEs/SAEs

According to the study design and the study objectives, gonococcal infections (either asymptomatic or symptomatic) are considered Disease-related-events (DREs) and will not be captured nor managed as AEs/SAEs, but instead will be reported in the eCRF and analyzed as ~~secondary~~***efficacy*** objectives in the POC part of the study.

CCI [redacted]

In Section 9.3.4 Other exploratory analyses

CCI

[redacted]

In Section 9.4. Handling of missing data

- ***In case a confirmed gonorrhea case is diagnosed prior to 1 month post-Dose 2 and is still ongoing (no treatment administered yet) after 1 month post-Dose 2, person-time at risk will start on the day after the initiation of antibiotic treatment for this infection.***

In Section 9.5.1. Sequence of analyses

A complete analysis will be performed when all data up to ~~study end (~~Day 451~~)~~ are available: at this stage, primary safety endpoints will be evaluated as well as primary and secondary efficacy ones. The conclusion of vaccine efficacy will be based on the analysis of the first 47 cases accrued for each comparison. Additional efficacy data (beyond 47 cases per comparison) will be ~~analyzed~~analysed for descriptive purposes.

If by the end of the study, the total number of cases is below 47 in any of the comparisons, the conclusion of vaccine efficacy will be based on the complete analysis i.e., all data up to ~~study end (~~Day 451~~)~~.

In Section 10.2.1. Protocol required safety laboratory assessments

Where tests are carried out locally, the results of each test carried must be entered in the eCRF ***for participants in the safety lead in part of the study, and for participants in the HIV-positive and HIV-negative subset for intensive safety monitoring in the efficacy PoC part of the study.***

In Section 10.2.3.1. ELISA-*like*

The optimized assay resulting from the set-up will then be used to measure all blood samples from all participants ~~and timepoints~~ in the PoC part of the study ***at the 5 scheduled timepoints (plus the timepoints of confirmed gonococcal infections when applicable)*** as an exploratory endpoint.

In Section 10.2.3.2. hSBA

The hSBA will be tested on samples collected from a subset of participants included in the PoC part of the study, as an exploratory endpoint. At least the first 100 ~~hundred~~ participants enrolled in each arm (n=300 total, ~~40% of the total study population~~), and all participants with ~~unscheduled visits~~ ***confirmed gonococcal infections*** will be tested for hSBA. This subset will be identified once the end of the study is reached and samples are unblinded in order to include all participants who ~~are~~ tested as positive for Ng using NAAT. By then, this subset will be completed with relevant control cases. For all these participants, at least 4**5** scheduled timepoints (plus the ~~unscheduled visit~~ timepoints ***of confirmed gonococcal infections*** when applicable) will be tested for hSBA: baseline (Visit 1), 1 month post-Dose 1 ***(Visit 3)***, pre-dose 2 (Visit ***4***), 1 month post-Dose 2 (Visit 6), and 13 months post-Dose 2 (Visit 10).

In Section 10.3.1. Definition of an Adverse Event (AE)

10.3.1.2. Events NOT Meeting the AE Definition
• ~~Pre-existing conditions or signs and/or symptoms present in a participant before the first dose of study intervention. These events will be recorded in the medical history section of the eCRF.~~

In Section 10.3.8. Recording and follow-up of AEs, SAEs and pregnancies

An Electronic Diary (eDiary) will be used in this study to capture solicited administration site or systemic events. ***If the data related to the study objectives/endpoints to be collected by the participants cannot be encoded in their eDiary (e.g., unresolved technical issues), they can be reported directly to the site staff and submitted via the eCRF.*** The participant should be trained on how and when to complete the eDiary.

Collect (or uninstall app) ***by end of study (Visit 8 for safety lead-in and Visit 10 for PoC)***. and verify completed eDiary during discussions with the participant on Visit ***2***~~8 (safety lead in) or~~ and Visit ***5***~~10 (PoC).~~

In Section 10.3.9.1. Assessment of intensity

The maximum intensity of fever will be scored at GSK as follows:

0:	<38.0°C (100.4°F)
1:	≥38.0 C but <39.0°C (≥100.4°F but <102.2°F)
2:	≥39.0°C but <40.0°C (≥102.2°F but <104.0°F)
3:	≥40.0°C (≥104.0°F)

In Section 10.8.2. Glossary of terms

Comparator:	***Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).***
Investigational vaccine:	A pharmaceutical form of an active ~~***ingredient***~~***substance or placebo*** being tested ***or used as a reference*** in a clinical study, including ~~a~~ product***s already*** with a marketing authorisation ***but used or assembled (formulated or packaged)*** ~~when used~~ in a way different from the ~~unapproved~~ ***unauthorised*** form, or when used for an unauthorised indication, or when used to gain further information about ~~an approved use~~***the authorised form***. Synonym: Investigational ~~Medicinal~~ Product
Placebo:	***An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.***
Standard of Care:	***Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term.*** ***1. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries***
SUSAR:	***Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting***

10.10.3. Protocol Amendment 4

Amendment 4: 27 April 2023

Overall Rationale for the Amendment: This protocol amendment follows the Part I Request for Information (RFI) issued by German Health Authority and it aims at applying requested changes including addition and modification of some exclusion criteria, addition of maximum sample size for PoC Part and information on handling of missing data, clarification of blinding requirements, and modification of the tertiary objective used to evaluate vaccine efficacy during the entire study to allow an analysis based on the ITT population. In addition, clarifications on the process for sample size readjustment were added and CCI CCI Minor edits for clarification and correction of typographical errors have been made (see below for information).

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
In Section 1.1 Synopsis, Section 2.1 Study rationale, Section 4.2 Scientific rationale for study design	Update of Rowley reference date of publication.	To correct publication date.
In Section 1.3 Schedule of Activities, Table 3	Update of cross-link in the footnote.	To correct table footnote cross-link.
In Section 3 Objectives, Endpoints, and Estimands, Table 5, Tertiary	CCI CCI CCI CCI CCI	CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI
In Section 3 Objectives, Endpoints, and Estimands, Table 5, Tertiary	CCI CCI CCI	CCI CCI
In Section 4.1.2 Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea	Addition of medication to be avoided prior to sampling.	To clarify sampling procedure.

Section # and Name	Description of Change	Brief Rationale
In Section 4.2 Scientific rationale for study design	Addition of information regarding Ng-Ct coinfection, and its potential effect on vaccine efficacy.	To provide rationale for secondary objective regarding Ng-CT coinfection and additional tertiary objective regarding CCI [redacted] CCI [redacted].
In Section 5.2.1.2 Efficacy PoC part: HIV negative intensive safety monitoring subset (i.e. first 30 HIV negative subjects per group)	Addition of exclusion criteria regarding any contraindication to intramuscular administration, history of severe allergic reactions and/or anaphylaxis; persons under guardianship or trusteeship and persons deprived of liberty for the participants in the PoC part of the study.	To clarify exclusion criteria.
In Section 5.2.1.3 Efficacy PoC part: HIV positive intensive safety monitoring subset (first 8 HIV positive subjects per group, enrolled in case of a positive safety outcome from the previous subset)	Addition of exclusion criteria regarding any contraindication to intramuscular administration, history of severe allergic reactions and/or anaphylaxis; persons under guardianship or trusteeship and persons deprived of liberty for the participants in the PoC part of the study.	To clarify exclusion criteria.
In Section 5.2.1.4 All remaining participants	Addition of exclusion criteria regarding any contraindication to intramuscular administration, history of severe allergic reactions and/or anaphylaxis; persons under guardianship or trusteeship and persons deprived of liberty for the participants in the PoC part of the study.	To clarify exclusion criteria.
In Section 5.5 Criteria for temporarily delaying study intervention administration	Addition of text.	To clarify criteria for delay of vaccination for participants who acquire HIV during the study.
In Section 6.3.5 Blinding and unblinding	Update of section on blinding requirements, to clarify that participants, site personnel involved in clinical evaluation	To clarify that study design is observer-blind.

Section # and Name	Description of Change	Brief Rationale
	of the participants, and sponsor personnel involved in data analysis are blinded.	
In Section 8.1.1 Biological samples	Addition of text and a footnote to Table 11 regarding CCI [redacted]	To add lab assays linked to additional tertiary endpoint.
In Section 8.1.2 Read-out for efficacy assessment	Addition of medication to be avoided prior to sampling.	To clarify sampling procedure.
In Section 9.2 Analysis sets, Table 18	Addition of Full Analysis – Efficacy (Intention-To-Treat population).	CCI [redacted]
In Section 9.3.4 Other exploratory analyses	Update of text regarding tertiary endpoints.	To include additional tertiary endpoint.
In Section 9.4 Handling of missing data	Addition of sub-section in the Statistical considerations section.	To provide information on handling of missing data.
In Section 9.4.1 Sequence of analyses	The term “bHTD” was replaced by “below HTD”, as it is not used elsewhere in the document.	Typographical correction.
In Section 9.5 Sample size determination	Text modified to include maximum number of sample size increases, and maximum number of participants in each treatment arm and overall. Additionally, clarifications on the process for sample size readjustment were added.	To clarify maximum sample size and the process for sample size readjustment.
In Section 10.1.8 Data quality insurance	Updated text regarding QTLs.	To clarify location of pre-defined QTLs.
In Section 10.2.4 Bacterial DNA sequencing	Addition of sub-section in Appendix 2 Clinical laboratory test.	To describe bacterial DNA sequencing techniques.
In Section 11 References	Addition of 3 references.	To support information provided in Section 10.2.4.

In the following sections, deleted text is indicated in ~~strikethrough~~ and changed text in ***bold italics***:

In Section 1.1 Synopsis, Section 2.1 Study rationale, Section 4.2 Scientific rationale for study design

Rationale: *Neisseria gonorrhoeae* (Ng) is a strictly human bacterial pathogen causing gonorrhea, the second most prevalent bacterial sexually transmitted infection (STI) worldwide, with 87 million new cases of infections estimated globally in 2016 [Rowley, ~~2016~~ ***2019***].

Neisseria gonorrhoeae (Ng) is a strictly human bacterial pathogen causing gonorrhea, the second most prevalent bacterial sexually transmitted infection (STI) worldwide, with 87 million new cases of infections estimated globally in 2016 [Rowley, ~~2016~~ ***2019***]

Ng is a strictly human bacterial pathogen causing gonorrhea, the second most prevalent bacterial sexually transmitted infection (STI) worldwide, with 87 million new cases of infections estimated globally in 2016 [Rowley, ~~2016~~ ***2019***]

In Section 1.3 Schedule of Activities, Table 3

Type of contact	Group 4a HTD Group 4b below HTD Group 4c Placebo	**Screening**	**V1**	**V2[4]**	**V3**	**V4[8]**	**V5[4]**	**V6**	**V7**	**V8**	**V9**	**V10**	**Unscheduled visit**
Blood sampling for haematology/biochemical analysis (6 ml)[2]		•		•		•	•						

[2]Only for participants in subset for safety monitoring (Refer to Section ~~4.1.1~~ ***4.1.2*** ~~**Safety monitoring**~~ **Safety monitoring** for details). Additional blood samples may be obtained during the unscheduled visit at the discretion of the investigator, to assess any perceived safety issues.

In Section 3 Objectives, Endpoints, and Estimands, Table 5, Tertiary

To evaluate the efficacy of the NgG vaccine in preventing gonorrhea cases during the entire study period.	• Incidence rates of confirmed gonorrhea cases from Day 1 after the first dose ~~to 13 months post Dose 2~~ ***until end of study*** (Day 451) overall, ***for urogenital or anorectal sites***, and by each anatomical site (urogenital, anorectal and pharyngeal).
CCI [redacted]	CCI [redacted]

In Section 4.1.2 Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea

Use of vaginal medicinal treatments, vaginal moisturizers, vaginal wash/hygiene products, containing carbomer should be avoided in the 7 days before planned visits when vaginal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test. ***Similarly, use of anorectal medicinal treatments, anorectal lubricants and anorectal wash/hygiene products containing carbomer, should be avoided in the 7 days before planned visits when anorectal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test.***

In Section 4.2 Scientific rationale for study design

Despite decades of vaccine research, no vaccines against gonorrhea have been successful in preventing the infection. However, N. meningitidis serogroup B vaccination has shown modest but clinically relevant effectiveness in preventing Ng infections: 3 case control studies from New Zealand [Petousis-Harris, 2017] and the United States [Abara, 2022; Bruxvoort, 2022] have shown that individuals who received meningitis B vaccination were less likely to contract gonorrhea, compared to their unvaccinated peers. Notably, in the aforementioned studies, a detrimental effect on vaccine effectiveness against gonococcus was observed in case of Ng-Ct coinfection. A consensus on the factors explaining this detrimental effect is not currently reached in the scientific community. Nevertheless, the current study was designed to evaluate the efficacy of GSK Biologicals' NgG investigational vaccine against Ng infections with and without Ct coinfection as a secondary objective.

Furthermore, the CCI [redacted] CCI [redacted] ***may be explored as a tertiary objective, to better understand the protection provided by the NgG investigational vaccine against infections caused by*** CCI [redacted] ***as well as*** CCI [redacted] CCI [redacted]. ***Finally, the humoral immune response to the NgG vaccine will be evaluated, and attempts will be made to identify an immune correlate of protection against gonorrhea infection.***

In Section 5.2.1.2 Efficacy PoC part: HIV negative intensive safety monitoring subset (i.e. first 30 HIV negative subjects per group)

- ***Persons under guardianship or trusteeship.***
- ***Persons deprived of liberty.***
- History of ***severe allergic reactions and/or anaphylaxis, or*** any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention(s).
- ***Bleeding diathesis or any other condition that would contraindicate intramuscular administration.***

In Section 5.2.1.3 Efficacy PoC part: HIV positive intensive safety monitoring subset (first 8 HIV positive subjects per group, enrolled in case of a positive safety outcome from the previous subset)

- ***Persons under guardianship or trusteeship.***
- ***Persons deprived of liberty.***
- History of ***severe allergic reactions and/or anaphylaxis, or*** any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention(s).
- ***Bleeding diathesis or any other condition that would contraindicate intramuscular administration.***

In Section 5.2.1.4 All remaining participants

- ***Persons under guardianship or trusteeship.***
- ***Persons deprived of liberty.***
- History of ***severe allergic reactions and/or anaphylaxis, or*** any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention(s).
- ***Bleeding diathesis or any other condition that would contraindicate intramuscular administration.***

In Section 5.5 Criteria for temporarily delaying study intervention administration

Participants who acquire HIV during the study may not receive further doses of study intervention until ~~they meet the criteria set in Section 5.1~~ ***a positive outcome of the unblinded iSRC evaluation of the HIV positive safety subset has been obtained and the immunological parameters of the participants are at stable levels (i.e., CD4 cell count >350 cells/mm³, viral load < 50 cp/ml) while under stable antiretroviral therapy (ART) for > 3 months.***

In Section 6.3.5 Blinding and unblinding

Data will be collected in an observer-blind manner. The participant, the site ~~and sponsor~~ personnel involved in the clinical evaluation of the participants ***and the sponsor personnel involved in data analysis***, are blinded ~~while~~. ~~o~~***O***ther study personnel ***that do not perform study activities related to data collection, data evaluation or data review***, may be aware of the treatment assignment. ~~To do so, s~~***S***tudy intervention(s) will be prepared and administered by ***a limited number of*** qualified ***unblinded site*** ~~study~~ personnel who will not participate in ***any*** data collection, ***data*** evaluation, ***data*** review or the entry of any study endpoint (i.e. reactogenicity, safety, efficacy).

In Section 8.1.1 Biological samples

Table 11 Laboratory assays

Test Classification	System	Component	Challenge	Method
Molecular Biology[2]	Swab: Urogenital sites	Ng Ct		NAAT
	Swab: anorectal sites	Ng Ct		NAAT
	Swab: pharyngeal sites	Ng Ct		NAAT
	Urine: First-catch urine[1]	Ng Ct		NAAT
Humoral Immunity (Antibody determination)	Serum	Anti-Gono GMMA Ab IgG		ELISA-like
	Serum	Anti-Gono GMMA Bactericidal Ab		hSBA

Ct: *Chlamydia trachomatis*; NAAT: Nucleic Acid Amplification Test; Ab: antibodies; IgG: Immunoglobulin G; ELISA: Enzyme Linked ImmunoSorbent Assay; hSBA: Human complement Serum Bactericidal Assay; Ng, *Neisseria gonorrhoeae*

[1]First-catch urine may be collected as an alternative to the urogenital swab from male participants and those with a penis

[2]Bacterial DNA sequencing of samples that resulted positive for Ng and/or Ct by NAAT may be performed on a subset of samples.

Further laboratory testing related to NgG investigational vaccines and/or gonorrhea disease, CCI [redacted] CCI [redacted] may be performed if deemed necessary or if assay(s) become available.

In Section 8.1.2 Read-out for efficacy assessment

Use of vaginal medicinal treatments, vaginal moisturizers, vaginal wash/hygiene products containing carbomer should be avoided in the 7 days before planned visits when vaginal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test. ***Similarly, use of anorectal medicinal treatments, anorectal lubricants and anorectal wash/hygiene products containing carbomer, should be avoided in the 7 days before planned visits when anorectal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test.***

In Section 9.2 Analysis sets, Table 18

Full Analysis – Efficacy (Intention-To-Treat population)	***All randomized participants who received at least one dose of study intervention. The allocation in a group will be done in function of the randomized intervention.***

In Section 9.3.4 Other exploratory analyses

CCI [redacted]

In Section 9.4 Handling of missing data

For the analysis of safety, missing and/or partial unsolicited AE data including start dates, end dates, severity, and relationship to study intervention, will be imputed according to GSK standard rules. All partial dates will be displayed as captured in participant listings. Other missing or unevaluable safety data, including safety laboratory measurements and eDiary data will not be imputed.

For the primary efficacy analysis, a person-time adjusted approach will be used. Missing or unobserved efficacy data will be accounted for in the calculation of person-time at risk as follows:

- ***For participants with an event, individual person-time at risk will be defined as the time from 1 month post dose 2 until the date of first confirmed gonorrhea case.***
- ***For participants without an event, individual person-time at risk will be defined as the time from 1 month post dose 2 until the earliest of withdrawal date, data cut-off date or date of last visit.***

Both for participants with an event and participants without an event, individual person-time at risk will be calculated regardless of the number of intermittent missed/unevaluable efficacy assessments.

Any missing or inconclusive test result will not be considered in the case definition. No other imputation of efficacy data is planned.

A similar approach will be used in the analysis of other efficacy endpoints, adapting to the corresponding case definition and/or time frame under evaluation.

In Section 9.4.1 Sequence of analyses

An analysis for the primary and secondary endpoints will be performed when 47 cases are reached for both the HTD vs placebo comparison (i.e., 47 cases overall, summing up the cases in the HTD and placebo groups) and for the ***below*** ~~b~~HTD vs placebo comparison (i.e., 47 cases overall, summing up the cases in the ***below*** ~~b~~HTD and placebo groups). In case of ties in event dates when identifying the 47th case, all eligible events will be taken into account in the analysis. If HTD efficacy is not demonstrated, then the comparison of ***below*** ~~b~~HTD vs placebo groups may be reported as a descriptive analysis.

In Section 9.5 Sample size determination

Considering an initial sample size of 209 evaluable subjects in the placebo arm and a yearly IR of 15%, 31 cases are expected to be seen. The placebo IR will be monitored ***approximately*** every two months from the start of the PoC enrolment, in accordance with the enrolment rate. If there is ~~strong~~ ***sufficient*** evidence against the original assumption of 15% (~~i.e.,~~ ***based on*** the probability of seeing a number of cases higher than the one observed***,*** ~~–~~ given a Poisson distribution with a yearly rate of 15% ~~– is greater than 80%~~), the sample size for each arm will be increased ~~of~~ ***by*** a fixed number of 50 subjects per arm. ~~At every interim estimate of the placebo IR, the same computations will be performed;~~ ~~w~~***W***henever a sample size increase is triggered, the assumed placebo IR will

be updated to the value needed to have 31 cases in the placebo group with the new increased sample size. ***If, based on the observed placebo IR, the evidence to support the newly assumed placebo IR is still low, the sample size for each arm can be further increased by a fixed number of 50 subjects per arm. At every re-estimation of the placebo IR, the same computations will be performed, but the sample size can be updated no more than 3 times, when a maximum of 400 participants per group is reached. The maximum number of potential participants randomized to the study will therefore be limited to 1200 participants in total.*** In order to guarantee the blinding, this assessment will be performed by an independent data analysis center (IDAC); further details on the statistical methodologies and how to perform the assessment will be provided in the main statistical analysis plan (SAP).

In Section 10.1.8 Data quality insurance

Quality tolerance limits (QTLs) will be pre-defined ~~in the study management plan~~ ***in the Quality Plan Quality Tolerance Limit review report*** to identify systematic issues that can impact participant safety and/or the reliability of study results

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[redacted]

In Section 11 References

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[redacted]

10.10.4. Protocol Amendment 3

Amendment 3: 10 March 2023

Overall Rationale for the Amendment: The aim of this protocol amendment is to apply changes linked to CBER feedback, including the addition of tertiary endpoints, clarification of the case definition in relation to the tertiary endpoints added and of the timing of the planned sequence of analyses. In addition, clarification of the vulnerable population and rescreening procedure, correction of typographical errors, and minor edits for clarification have been made (see below for information).

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
In Section 1.3 Schedule of Activities, Table 2	Addition of text to note that all study activities except recording of administered intervention number and recording of AEs post-vaccination, will be performed before the administration of vaccine or placebo. Correction of typographical errors	To clarify that all study activities except recording of administered intervention number and recording of AEs post-vaccination, will be performed before the administration of the second dose of vaccine or placebo during Visit 4.

Section # and Name	Description of Change	Brief Rationale
In Section 1.3 Schedule of Activities, Table 3	Addition of wording to footnote 2 to state that additional blood samples may be obtained during the unscheduled visit at the discretion of the investigator, to assess any perceived safety issues. Addition of text to footnote 4 to note the study activities (including sampling) that will be performed for study participants who show signs and/or symptoms suggestive of gonococcal infection, tested positive for Ng outside of the study schedule and has not yet received treatment, or had a recent sexual contact with a partner with a confirmed diagnosis of gonococcal infection Addition of text to footnote 8 that all study activities except recording of administered intervention number and recording of AEs post-vaccination, will be performed before the administration of vaccine or placebo. Correction of typographical errors	To clarify that additional blood samples for hematology/biochemical analysis may be obtained during the unscheduled visit at the discretion of the investigator, to assess any perceived safety issues. To clarify the study activities (including sampling) that will be performed for study participants who show signs and/or symptoms suggestive of gonococcal infection, tested positive for Ng outside of the study schedule and has not yet received treatment, or had a recent sexual contact with a partner with a confirmed diagnosis of gonococcal infection To clarify that all study activities except recording of administered intervention number and recording of AEs post-vaccination, will be performed before the administration of the second dose of vaccine or placebo during Visit 4.
Section 3 Objectives, endpoints and estimands, Table 5, Tertiary	Inclusion of three additional tertiary endpoints. Adaptation of table footnotes to add information linked to the tertiary endpoints that were	To include three additional tertiary endpoints: two endpoints to evaluate vaccine efficacy taking different case definitions into account as requested by CBER, and an endpoint

Section # and Name	Description of Change	Brief Rationale
	added	to evaluate time to onset of gonorrhea cases following vaccination
Section 4.1.2, Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea, Sampling schedule:	Text added to clarify sampling in *male participants (and those with a penis)* Text added to clarify that use of vaginal medicinal treatments, vaginal moisturizers, vaginal wash/hygiene products, containing carbomer should be avoided in the 7 days before planned visits when vaginal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test	To clarify sampling procedure in male participants (and those with a penis). To clarify products that should be avoided in the 7 days before planned visits when vaginal swabs will be collected.
Section 4.1.2, Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea, Unscheduled visits:	Text added around use of results from local vs GSK designated laboratories in relation to one of the tertiary endpoints added. Text added to describe approach if participants should test positive for Ng outside of the study	To clarify how results from local vs GSK designated laboratories should be used in relation to one of the tertiary endpoints added and to clarify approach if participants should test positive for Ng outside of the study schedule
Section 4.1.2 Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea, Subsets for intensive safety monitoring in the efficacy PoC part	Text added to clarify the rationale for and timing of the administration of the first doses in HIV positive participants: The administration of the first doses in HIV positive participants will be allowed in more than 1 participant per day but vaccination of 2 participants simultaneously will not be	To clarify the rationale for and timing of the administration of the first doses in HIV positive participants

Section # and Name	Description of Change	Brief Rationale
	possible, i.e., minimum 2 hours apart and 4 participants per day per study center at maximum, to ensure that, in the event of an acute adverse reaction, the site can provide the required medical attention for the individual concerned	
Section 4.2.2 Case definition	Addition of text to confirm case definition in relation to the tertiary endpoints added	To clarify case definition in relation to the tertiary endpoints added
Section 5.1.1, Inclusion criteria for the dose-escalation safety lead-in part:	Addition of cross reference to Section 10.4.1 for definitions	To update cross referencing to ensure consistency within the protocol
Section 5.1.2, Inclusion criteria for the efficacy PoC part	Addition of cross reference to Section 10.4.1 for definitions to ensure consistency within the protocol	To update cross referencing to ensure consistency within the protocol
Section 5.2.1.1, Dose-escalation safety lead-in part:	Alignment of hematological laboratory tests specified in the exclusion criterion with the hematological laboratory tests that are planned in the study	To align the hematological laboratory tests listed with those that are planned in the study
Section 5.2.1.2, Efficacy PoC part: HIV negative intensive safety monitoring subset (i.e. first 30 HIV negative subjects per group) and Section 5.2.1.3 Efficacy PoC part: HIV positive intensive safety monitoring subset (first 8 HIV positive subjects per group, enrolled in case of a	Alignment of hematological laboratory tests specified in the exclusion criterion with the hematological laboratory tests that are planned in the study	To align the hematological laboratory tests listed with those that are planned in the study

Section # and Name	Description of Change	Brief Rationale
positive safety outcome from the previous subset):		
Section 5.3 Lifestyle considerations, Drugs and alcohol abuse:	Wording added on the enrolment of vulnerable individuals	To clarify enrolment of vulnerable individuals
Section 5.4 Screening failures:	Inclusion of wording on rescreening after prior screen failure	To clarify process for rescreening after prior screen failure
In Section 5.5 Criteria for temporarily delaying study intervention administration:	Wording added	To clarify the criterion related to the administration of the second dose of study intervention
Section 6.3.3 Intervention allocation to the participant:	Inclusion of race (black, white, other) as a minimization factor accounted for in the minimization procedure	To include race (black, white, other) as a minimization factor in the minimization procedure
Section 6.8 Concomitant therapy	Inclusion of medications taken as post-exposure prophylaxis in the list of concomitant medication(s)/product(s)/ vaccine(s) that must be recorded in the eCRF/CRF	To ensure medications taken as post-exposure prophylaxis are recorded in the eCRF/CRF
Section 7.3 Lost to follow-up	Text added on participants who will be considered “lost to follow-up”	To clarify the definition of “lost to follow-up”
Section 8, Study assessments and procedures, Burden of the study, degree of strain and risk threshold in Dose-escalation safety lead-in part:	Inclusion of the completion of the eDiary in the list of study-related tasks required under burden of the study	To ensure the list of study-related tasks required accurately reflected the full tasks required in the study
Section 8, Study assessments and procedures, Burden of the study, degree of strain and	Inclusion of the completion of the eDiary in the list of study-related tasks required	To ensure the list of study-related tasks required accurately reflected the full

Section # and Name	Description of Change	Brief Rationale
risk threshold in Efficacy PoC part:	under burden of the study	tasks required in the study
Section 8, Study assessments and procedures, Repetition of inconclusive Ct/Ng NAATs:	Inclusion to note that inconclusive test results will be documented in the eCRF.	To clarify study process around inconclusive test results
Section 8.1.1 Biological samples:	Wording added as to how biological samples may be used in the study	To clarify that biological samples may be used to characterise the immune response elicited by the study vaccine
Section 8.1.2 Read-out for efficacy assessment:	Wording added on the use of laboratory tests in relation to the tertiary endpoints added and how participants that tested positive for Ng outside of the study schedule who already received anti gonococcal treatment should be handled	To clarify the use of laboratory tests in relation to the tertiary endpoints added and the handling of participants who have tested positive for Ng outside of the study
Section 8.8.1.2 Gonorrhea-related hospitalizations as well as ER/A&E visits:	Inclusion of wording on the handling and recording of other healthcare professional visits	To clarify the handling and recording of other healthcare professional visits
Section 9.3.3 Additional exploratory analyses on vaccine efficacy:	Inclusion of the tertiary endpoints in the list of vaccine efficacy tertiary endpoints assessed	To update the text to reflect the new endpoints added
Section 9.4 Interim analyses	Text added to describe the planned interim analyses.	To clarify the planned interim analyses
Section 9.4.1 Sequence of analyses	Text added to describe the sequence of analyses aligned with changes to the timing of the planned analyses.	To clarify the sequence of analyses in Part 1 and Part 2 of the study
Appendix 2: Clinical laboratory test, Section	Correction to table footnote and additional text	To correct table footnote text and add clarification

Section # and Name	Description of Change	Brief Rationale
10.2.1. Protocol required safety laboratory assessments, Table 19:	clarifying that unscheduled clinical laboratory measurements may be obtained at any time during the study at the discretion of the investigator, to assess any perceived safety issues.	that unscheduled clinical laboratory measurements may be obtained at any time during the study at the discretion of the investigator, to assess any perceived safety issues.
Appendix 4: Contraceptive guidance and collection of pregnancy information, Section 10.4.1. Definitions, Section 10.4.1.1. Woman of Childbearing Potential (WOCBP):	Addition of wording regarding confirmation of reproductive status in permanently sterile individuals	To clarify how to confirm reproductive status in permanently sterile individuals

In the following sections, deleted text is indicated in ~~strikethrough~~ and changed text in ***bold italics***:

In Section 1 Protocol Summary, Rationale:

Neisseria gonorrhoeae (Ng) is a strictly human bacterial pathogen causing gonorrhea, the second most prevalent bacterial sexually transmitted infection (STI) worldwide, with 87 million new cases of infections estimated globally in 2016 [~~Unemo 2016~~***Rowley, 2016***].

This ***first time in human - proof of concept (***FTiH-PoC***)*** study aims to provide an early evaluation of the efficacy of the investigational vaccine as there are no established immunogenicity correlates of protection against infections caused by Ng.

In Section 1.3 Schedule of Activities, Table 2:

Type of contact	Group 1a/b: low dose/placebo Group 2a/b: medium dose/placebo Group 3a/b: high dose/placebo	**Screening**	**V1**	**V2**	**V3 phone call**	**V4[3]**	**V5**	**V6 phone call**	**V7 phone call**	**V8 phone call**
Check criteria for temporary delay for ~~enrollment~~***enrolment*** and study intervention administration		O	O			O				

3All study activities except recording of administered intervention number and recording of AEs post-vaccination, will be performed before the administration of vaccine or placebo.

In Section 1.3 Schedule of Activities, Table 3:

Type of contact	Group 4a HTD Group 4b below HTD Group 4c Placebo	Screening	V1	V2[4]	V3	V4[8]	V5[4]	V6	V7	V8	V9	V10	Unscheduled visit
Check criteria for temporary delay for ~~enrollment~~***enrolment*** and study intervention administration		O	O			O							

[2]Only for participants in subset for safety monitoring (Refer to Section 4.1.1, Safety monitoring for details). ***Additional blood samples may be obtained during the unscheduled visit at the discretion of the investigator, to assess any perceived safety issues.***

[4]For participants in the safety subset, a clinic visit will apply at Visit 2 (Day 8) and Visit 5 (Day 68), for all other study participants a phone call will apply. ***If, at Visit 2 or Visit 5, a study participant shows signs and/or symptoms suggestive of gonococcal infection, tested positive for Ng outside of the study schedule and has not yet received treatment, or had a recent sexual contact with a partner with a confirmed diagnosis of gonococcal infection, the investigator will collect samples from the 3 anatomical sites (urogenital, anorectal and pharyngeal), double samples of affected sites in case of symptoms, and blood samples for immunogenicity as described in Section 8.1.1. Additionally, the investigator will record information on occurrence of any gonorrhea-specific symptom and Disease-Related- Events (DREs) as described in1 Section 8.3.1, and the study participant will be required to complete a sexual behavior questionnaire as described in Section 8.2.1.5.***

[7]***If a device is given it should be returned by Day 451, Visit 10***

[8]***All study activities except recording of administered intervention number and recording of AEs post-vaccination, will be performed before the administration of vaccine or placebo.***

In Section 2.3 Benefit/Risk assessment:

- Potential benefit of developing protection against infection caused by ~~*N. gonorrhoeae*~~ ***Ng.***
- Swabbing and collection of urine samples are routine procedures performed to diagnose STIs. Swabbing ~~Ct/Ng~~ must be performed by qualified healthcare professionals.

In Section 3 Objectives, endpoints and estimands, Table 5, Phase 2 Efficacy PoC Secondary:

To evaluate the efficacy of the NgG vaccine in preventing CCI [redacted]	• Incidence rates of CCI [redacted] with positive ~~NG~~***Ng*** detected by NAAT CCI [redacted] CCI [redacted] or culture** from 1 month (Day 91) to 13 months post-Dose 2 (Day 451).

In Section 3 Objectives, endpoints and estimands, Table 5, Tertiary:

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[redacted]

To evaluate the humoral immune responses to the NgG vaccine.	• Anti-NgG IgG antibodies Geometric mean concentrations (GMCs) at Day 1, Day 31, Day 61, Day 91 and Day 451, and unscheduled visits where applicable. • hSBA Geometric mean titres (GMTs) against *Ng* strain at Day 1, Day 31, Day 61, Day 91 and Day 451, and unscheduled visits where applicable.[48]

[1]A gonorrhea case is defined as a participant with at least 1 sample collected during the defined period confirmed by FDA-approved (nucleic acid amplification test) NAAT as positive for N. gonorrhoeae ***Ng*** by central laboratory, regardless of the presence or absence of symptoms and irrespective of participant history of gonococcal infection. For the efficacy primary objective, only cases from urogenital and/or anorectal sites will be considered. For the secondary and tertiary efficacy objectives, cases from urogenital, anorectal and/or pharyngeal sites will be considered, ***unless otherwise specified***. For the purpose of the case definition only the first confirmed gonococcal infection will contribute.

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[redacted]

In Section 4.1.1, Phase 1: study design of dose-escalation safety lead-in part in healthy participants, Safety monitoring:

For each group in the dose-escalation safety lead-in, all the available safety data collected up to the Day 8 post-dose 1 visit from the participants (including laboratory assessments at Day 8) will be evaluated. The Safety Review Team (SRT) and the internal Safety Review Committee (iSRC) Chair will evaluate all available cumulative blinded safety data and will confirm the administration of the second dose in the concerned group and the start of ~~enrollment~~***enrolment*** in the subsequent group. In case blinded data are of concern for SRT and iSRC Chair, unblinded data may be evaluated by iSRC (conditional iSRC) and only after positive opinion by iSRC the next step can start.

After the SRT/iSRC data review of all cumulative data collected for Group 1, Group 2 and Group 3 after dose 2 of the third group of the dose-escalation safety lead-in, the ~~enrollment~~***enrolment*** of the PoC participants (Groups 4a/b/c) in the vaccine target population can start.

In Section 4.1.2, Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea, Figure 3:

[a]The ~~enrollment~~***enrolment*** in the PoC part will proceed stepwise with HIV negative individuals to be enrolled first and then opening the recruitment to HIV positive participants. Refer to Safety monitoring for more information

In Section 4.1.2, Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea, Duration of the study:

The total duration of the study, per participant, will be approximately 15 months. All participants will have to attend a screening visit; participants in the safety subset will have to attend/perform 10 visits, all other participants will have to attend/perform 8 visits and 2 phone calls. Unscheduled visit will be arranged in case ***of*** symptoms suggestive of possible gonococcal infection

In Section 4.1.2, Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea, Sampling schedule:

NAAT samples* including swabs (urogenital, anorectal, and pharyngeal sites) and first-catch urine sample ***which may be collected*** as an alternative to the urogenital swab for male participants and those with a penis will be collected from all participants at Screening, Visit 3 (Day 31), Visit 4 (Day 61), Visit 6 (Day 91), Visit 7 (Day 181), Visit 8 (Day 271), Visit 9 (Day 361), Visit 10 (Day 451), and at unscheduled visit(s) when performed.

Sampling for Ct/Ng must be performed by qualified healthcare professionals. Self-swabbing is only allowed to collect vaginal swab. Participants must be trained on how to perform self-sampling if this is going to occur. All participants will be tested from all 3 anatomical sites (urogenital, rectal, and pharyngeal). ***Preferably,*** ~~*A*~~***a*** *first-catch urine sample* ~~*is required*~~***will be collected*** *instead of a swab for the detection of genital infection in male participants (and those with a penis)* ***but urogenital swab is acceptable****, whereas a vulvo/vaginal or cervical swab* ~~*is preferred*~~ ***will be required*** *over the urine sample in female participants (and those with a vagina****). Use of vaginal medicinal treatments, vaginal moisturizers, vaginal wash/hygiene products, containing carbomer should be avoided in the 7 days before planned visits when vaginal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test.***

In Section 4.1.2, Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea, Unscheduled visits:

Participant tested positive for Ng ~~at NAAT~~ outside of the study schedule and has not yet received treatment.

Should a study participant show signs and/or symptoms suggestive of gonococcal infection either at a scheduled or unscheduled visit, a double sampling at the affected anatomical site will be executed: one will be processed by the local laboratory of reference, the other one will be processed by the GSK designated laboratory. Test execution at local laboratory will ensure results availability in shorter timeframe and a timely treatment of confirmed positive cases. In case of discrepant results between the local and the GSK designated laboratory, only the result from the GSK designated lab will be considered for the study endpoints. CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] The investigators will be informed about every positive result obtained at GSK designated laboratory.

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In Section 4.1.2, Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea, Subsets for intensive safety monitoring in the efficacy PoC part:

The ~~enrollment~~***enrolment*** in the PoC part will proceed stepwise with HIV negative individuals to be enrolled first and then opening the recruitment to HIV positive participants

For both HIV positive and HIV negative participants an intensive safety monitoring will be applied to a subset composed of the first subjects enrolled as detailed below:

After positive outcome of the ~~Part 1~~***dose escalation safety lead-in part*** of the study (blinded SRT/iSRC chair review post-dose 2) a safety subset of 30 HIV negative participants per group (**HIV negative safety subset**) will be enrolled and administered with first and second dose. A blood sample will be taken from these participants specifically for hematology/biochemical analysis at screening and pre-dose 2 (screening and Day 61) as baseline values and 7 days post each dose.

~~The~~ ***All*** cumulative safety data collected up to 7 days **post-dose 1** of the last participant belonging to the HIV negative safety subset (along with available safety data collected after the second dose administered to the HIV negative safety subset, if applicable) will undergo an unblinded ~~interim~~ analysis by the iSRC. Only in case of a positive outcome of the unblinded iSRC evaluation, the administration of dose 1 and dose 2 can proceed in all HIV negative participants and ~~enrollment~~***enrolment*** can be opened to people living with HIV matching with the inclusion/exclusion criteria depicted below. The first 8 HIV positive participants per group will constitute the **HIV positive safety subset** from whom blood sample for safety evaluation will be taken at screening and pre-dose 2 (screening and Day 61) as baseline values and 7 days post each dose, similarly to what is described above.

The safety data 7 days **post-dose 2** administered to last participant belonging to the HIV positive safety subset will undergo an unblinded ~~interim~~ analysis by the iSRC and will determine whether the ~~enrollment~~ ***enrolment*** can progress to further HIV positive participants. The administration of the first doses in HIV positive participants will be allowed in more than 1 participant per day but vaccination of 2 participants simultaneously will not be possible***,*** ~~(~~i.e., minimum 2 hours apart and 4 participants per day ***per study center*** at maximum***, to ensure that, in the event of an acute adverse reaction, the site can provide the required medical attention for the individual concerned***~~)~~.

In Section 4.2 Scientific rationale for study design:

The purpose of this Phase 1/2 first time in human - proof of concept (FTiH-PoC) study is to evaluate safety and reactogenicity, to demonstrate efficacy and to explore immunogenicity of GSK Biologicals' ~~*Neisseria gonorrhoeae* GMMA (~~NgG~~)~~ investigational vaccine compared to placebo (saline), both administered in a 2-dose schedule (0-2 month).

In Section 4.2.1 Participant input into study design:

Participants were not involved in the design of the study as the study ***plans to*** recruit~~ed~~ healthy adults at risk for gonorrhea.

In Section 4.2.2 Case definition:

A gonorrhea case is defined as a participant with at least 1 sample collected during the defined period that is confirmed at the central lab by NAAT as positive for ~~*N. gonorrhoeae*~~ ***Ng***, regardless of the presence or absence of symptoms and irrespective of participant history of gonococcal infection. For the purpose of the case definition only the first confirmed gonococcal infection will contribute.

- **For the primary objective**, only cases from **urogenital or anorectal** samples occurring from 1 month after the second vaccination (Visit 6, Day 91) until study end (Visit 10, Day 451) will be considered.
- **For the secondary and tertiary objectives**, overall cases (**urogenital, anorectal or pharyngeal**), and by each anatomical site (urogenital/anorectal/pharyngeal) will be considered ***unless otherwise specified,*** in accordance with the timepoints defined in Table 3.

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Disseminated gonococcal infection (DGI): it usually comprises 2 major clinical syndromes: (1) arthritis-dermatitis syndrome; and, (2) localized purulent arthritis without associated skin lesions. There are, however, patients who present with symptoms that overlap between these 2 classic presentations. Although localized infection of the genitourinary tract, rectum, or pharynx by ~~*N. gonorrhoeae*~~ ***Ng*** is a prerequisite for dissemination, patients with clinical manifestations of DGI often do not manifest symptoms of localized gonococcal infection.

Definitive diagnosis of DGI or gonococcal arthritis is made through the identification of the etiologic pathogen in a specimen taken from a non-mucosal site (such as blood, synovial fluid, or skin lesions). Microbiologic tests, however, are not always positive and in such cases, diagnosis is made clinically. A clinical diagnosis may be supported by evidence of ~~*N. gonorrhoeae*~~ ***Ng*** infection from specimens obtained from mucosal sites.

In Section 4.3 Rationale for dose:

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[redacted]

In Section 5.1.1, Inclusion criteria for the dose-escalation safety lead-in part:

- Female participants of non-childbearing potential may be enrolled in the study ***(refer to Section 10.4.1 for definition of women of non-childbearing potential).*** ~~Non-childbearing potential is defined as pre-menarche, hysterectomy, bilateral ovariectomy or salpingectomy, or post-menopause.~~

- Female participants of childbearing potential ***(refer to Section 10.4.1 for definition of women of childbearing potential)*** may be enrolled in the study if the participant:

In Section 5.1.2, Inclusion criteria for the efficacy PoC part

- Participants of non-childbearing potential may be enrolled in the study ***(refer to Section 10.4.1 for definition of women of non-childbearing potential).*** This includes transmen that have not undergone gender affirming surgery of their genitals.
- Participants of childbearing potential (refer to Section 10.4.1 for definition of women of childbearing potential~~, menarche and menopause~~) may be enrolled in the study if the participant:

In Section 5.2.1.1, Dose-escalation safety lead-in part:

- Any clinically significant** h~~a~~ematological (h~~a~~emoglobin level, white blood cell, lymphocyte, neutrophil, ~~eosinophil,~~ platelet~~red blood cell count and erythrocyte mean corpuscular volume~~) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen) laboratory abnormality

In Section 5.2.1.2, Efficacy PoC part: HIV negative intensive safety monitoring subset (i.e. first 30 HIV negative subjects per group):

*Participants that are confirmed as positive for ~~*N. gonorrhoeae*~~ ***Ng*** by NAAT will be invited to participate in a re-screen visit after receiving appropriate antibiotic treatment.

- Any clinically significant** hematological (hemoglobin level, white blood cell, lymphocyte, neutrophil, ~~eosinophil,~~ platelet~~, red blood cell count and erythrocyte mean corpuscular volume~~) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen) laboratory abnormality.

In Section 5.2.1.3, Efficacy PoC part: HIV positive intensive safety monitoring subset (first 8 HIV positive subjects per group, enrolled in case of a positive safety outcome from the previous subset):

* Participants that are confirmed as positive for ~~*N. gonorrhoeae*~~ ***Ng*** by NAAT will be invited to participate in a re-screen visit after receiving appropriate antibiotic treatment.

- Any clinically significant** hematological (hemoglobin level, white blood cell, lymphocyte, neutrophil, ~~eosinophil,~~ platelet~~, red blood cell count and erythrocyte mean corpuscular volume~~) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, blood urea nitrogen) laboratory abnormality.

In Section 5.2.1.4 All remaining participants:

* Participants that are confirmed as positive for ~~*N. gonorrhoeae*~~ ***Ng*** by NAAT will be invited to participate in a re-screen visit after receiving appropriate antibiotic treatment.

Of note, ~~S~~***s***hould any safety concerns be identified within the HIV positive safety subset, the ~~enrollment~~ ***enrolment*** will progress with the ~~only~~ inclusion of HIV negative individuals ***only***. For them, the medical conditions listed in this section, apart from those related to the HIV positivity condition, will determine exclusion from the study.

In Section 5.3 Lifestyle considerations, Drugs and alcohol abuse:

In general, when facing vulnerable individuals and those who regularly use recreational drugs or abuse alcohol, the investigator must evaluate if the participation in the study poses any additional risk to the safety, rights, and wellbeing of these participants, and assess the capacity of the participant to understand and comply with the requirements. ***Vulnerable individuals and those who regularly use recreational drugs or abuse alcohol should not be enrolled in the intensive safety monitoring subsets. Only in case of a positive outcome of the unblinded iSRC evaluation of the cumulative safety data collected in the intensive safety monitoring subsets, can enrolment be opened to vulnerable individuals and those who regularly use recreational drugs or abuse alcohol.***

In Section 5.4 Screening failures:

A screening failure is an individual who consents to participate in this study but is not randomized to a study intervention because he/she doesn't meet inclusion***/exclusion criteria. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at the discretion of the investigator if the reason for screening failure no longer applies.***

Participants that are confirmed as positive for ~~*N. gonorrhoeae*~~ ***Ng*** by NAAT at the screening visit are considered screening failure, but they will be invited to participate in a re-screen visit after receiving appropriate antibiotic treatment.

In Section 5.5 Criteria for temporarily delaying study intervention administration:

- Presence of uncomplicated symptoms of gonorrhea or other STIs (e.g., urethritis or vulvo-vaginitis, syphilitic rash with no fever) is not a reason for delaying the administration of the ***second dose of*** study intervention.
- Participants living with HIV who experience a deterioration of their immunological parameters may not be administered further doses of study intervention until such parameters return to immunological stable levels (i.e., CD4 cell count >350 cells/mm^3, viral load < 50 ***cp/ml***). Any significant delay in receiving further doses of the study vaccine will result in their exclusion from the Per Protocol (PP) analysis Set.

In Section 6 Study intervention and concomitant therapy, Table 8 footnotes:

****GSK Biologicals' ~~*Neisseria gonorrhoeae* GMMA (~~NgG~~)~~ investigational vaccine is an intramuscular (IM) injectable vaccine that can be presented as 1 vial or 2 vials to be mixed immediately before the injection, depending on the antigen dose. CCI [redacted] CCI [redacted]

In Section 6.3.1 Participant identification:

Participant identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study ~~centre~~***center***.

In Section 6.3.2 Randomization to study intervention, Efficacy PoC:

The target enrolment for the efficacy PoC will be about 750 participants (refer to Section 9.5 for details about sample size assessment and re-assessment). The ~~enrollment~~***enrolment*** in the PoC part will proceed stepwise with HIV negative individuals to be enrolled first and administered the first dose. Following unblinded iSRC evaluation, enrolment can be opened to HIV positive subjects. Refer to Section 4.1.2 "Safety monitoring".

In Section 6.3.3 Intervention allocation to the participant:

The randomization algorithm during the efficacy PoC will use a minimization procedure accounting for sex, site, age group (18–30 years of age, 31–50 years of age), ***race (black, white, other),*** belonging to specific risk group (i.e. men having sex with men under pre-exposure prophylaxis for HIV vs others).

In Section 6.8 Concomitant therapy

- ***Medications taken as post-exposure prophylaxis following sexual contact to prevent gonorrhea and other STIs (e.g. doxycycline).***

In Section 7.3 Lost to follow-up:

Participants will be considered 'lost to follow-up' if they ***repeatedly*** fail to return for scheduled visits and cannot be contacted by the study site ~~for 7 consecutive months~~.

In Section 8, Study assessments and procedures, Burden of the study, degree of strain and risk threshold in Dose-escalation safety lead-in part:

Participants are required to undergo blood sampling as screening procedure. Participants are required to attend 4 clinic visits and complete 4 phone calls during the course of the study, to receive the study intervention, ***to complete the eDiary to collect solicited adverse events in the 7 days following administration of study vaccine*** and undergo blood samplings. A basic, routine medical assessment, including interview on past and current medical history will also be performed by the investigator or designated person.

On study Day 1 a urine pregnancy test for female participants of childbearing potential will be required.

In Section 8, Study assessments and procedures, Burden of the study, degree of strain and risk threshold in Efficacy PoC part:

Participants are required to undergo swab sampling and/or urine tests as screening procedure. Participants are required to attend or perform at least ***8*** ~~10~~ visits during the duration of the study, to receive the study intervention, ***to complete the eDiary to collect solicited adverse events in the 7 days following administration of study vaccine, to*** perform multiple swabs and/or urine tests and undergo blood samplings. A basic, routine medical assessment, including interview on past and current medical history and sexual history of last 30 days will also be performed by the investigator or designated person. On study Day 1 a urine pregnancy test for female participants (including *trans*men that have not undergone gender affirming surgery of their genitals) of child-bearing potential will be required. Swab sampling will be performed by qualified healthcare professionals. Self-swabbing is only allowed to collect vaginal swab. Participants must be trained on how to perform self-sampling if this is going to occur.

In Section 8, Study assessments and procedures, Repetition of inconclusive Ct/Ng NAATs:

Participants with an "invalid", "equivocal" or otherwise inconclusive result at NAAT are invited to repeat the test within a reasonable time frame. If they received anti gonococcal treatment meanwhile, there is ~~very~~ little chance to detect bacterial genetic material and the repetition of NAAT ~~is~~ ***may*** not ***be*** needed. ***All inconclusive test results will be documented in the eCRF.***

In Section 8.1.1 Biological samples:

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. ***Additionally, biological samples may also be used to*** CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

~~Additional serological assays may be performed in the future to further characterize the disease and/or the immunological response elicited by study intervention. These assays may not be represented in the objectives/endpoints of the study protocol.~~

In Section 8.1.1 Biological samples, Table 10 footnotes:

[1]First-catch urine ~~will~~ ***may*** be collected as an alternative to the urogenital swab

In Section 8.1.1 Biological samples:

All laboratory testing for efficacy endpoint and humoral immune responses will be performed at GSK laboratory or in a laboratory designated by GSK. The testing of blood samples for safety evaluation and NAAT* testing for screening ***or when double sampling is performed in case of symptoms suggestive of possible gonococcal infection,*** will be performed by the local laboratory at the investigator's site.

*Store NAAT in accordance with laboratory and manufacturer recommended conditions.

In Section 8.1.1 Biological samples, Table 11

Test Classification	System	Component	Challenge	Method
Molecular Biology	Swab: Urogenital sites	~~*N. gonorrhoeae*~~***Ng*** Ct		NAAT
	Swab: anorectal sites	~~*N. gonorrhoeae*~~***Ng*** Ct		NAAT
	Swab: pharyngeal sites	~~*N. gonorrhoeae*~~***Ng*** Ct		NAAT
	Urine: First-catch urine[1]	~~*N. gonorrhoeae*~~***Ng*** Ct		NAAT
Humoral Immunity (Antibody determination)	Serum	Anti-Gono GMMA Ab IgG		ELISA-like
	Serum	Anti-Gono GMMA Bactericidal Ab		hSBA

Ct: *Chlamydia trachomatis*; NAAT: Nucleic Acid Amplification Test; Ab: antibodies; IgG: Immunoglobulin G; ELISA: Enzyme Linked ImmunoSorbent Assay; hSBA: Human complement Serum Bactericidal Assay; **Ng, *Neisseria gonorrhoeae***

[1]First-catch urine ~~will~~ ***may*** be collected as an alternative to the urogenital swab from male participants and those with a penis

In Section 8.1.2 Read-out for efficacy assessment:

NAAT samples include swabs (urogenital, anorectal, and pharyngeal sites) and first-catch urine sample as an alternative to the urogenital swab for male participants and those with a penis. They will be collected at specific time points during the study as illustrated in Figure 3. Diagnostic tests (NAAT) for the detection of Ng and Ct nucleic acids will be used. ***Use of vaginal medicinal treatments, vaginal moisturizers, vaginal wash/hygiene products containing carbomer should be avoided in the 7 days before planned visits when vaginal swabs will be collected, to avoid potential inhibition of carbomer on the NAAT test.***

All laboratory procedures for sampling and the detection of gonococcal infection will follow the standard of care at the study centers. The respective testing for gonorrhea (NAAT) in scope for the primary and secondary endpoints will be conducted in a central laboratory designated by GSK, using FDA-approved NAAT method.

Should a study participant show signs and/or symptoms suggestive of gonococcal infection either at a scheduled or unscheduled visit, a double sampling at the affected anatomical site will be executed: one will be processed by the local laboratory of reference, the other one will be processed by the GSK designated laboratory. Test execution at local laboratory will ensure results availability in shorter timeframe and a timely treatment of confirmed positive cases. In case of discrepant results between the local laboratory and the GSK designated laboratory, only the result from the GSK designated lab will be considered for the study endpoints. CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] The investigators will be informed about every positive result obtained at GSK designated laboratory.

CCI [redacted]

In Section 8.1.3 Immunological read-outs:

To further characterize the immune response, serum samples of a subset of the PoC participants will also be analyzed using a hSBA to assess the functionality of antibodies generated by the candidate vaccine to induce complement mediated killing of ~~*N. gonorrhoeae*~~ *Ng* homologous strain at the same timepoints. The subset will represent at least the first 100 ~~hundred~~ participants enrolled in each arm (n=300 total, 40% of the total study population), and all participants with unscheduled visits. Evaluation of the humoral immune responses (tertiary objective) is subject to the assay availability and the respective blood samples will also be used to the assay's development.

In Section 8.1.5 Immunological correlates of protection:

No generally accepted immunological correlate of protection has been demonstrated so far for ~~*N. gonorrhoeae*~~ ***Ng***. Attempts will be made to identify an immunological correlate of protection in the efficacy PoC study.

In Section 8.2.1.4 History or symptoms directed physical examination:

For male participants (and those with a penis) with suspected urethritis: first catch urine, with the participant having held urine for at least 1 hour, ~~is required~~***may be collected*** instead of the collection of exudates with a swab. Microscopy and cultures of the exudate are not required by this protocol but may be performed to support the diagnosis and isolation of other infective agents as per routine practice.

In Section 8.2.3.3 Study holding rules, Phase 1, dose-escalation safety lead-in part:

A staggered ~~enrollment~~***enrolment*** of healthy participants for the Phase 1 dose-escalation safety lead-in part is chosen. In case blinded data are of concern for SRT and iSRC Chair, unblinded data may be evaluated by iSRC (conditional iSRC) and only after positive opinion by iSRC can the next step start.

Holding rules 2a-c will be assessed by the SRT in a blinded way. If no safety concerns are identified, SRT will confirm the administration of the second dose in the concerned group and the start of ~~enrollment~~***enrolment*** in the subsequent group.

In Section 8.2.3.3 Study holding rules, Phase 2 PoC part, Table 12, footnote 2:

[2] This applies to the subset composed of the first 8 HIV positive participants from each study group enrolled in case of a positive safety outcome of the unblinded ~~interim~~ analysis of the first 30 HIV negative participants

In Section 8.8.1.2 Gonorrhea-related hospitalizations as well as ER/A&E visits:

CCI

[redacted]

In Section 9.3.3 Additional exploratory analyses on vaccine efficacy:

CCI

[redacted]

CCI [redacted]

In Section 9.3.4 Other exploratory analyses:

Additional details on the analyses associated to the tertiary endpoints on immunogenicity ***and*** its association with efficacy and safety will be provided in a dedicated statistical analysis plan for tertiary endpoints.

In Section 9.4 Interim analyses:

~~All comparative analyses to demonstrate VE will be conducted on final data.~~ ***No interim analysis is planned in the dose escalation safety lead-in part of the study.***

~~An~~ ***In the PoC part, an*** interim futility assessment will be performed to evaluate potential significant evidence of lack of efficacy. ***An analysis of the primary and secondary endpoints will be performed when sufficient gonorrhea cases are accrued as described in Section 9.4.1. There will be no related clinical study report (CSR) for these analyses.***

In Section 9.4.1 Sequence of analyses:

In preparation ~~to~~ ***for*** the SRT/iSRC safety evaluations during the dose-escalation safety lead-in and PoC part, analyses of available safety data will be performed by an independent data analysis ~~centre~~ ***center*** (IDAC) to maintain the study blind. ***Following completion of the dose-escalation safety lead-in part, all data collected in this part (up to Day 241) will be analyzed. However, a CSR will not be generated at the time of this analysis.***

During the efficacy PoC part, ~~interim~~ ***ongoing*** estimates of the gonorrhea IR in the placebo group will be generated to inform the sample size adaptation plan. ~~In addition, w~~***W***hen approximately 65% of the expected number of gonorrhea cases in HTD vs placebo comparison (i.e., 31 cases overall, summing up the cases in the HTD and placebo groups) will be accrued, a futility assessment will be performed. ~~Such~~ ***The*** ~~interim~~ ***ongoing*** estimates ***of the gonorrhea IR in the placebo group as well the futility assessment*** will be produced by IDAC and checked by an unblinded statistician independent from the study team to maintain study integrity. ***At the time of the interim futility assessment, key safety data will be evaluated as well by the iSRC.***

A***n*** analysis for ***the*** primary ***and secondary*** endpoint***s will be***~~is~~ performed when 47 cases are reached for ***both*** the HTD vs placebo comparison (i.e., 47 cases overall, summing up the cases in the HTD and placebo groups) ***and for the bHTD vs placebo comparison (i.e., 47 cases overall, summing up the cases in the bHTD and placebo groups). In case of ties in event dates when identifying the 47th case, all eligible events will be taken into account in the analysis.*** If HTD efficacy is ***not*** demonstrated, then the comparison of bHTD vs placebo groups ~~has to be tested:~~ ***may be reported as a descriptive analysis. This analysis will be produced by IDAC and group unblinded results will be shared with a restricted group of study team members, as described in the SAP. In this analysis, by participant listings will not be shared and frequency counts below 5 participants will***

not be reported in summary tables. ~~in an analogous way to the first comparison, this second analysis has to be performed when 47 cases overall are observed in the bHTD and placebo groups.~~

~~A final analysis will be performed when all data up to study end (Day 451) are available: at this stage, primary safety endpoints will be evaluated as well as primary and secondary efficacy ones; but, this additional data (beyond 47 events per comparison) will not be taken into account for the conclusion of vaccine efficacy.~~ ***A complete analysis will be performed when all data up to study end (Day 451) are available: at this stage, primary safety endpoints will be evaluated as well as primary and secondary efficacy ones. The conclusion of vaccine efficacy will be based on the analysis of the first 47 cases accrued for each comparison. Additional efficacy data (beyond 47 cases per comparison) will be analyzed for descriptive purposes.***

If by the end of the study, the total number of cases is below 47 in any of the comparisons, the conclusion of vaccine efficacy will be based on the complete analysis i.e., all data up to study end (Day 451).

Tertiary endpoints will be evaluated ~~at the final~~***as part of the complete*** analysis but if the data become available at a later stage, (an) additional analysis/analyses will be performed.

In Section 9.5 Sample size determination:

Considering an initial sample size of 209 evaluable subjects in the placebo arm and a yearly IR of 15%, 31 cases are expected to be seen. The placebo IR will be monitored every two months from the start of the PoC enrolment, in accordance with the enrolment rate. If there is strong evidence against the original assumption of 15% (i.e., the probability of seeing a number of cases higher than the one observed - given a Poisson distribution with a yearly rate of 15% - is greater than 80%), the sample size for each arm will be increased of a fixed number of 50 subjects per arm. At every interim estimate of the placebo IR, the same computations will be performed; whenever a sample size increase is triggered, the assumed placebo IR will be updated to the value needed to have 31 cases in the placebo group with the new increased sample size. In order to guarantee the blinding, this assessment will be performed by an independent data analysis ~~centre~~***center*** (IDAC); further details on the statistical methodologies and how to perform the assessment will be provided in the main statistical analysis plan (SAP).

In Section 10.1.3 Informed consent process:

The content of the informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study ~~centre~~ ***center***.

In Section 10.2 Appendix 2: Clinical laboratory test, Section 10.2.1. Protocol required safety laboratory assessments, Table 19:

All events of ALT [or AST] ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (> 35% direct bilirubin) or ALT [or AST] ≥3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to GSK in 24 hours.

~~All events of ALT ≥3 × upper limit of normal (ULN) and) or ALT ≥3 × ULN must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).~~

Local urine ***pregnancy*** testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

The tests detailed in Table 19 will be performed by the laboratory designated by the sponsor. ***Unscheduled clinical laboratory measurements may be obtained at any time during the study at the discretion of the investigator, to assess any perceived safety issues.*** Where tests are carried out locally, the results of each test carried must be entered in the eCRF.

In Section 10.2.2 Assay use for efficacy assessment:

NAATs are designed to amplify and detect nucleic acid sequences that are specific for the organism being detected (Ng and Ct nucleic acids in this case). NAATs are the CDC-recommended assays for screening or diagnostic of ~~N. gonorrhea~~ *Ng* and Ct infections [Papp, 2014].

This high sensitivity has allowed for shed organisms to be detected in specimens collected through less invasive procedures, such as first-catch urine *samples* and vaginal swabs [Papp, 2014].

In Section 10.2.3.1 ELISA:

Change in heading title from ELISA to ELISA***-like***

In Section 10.3.3 Solicited events:

Note: Participants will be instructed to measure and record the oral temperature in the evening. If temperature is measured via routes other than oral this should be recorded in the eDiary. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the ~~diary card~~ ***eDiary*****.**

In Appendix 4: Contraceptive guidance and collection of pregnancy information, Section 10.4.1. Definitions, Section 10.4.1.1. Woman of Childbearing Potential (WOCBP):

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview. ***For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.***

In Section 10.8.1 List of abbreviations:

FTiH-PoC	***first time in human - proof of concept***

In Section 11 References:

Abara WE, Bernstein KT, Lewis FMT, et al. Effectiveness of a serogroup B outer membrane vesicle meningococcal vaccine against gonorrhoea: a retrospective observational study. Lancet Infect Dis. 2022;12:S1473-3099(21)00812-4.

Bruxvoort KJ, Lewnard JA, Chen LH, et al. Prevention of Neisseria gonorrhoeae with meningococcal B vaccine: a matched cohort study in Southern California. Clin Infect Dis. 2022; Jun 1:ciac436. doi: 10.1093/cid/ciac436. Epub ahead of print.

Food and Drug Administration. Adaptive Designs for Clinical Trials of Drugs and Biologics (FDA) December, 2019. https://www.fda.gov/media/78495/download (accessed March 2022)

Petousis-Harris, H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. Lancet. 2017;390(10102):1603-10.

10.10.5. Protocol Amendment 2

Amendment 2: 20 January 2023

Overall Rationale for the Amendment: The aim of this protocol amendment is to clarify the minimum constitution of the safety review team (SRT), contraceptive guidance and collection of pregnancy information in pregnant partners of male participants; linked to Medicines and Healthcare products Regulatory Agency (MHRA) requirements.

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Section 5.1.1 Inclusion criteria for the dose-escalation safety lead-in part	Definition of non-childbearing potential updated	To clarify the definition of non-childbearing potential
Section 8.2.3.3 Study holding rules:	A description of the minimum constitution of the safety review team (SRT) was added.	To clarify the minimum constitution for the safety review team (SRT)
Section 10.4.1.2 Women not considered as women	'Current bilateral tubal ligation or occlusion' removed as possible cause	To clarify the definition of premenopausal female of non-childbearing potential,

Section # and Name	Description of Change	Brief Rationale
of childbearing potential:	for non-childbearing potential	bilateral tubal ligation or occlusion will be considered as highly effective method of contraception that is user-independent as described in Table 23
Section 10.4.2 Contraception guidance	Updated list of highly effective contraceptive methods and related text: add 'sexual abstinence (refraining from heterosexual intercourse)' as highly effective contraceptive method, and update the clarification that sexual abstinence should not be considered a valid form of contraception in the PoC part of the study	To clarify the highly effective contraceptive methods and to clarify that sexual abstinence, despite considered a valid form of contraception for the dose escalation safety lead-in part of the study, should not be considered a valid form of contraception in the PoC part of the study where the target participants must be sexually active in order to be eligible.
Section 10.4.2.2 Female participants who become pregnant	Edited to include information that pregnant partners of male participants will not be followed to determine the outcome of the pregnancy	To clarify that pregnant partners of male participants will not be followed to determine the outcome of the pregnancy, since no impact of the vaccine on spermatogenesis nor transfer via semen is anticipated
Section 10.7 Appendix 7: Country-specific requirements	Addition of a new section 10.7.4 Requirements for UK	To clarify the study holding rules in relation to UK-specific requirements

In the following sections, deleted text is indicated in ~~strikethrough~~ and changed text in ***bold italics***:

In Section 5.1.1 Inclusion criteria for the dose-escalation safety lead-in part:

- Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, ~~current bilateral tubal ligation or occlusion,~~ hysterectomy, bilateral ovariectomy ***or salpingectomy***, or post-menopause.

In Section 8.2.3.3 Study holding rules:

Phase 1, dose-escalation safety lead-in part

A staggered enrolment of healthy participants for the Phase 1 dose-escalation safety lead-in part is chosen. In case blinded data are of concern for SRT and iSRC Chair, unblinded data may be evaluated by iSRC (conditional iSRC) and only after positive opinion by iSRC can the next step start. ***At minimum the SRT will consist of the following core members: the study safety lead (safety representative), a safety product specialist, the study clinical science lead (clinical representative), the project epidemiologist, the project biostatistician and the global regulatory affairs lead.*** The iSRC will include 3 core members independent from the clinical development project to ensure an unbiased assessment: a clinician, a safety representative and a statistician and their respective delegates. The Chair is usually the safety representative.

In Section 10.4.1.2 Women not considered as women of childbearing potential:

- **Premenopausal female with ONE of the following:**
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - ~~Current bilateral tubal ligation or occlusion~~
  - Transgender men taking gender affirming hormonal therapy with testosterone cannot be considered of not childbearing potential, even in the presence of amenorrhea.

  Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

In Section 10.4.2 Contraception guidance:

Table 23 Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent[a] ***Failure rate of <1% per year when used consistently and correctly.***
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Injectable • Oral
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal ***ligation or*** occlusion
Sexual abstinence ***Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*** ***Sexual abstinence should not be considered a valid method of contraception in the PoC part of this trial, given that participants must be sexually active. If, however, changes in personal circumstances occur for which a participant is no longer sexually active, abstinence may be considered acceptable.***

*Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies

~~Sexual abstinence should not be considered a valid method of contraception in this trial, given that participants must be sexually active at the time of enrolment. If, however, changes in personal circumstances occur for which a participant is no longer sexually active, abstinence may be considered acceptable.~~

In Section 10.4.2.2 Female participants who become pregnant:

Refer to Sections 8.3.1, 8.3.2, 10.3.8.1, 10.3.8.2 and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study will not receive any further dose of study intervention until the pregnancy/breastfeeding is concluded.

Pregnant partners of male participants will not be followed to determine the outcome of the pregnancy, since no impact of the vaccine on spermatogenesis nor transfer via semen is anticipated, and therefore no teratogenicity is expected in pregnant partners.

In Section 10.7 Appendix 7: Country-specific requirements a new section was added:

10.7.4. Requirements for UK

Study holding rules

Holding rules are defined to ensure well-controlled exposure to the NgG investigational vaccine and they will apply to study participants who have received investigational vaccine in the study as detailed in section 8.2.3.3. The holding rules will hence serve as criteria to point attention to safety signals that require escalation within GSK, and meeting any of the holding rules will trigger a hold of vaccination. If any of the study holding rules in Tables 12 or 13 of section 8.2.3.3. are met and confirmed following unblinded review, any subsequent restart of the study in the UK will require prior approval by the Medicines and Healthcare products Regulatory Agency (MHRA) of a substantial amendment summarising the clinical data and rationale for the restart.

10.10.6. Protocol Amendment 1

Amendment 1: 19 October 2022

Overall Rationale for the Amendment: The aim of this protocol amendment is to incorporate a study holding rule that applies to all Phase 2 participants. In addition, changes linked to EU-CTR requirements have been implemented and correction of typographical errors, and minor edits for clarification have been made (see below for information).

List of main changes in the protocol and their rationale:

Section # and Name	Description of Change	Brief Rationale
4.1.2 Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea, subsection "Subsets for intensive safety monitoring in the efficacy PoC part"	Additional wording added to clarify the study holding rules for PoC participants not belonging to the intensive safety monitoring subset	To incorporate a study holding rule that applies to all Phase 2 participants that specifies a pause in study activities in the event that ≥ 1 participant experiences a death or life-threatening serious adverse event (SAE) that is at least possibly related to the study product. Study activities may proceed if review of safety data does not demonstrate safety concerns.
4.2. Scientific rationale for study design a new section was added, Section 4.2.1 Participant input into study design	New section added (Section 4.2.1 Participant input into study design) to describe participant involvement in the design of the study and any participant/patient suggestions implemented	To comply with requirements for the EU-CTR process and alignment with updated template
8.2.3.3 Study holding rules, subsection "Phase 2 PoC part"	Additional wording and a new table (Table 13) added to clarify the study holding rules for PoC participants not belonging to the intensive safety monitoring subset. Adjustment of wording used in table caption for Table 12 to	To incorporate a study holding rule that applies to all Phase 2 participants that specifies a pause in study activities in the event that ≥ 1 participant experiences a death or life-threatening serious adverse event (SAE) that is at least

Section # and Name	Description of Change	Brief Rationale
	clarify that the table reports study holding rules for Phase 1 and of Phase 2 PoC intensive safety monitoring subset. With the addition of the new table, subsequent table numbering udpated	possibly related to the study product. Study activities may proceed if review of safety data does not demonstrate safety concerns.
8.3.3 Regulatory reporting requirements for SAEs, pregnancies and other events	Removal of 2 footnotes not used in Table 16 linked to timeframe for collecting DREs	To clarify as DREs are collected in the eCRF and not included in Table 16.
10.1.4 Recruitment strategy	New section added to Appendix 1 (Regulatory, ethical, and study oversight considerations), to include a brief description of the recruitment strategy and the tools used	To comply with requirements for the EU-CTR process and alignment with updated template.
10.1.5 Data protection	Additional bullet points added to the appendix on data protection (sponsor/study site responsibilities and use of secured information technology systems), and application of bullet point list format to existing text	To comply with requirements for the EU-CTR process and alignment with updated template.
10.2.1 Protocol required safety laboratory assessments	Updated text to clarify safety laboratory assessments needed and the laboratories responsible for the tests	To provide clarification on required protocol required safety laboratory assessments.
10.3.8.1 Time period for collecting and recording AEs, SAEs, and pregnancies:	Correction to days cited for the time period for collecting and recording all solicited events that occur during 7 days following administration of the second dose of study	To correct the time period for collecting and recording all solicited events that occur during 7 days following administration of the second dose of study

Section # and Name	Description of Change	Brief Rationale
	intervention	intervention

In the following sections, deleted text is indicated in ~~strikethrough~~ and changed text in ***bold italics***:

In the title page the following information was added:

EudraCT number 2022-001060-10

In Section 2.2 Background:

In men, *Ng* is a common cause of urethritis and can lead to epididymo-orchitis, and prostatitis. In women, it causes cervicitis, which is frequently asymptomatic but can lead to pelvic inflammatory disease (PID). Up to 50% of women with an untreated infection caused by Ng and/or *Chlamydia trachomatis* ***(Ct)*** may develop PID …

In Section 2.3 Benefit/Riks assessment:

Medical evaluations/assessments associated with study procedures (e.g., physical examination) and frequent testing for ~~*Chlamydia trachomatis (C. trachomatis* [*Ct*]~~) and *N. gonorrhoeae* associated with the study conduct.

In Section 3 Objectives, endpoints, and estimands:

Phase 2 - Efficacy PoC Secondary	
To evaluate the efficacy of the NgG vaccine in preventing gonorrhea cases with and without ***Ct***~~*hlamydia trachomatis*~~ co-infection.	• Incidence rates of confirmed gonorrhea cases with and without ***Ct***~~*hlamydia trachomatis*~~ co-infection from 1 month (Day 91) to 13 months post-Dose 2 (Day 451).

A&E = Accident & Emergency; ***Ct = Chlamydia trachomatis***; ER = emergency room; PoC = Proof of Concept, HTD = highest tolerated dose

In Section 4.1.2 Phase 2: study design of efficacy PoC part in healthy participants at risk for gonorrhea, subsection "Subsets for intensive safety monitoring in the efficacy PoC part":

After completion of the above-mentioned intensive safety monitoring evaluations, for the whole study duration, in case ≥ 1 participant in the PoC part experiences a death or life-threatening serious adverse event (SAE) that is at least possibly related to the study product, the study will be paused (Section 8.2.3.3, Table 13). Study activities may proceed if review of safety data does not demonstrate safety concerns.

In Section 4.2. Scientific rationale for study design a new section was added:

Section 4.2.1 **Participant** ***input into study design***

Participants were not involved in the design of the study as the study recruited healthy adults at risk for gonorrhea.

In Section 4.2.2 Case definition:

The primary endpoint will be independent of the presence or absence of co-infection with ***Cthlamydia*** ~~*trachomatis*~~ (i.e., NAAT confirmed gonococcal and ***Ct***~~*C. trachomatis*~~ infections identified at the same visit). Co-infection will be assessed in the corresponding secondary endpoint and positivity for ***Ct***~~*C. trachomatis*~~ during the study execution, will not exclude the participant from the study.

In Section 8.1.1 Biological samples:

Table 11 Laboratory assays

Test Classification	System	Component	Challenge	Method
Molecular Biology	Swab: Urogenital sites	*N. gonorrhoeae* ***Ct***~~*C. trachomatis*~~		NAAT
	Swab: anorectal sites	*N. gonorrhoeae* ***Ct***~~*C. trachomatis*~~		NAAT
	Swab: pharyngeal sites	*N. gonorrhoeae* ***Ct***~~*C. trachomatis*~~		NAAT
	Urine: First-catch urine[1]	*N. gonorrhoeae* ***Ct***~~*C. trachomatis*~~		NAAT
Humoral Immunity (Antibody determination)	Serum	Anti-Gono GMMA Ab IgG		ELISA-like
	Serum	Anti-Gono GMMA Bactericidal Ab		hSBA

***Ct: Chlamydia trachomatis*;** NAAT: Nucleic Acid Amplification Test; Ab: antibodies; IgG: Immunoglobulin G; ELISA: Enzyme Linked ImmunoSorbent Assay; hSBA: Human complement Serum Bactericidal Assay

[1] First-catch urine will be collected as an alternative to the urogenital swab from male participants and those with a penis

In Section 8.1.2 Read-out for efficacy assessment:

NAAT samples include swabs (urogenital, anorectal, and pharyngeal sites) and first-catch urine sample as an alternative to the urogenital swab for male participants and those with a penis. They will be collected at specific time points during the study as illustrated in Figure 3. Diagnostic tests (NAAT) for the detection of Ng and ~~*Chlamydia trachomatis (C. trachomatis)*~~ ***Ct*** nucleic acids will be used.

In Section 8.2.3.3 Study holding rules, subsection "Phase 2 PoC part":

Enrolment will proceed stepwise in Part II where intensive safety monitoring will be put in place for the first 30 HIV- participants per group, and then for the first 8 HIV+ participants per group. The iSRC in charge for the safety evaluation in the PoC part (i.e. for HIV positive and HIV negative safety subsets) will include a member who is expert in the area of concern and who is external to GSK.

Holding rules 1a-d will also apply to the HIV negative subset for safety monitoring (consisting in the first 30 HIV negative participants enrolled per group) after first and second dose and holding rules 1a-d and 2a-c will apply to the HIV positive subset for

safety monitoring (consisting of the first 8 HIV positive participants enrolled per group) after first and second dose.

For the rest of the study participants of the PoC part, not belonging to the intensive safety monitoring subset, for the whole study duration, in case ≥1 participant experiences a death or life-threatening SAE that is at least possibly related to the study product, the study will be paused. Study activities may proceed if review of safety data does not demonstrate safety concerns.

Meeting any of these holding rules will trigger a hold of vaccination. The holding rules will hence serve as criteria to point attention to safety signals and require escalation within GSK, in order to decide whether other participants can be exposed. However, medical judgment considering all available safety data at the time of safety review should be the basis for decision to continue the study or not.

Holding rules (Table 1~~1~~*2 and Table 13*) are not designed to assess the acceptability of the reactogenicity profile of a specific candidate vaccine.

Table 12 Study holding rules for Phase 1 and of Phase 2 PoC intensive safety monitoring subset

Holding rule	Event	Number of participants needed to trigger the hold in Phase 1 part (Safety lead-in)	Number of HIV negative participants needed to trigger the hold in Phase 2 part (PoC)[1]	Number of HIV positive participants needed to trigger the hold** in Phase 2 part (Poc)[2]
1a	Death or any life-threatening SAE regardless of causality	≥ 1	≥ 1	≥ 1
1b	Any non-life-threatening SAE that cannot be reasonably attributed to a cause other than vaccination as per Investigator or Sponsor assessment	≥ 1	≥ 1	≥ 1
1c	Any withdrawal from the study (by investigator or participant request) following a Grade 3 AE	≥ 1	≥ 1	≥ 1
1d	Any local or general solicited AE leading to hospitalization, OR Necrosis at the injection site Each with an event onset within the 7-day (Day 1-7) post-vaccination period	≥ 1	≥ 1	≥ 1
2a	Any Grade 3 solicited administration site event (lasting 48h or more as Grade 3), with an event onset within the 7-day (Day 1-7) post-vaccination period	≥ 1	N/A	≥ 1
2b	Any Grade 3 solicited systemic events (lasting 48h or more as Grade 3), with an event onset within the 7-day (Day 1-7) post-vaccination period	≥ 2	N/A	≥ 2
2c	Any Grade 3 unsolicited AE that can be reasonably attributed to the vaccination as per Investigator or Sponsor assessment, with an event onset within the 7-day (Day 1-7) post-vaccination period OR	≥ 1	N/A	≥ 1*

Holding rule	Event	Number of participants needed to trigger the hold in Phase 1 part (Safety lead-in)	Number of HIV negative participants needed to trigger the hold in Phase 2 part (PoC)[1]	Number of HIV positive participants needed to trigger the hold** in Phase 2 part (Poc)[2]
	Any Grade 3 or above abnormality in pre-specified haematological or biochemical laboratory parameters in an investigational group with an event onset within the 7-day (Day 1-7) post-vaccination period			

AE = Adverse event; SAE = Serious adverse event; h = hours.

[1] This applies to the subset composed of the first 30 HIV negative participants from each study group

[2] This applies to the subset composed of the first 8 HIV positive participants from each study group enrolled in case of a positive safety outcome of the unblinded interim analysis of the first 30 HIV negative participants

* DAIDS Guidance for grading the severity in pre-specified haematological or biochemical laboratory parameters of HIV positive subjects.

** Holding rules will trigger a temporary pause of vaccinations in all study groups, as soon as they are identified. While vaccination will be paused, the responsible safety committee(s) providing study oversight will analyze available information related to the events triggering the hold. The Sponsor will then decide to suspend, modify or continue the conduct of the study, based on available evidence. The outcome of the decision will be documented and provided in writing to the investigators.

Table 13 Study holding rules for Phase 2 PoC participants not belonging to the intensive safety monitoring subset

Holding rule (Event)	*Number of participants needed to trigger the hold in Phase 2 part (PoC)*
Death or any life-threatening SAE that is at least possibly related to the study product	***≥ 1***

In Section 8.3.3 Regulatory reporting requirements for SAEs, pregnancies and other events:

~~Table 14~~ *Table 16* Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*, ‡, ‡‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	24 hours*	electronic pregnancy report	24 hours*	electronic pregnancy report

SAEs = serious adverse event

Refer to Table 2 and Table 13 for the timing for collection of DREs

*Timeframe allowed after receipt or awareness of the information by the investigator/site staff.

~~**Timeframe allowed once the investigator determines that the event meets the protocol definition of a DRE.~~

~~***The SRT should determine the appropriate time frame for completion of the eCRF for DRE~~

‡Paper Expedited Adverse Events Report will be dated and signed by the investigator (or designee)

‡‡ For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

In Section 10.1 Appendix 1: Regulatory, ethical, and study oversight considerations a new section was added (and subsequent subsection numbering was updated):

10.4.1 Recruitment strategy

Potential participants will be invited to participate in this clinical study by the study personnel or clinical staff (including participants' primary health physicians) in the clinic.

For Phase 2, advertisements will be placed in appropriate resources such as, but not limited to, printed media, Internet, or social media.

In Section 10.1.5 Data protection:

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets transferred to the sponsor will contain only the identifier. Name and any other information which would identify the participant will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participants must be informed that:
  - Their personal study-related data will be used by the sponsor in accordance with local data protection law.
  - Their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- ~~The participants must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF.~~
- ***The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.***
- ***Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.***

In Section 10.2.1 Protocol required safety laboratory assessments:

Table 19 Protocol required safety laboratory assessments

Laboratory assessments	Parameters	
Haematology	Platelet Count Haemoglobin	WBC count with Differential: Neutrophils Lymphocytes
Clinical chemistry	BUN	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)
	Creatinine	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)
~~**Other screening tests**~~	~~• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women/ transgender men of childbearing potential)]~~ ~~All study-required laboratory assessments will be performed by a central laboratory except blood tests for screening must be performed at the local laboratory. The results of each test carried out locally must be entered in the eCRF.~~	

hCG = human chorionic gonadotropin; SGOT = Serum Glutamic-Oxaloacetic Transaminase; SGPT = Serum Glutamic-Pyruvic Transaminase

Notes:

All events of ALT ≥3 × upper limit of normal (ULN) and) or ALT ≥3 × ULN ~~and international normalised ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law),~~ must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

Local urine ***pregnancy*** testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

The tests detailed in Table 19 will be performed by the laboratory designated by the sponsor. ***Where tests are carried out locally, the results of each test carried must be entered in the eCRF.***

In Section 10.2.2 Assay use for efficacy assessment:

NAATs are designed to amplify and detect nucleic acid sequences that are specific for the organism being detected (Ng and C***t.*** ~~*trachomatis*~~ nucleic acids in this case). NAATs are the CDC-recommended assays for screening or diagnostic of *N. gonorrhea* and C***t.*** ~~*trachomatis*~~ infections [Papp, 2014].

In Section 10.3.8.1 Time period for collecting and recording AEs, SAEs, and pregnancies:

All solicited events that occur during 7 days following administration of each dose of study intervention (Day 1 to Day 8 and Day ***6***1 to Day ***6***8) must be recorded into the eDiary, irrespective of intensity. An automatic reminder to complete the eDiary will be sent to the participants during this time frame. All other AEs occurring within this time frame should be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

In Section 10.7 Appendix 7 Country specific requirements:

10.7.3 Requirements for Brazil

Data quality assurance

In accordance with local legislation, study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 5 years from issuance of the final CSR/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In Section 10.9 Toxicity grading scales

10.9. Appendix 9: Toxicity ***g*~~G~~rading ***s*~~S~~cales

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