

## **Statistical Analysis Plan Amendment 6**

**Study ID:** 216156

**Official Title of Study:** 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

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**TITLE PAGE**

**Protocol 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

**Study Number:** 216156

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**Sponsor Name:** GlaxoSmithKline Biologicals SA (GSK)

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## TABLE OF CONTENTS

	PAGE
TITLE PAGE .....	1
VERSION HISTORY .....	7
1. INTRODUCTION.....	14
1.1. Objectives, Estimands and Endpoints.....	14
1.2. Study Design .....	18
2. STATISTICAL HYPOTHESES .....	23
2.1. Multiplicity Adjustment .....	23
3. ANALYSIS SETS .....	24
3.1. Definition.....	24
3.2. Criteria for eliminating data from Analysis sets .....	25
3.2.1. Elimination from the Enrolled Set.....	25
3.2.2. Elimination from the Exposed Set (ES).....	26
3.2.3. Elimination from the Full Analysis Set (FAS).....	26
3.2.4. Elimination from the Modified Full Analysis Set (mFAS).....	26
3.2.5. Elimination from the Per Protocol Set (PP) .....	26
3.2.6. Elimination from the unsolicited and solicited safety sets .....	28
3.2.6.1. Unsolicited safety set.....	28
3.2.6.2. Solicited safety set.....	28
3.2.6.3. Solicited safety 60m set.....	28
4. STATISTICAL ANALYSES.....	29
4.1. General Considerations .....	29
4.1.1. General Methodology .....	29
4.1.2. Baseline Definition .....	29
4.1.3. Handling of missing data.....	29
4.1.4. Sequence of analyses.....	30
4.2. Primary Endpoint(s) Analyses.....	30
4.2.1. Phase I – Dose-escalation safety lead-in analysis .....	30
4.2.1.1. Solicited AEs .....	31
4.2.1.2. Unsolicited AEs and SAEs.....	32
4.2.1.3. Other safety lead-in analyses .....	33
4.2.2. Phase II – PoC .....	34
4.2.2.1. Primary case definition .....	34
4.2.2.2. Vaccine efficacy .....	34
4.2.2.3. Safety and reactogenicity .....	37
4.2.2.3.1. Solicited AEs .....	37
4.2.2.3.2. Unsolicited AEs, SAEs and DREs.....	38
4.2.2.3.3. Other safety PoC analyses .....	40
4.2.3. Sensitivity analyses .....	40
4.2.3.1. Handling of early gonococcal infections.....	40
4.2.3.2. Handling infections confirmed at Visit 6 (Day 91).....	41
4.2.3.3. Exclusion of MSM participants on PrEP.....	41
4.2.3.4. Handling of at risk sexual contact prior to NAAT.....	41

4.2.3.5.	Permutation test .....	42
4.2.4.	Additional estimands.....	42
4.3.	Secondary Endpoint(s) Analyses .....	42
4.3.1.	Secondary endpoint(s).....	42
4.3.1.1.	Definition of endpoint(s)/estimands.....	43
4.3.1.2.	Case Definitions .....	44
4.3.1.3.	Main analytical approach .....	45
4.4.	Other Safety Analyses .....	45
4.4.1.	Adverse Events.....	45
4.4.1.1.	Adverse Events of Special Interest (AESIs).....	45
4.4.1.2.	Laboratory Data.....	45
4.4.1.3.	Vital Signs .....	45
4.5.	Other Analyses .....	45
4.5.1.	Subgroup analyses .....	45
4.6.	Interim Analyses .....	46
4.7.	Changes to Protocol Defined Analyses.....	47
5.	SAMPLE SIZE DETERMINATION .....	47
5.1.	Sample size adaptation.....	47
6.	SUPPORTING DOCUMENTATION .....	49
6.1.	Appendix 1 Study Population Analyses.....	49
6.1.1.	Participant Disposition .....	49
6.1.2.	Minimization algorithm .....	49
6.1.3.	Demographic and Baseline Characteristics.....	51
6.1.4.	Protocol Deviations.....	51
6.1.5.	Prior and Concomitant Medications .....	51
6.1.6.	Medical history.....	52
6.1.7.	Study Intervention Compliance .....	52
6.1.8.	Participants listings .....	52
6.2.	Appendix 2 Electronic Clinical Outcome Assessment Compliance.....	53
6.2.1.	eDiary compliance .....	53
6.3.	Appendix 3 Data Derivations Rule .....	54
6.3.1.	Laboratory data and criteria for Potential Clinical Importance.....	54
6.3.2.	Study Period .....	54
6.3.3.	Study Day and Reference Dates with Partial Dates .....	55
6.3.4.	Studies with electronic diaries.....	56
6.3.5.	Unsolicited adverse events .....	56
6.3.6.	Multiple measurements at One Analysis Time Point .....	56
6.3.7.	Treatment of gonococcal infections.....	56
6.3.8.	Data derivation .....	57
6.3.8.1.	Weight.....	57
6.3.8.2.	Height.....	57
6.3.8.3.	Body mass index (BMI) .....	57
6.3.8.4.	Temperature.....	57
6.3.8.5.	Onset day .....	57
6.3.8.6.	Duration of events .....	57
6.3.8.7.	Counting rules for combining solicited and unsolicited adverse events .....	57
6.3.8.8.	Counting rules for occurrences of solicited adverse events .....	58

6.3.9.	Display of decimals .....	58
6.3.9.1.	Percentages .....	58
6.3.9.2.	Differences in percentages .....	58
6.3.9.3.	Demographic/baseline characteristics statistics .....	59
6.3.10.	Trademarks .....	59
6.4.	Appendix 4 Calculations for sample size adaptation .....	60
7.	REFERENCES.....	61

LIST OF TABLES

PAGE

Table 1	Complicated and uncomplicated Ng infections .....	40
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LIST OF FIGURES

		PAGE
Figure 1	Overall design .....	18
Figure 2	Study design overview of dose-escalation safety lead-in in healthy participants .....	19
Figure 3	Study design overview of efficacy Proof of Concept (PoC) in participants considered at risk for gonorrhea .....	20

**VERSION HISTORY**

<b>SAP Version</b>	<b>Approval Date</b>	<b>Protocol Version (Date) on which SAP is Based</b>	<b>Change</b>	<b>Rationale</b>
First Version	02 August 2022	Protocol (12 July 2022)	Not Applicable	Original version
Amendment 1	16 March 2023	Protocol amendment 3 (10 March 2023)	Updated sequence of analysis, minimization factors and other minor spelling errors	To align with protocol amendment 3.
Amendment 2	07 June 2023	Protocol amendment 4 (27 April 2023)	Section 4.2.2.1 Vaccine efficacy: corrected alpha in SAS code snippet	Corrected two-sided alpha to correct value of 0.15 (one-sided alpha is 0.075)
			Section 3 Analysis sets: Full analysis set removed	This analyses set is not used for primary or secondary objectives analysis
			Section 4.1 General considerations: Added a section to describe handling of missing data	To align with protocol amendment 4
			Section 5.1 Sample size adaptation: Criteria for triggering a sample size increase updated	To align with protocol amendment 4

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
Amendment 3	14 December 2023	Protocol amendment 5 (28 November 2023)	<p>Section 1.1 Objectives, Estimands and Endpoints:</p> <p>Updated third secondary endpoint description according to protocol amendment 5.</p> <p>Added intercurrent event of confirmed gonorrhea cases prior to 1 month post-Dose 2.</p> <p>Other minor edits to the text.</p>	To align with protocol amendment 5.
			<p>Section 4.1.3 Handling of missing data:</p> <p>Updated the calculation of time at risk in case of an intercurrent gonorrhea infection prior to 1 month post-Dose 2.</p>	To align with protocol amendment 5.
			<p>Section 4.2.1.1 Solicited AEs:</p> <p>Definition of severe fever updated to <math>\geq 40.0^{\circ}\text{C}</math></p>	To align with protocol amendment 5.
			<p>Section 4.2.2.1 Vaccine efficacy:</p> <p>Updated the calculation of time at risk in case of an intercurrent gonorrhea infection prior to 1 month post-Dose 2.</p>	To align with protocol amendment 5.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			<p>Section 4.2.2.2.2 Unsolicited AEs, SAEs and DREs:</p> <p>Updated the derivation of disease related events (DREs) based on data collected in dedicated forms instead of adverse event preferred terms.</p>	Per protocol, disease related events are not handled as regular adverse events and are captured in dedicated forms.
			<p>Section 4.3.1.1 Definition of endpoint(s)/estimands:</p> <p>Added intercurrent event of gonorrhea cases (according to the endpoint definition) prior to 1 month post-Dose 2.</p> <p>Updated the definition of symptomatic and complicated gonorrhea cases by referring to symptoms instead of DREs.</p>	To align with protocol amendment 5.
Amendment 4	11 June 2024	Protocol amendment 6 (05 June 2024)	<p>Section 1.1 Objectives, Estimands and Endpoints</p> <p>Section 4.1.3 Handling of missing data</p> <p>Updated the definition of gonococcal infection resolution according to updated case definition</p>	To align with protocol amendment 6

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			<p>Section 1.2 Study Design</p> <p>Section 4.1.4 Sequence of analyses</p> <p>Updated the sequence of analysis: Interim for futility with a median observation time of approximately 6 months. Conclusion of vaccine efficacy using all data until end of study.</p>	To align with protocol amendment 6
			<p>Section 2 Statistical Hypotheses:</p> <p>Conclusion of vaccine efficacy using all data until end of study and not based on the first 47 cases observed in HTD and placebo groups.</p>	To align with protocol amendment 6
			<p>Section 4.2.2.1 Primary case definition</p> <p>4.3.1.2 Case Definitions</p> <p>Sections added with further details on the primary case definition</p>	To align with protocol amendment 6 ad to further clarify the primary case definition
			<p>Section 4.2.2.3.2. Unsolicited AEs, SAEs and DREs</p> <p>Added additional symptoms of gonorrhea</p>	To align with protocol amendment 6

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			<p>Section 4.2.3. Sensitivity analyses</p> <p>Two sensitivity analyses for the primary vaccine efficacy analysis specified:</p> <p>1) excluding participants with an early infection</p> <p>2) Counting cases after Visit 6 (Day 91) i.e., cases identified at Visit 6 considered early infections.</p>	To evaluate the sensitivity of the primary analyses under alternative strategy for the early infection intercurrent event.
			<p>4.7.4.6 Interim Analyses</p> <p>Interim for futility with a median observation time of approximately 6 months.</p> <p>Conditional power based on expected number of events at the study end and no longer based on fixed number of events. Futility threshold unchanged.</p>	To align with protocol amendment 6 and to further clarify the statistical details of the futility boundary.
			<p>6.4. Appendix 4 Electronic Clinical Outcome Assessment Compliance</p> <p>Added appendix for eDiary compliance reporting</p>	To provide a more comprehensive summary of solicited AE reporting compliance in the study

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Other minor corrections and clarifications	
Amendment 5	11 July 2024	Protocol amendment 6 (05 June 2024)	Updated appendix order in section 6. Electronic Clinical Outcome Assessment Compliance moved to Section 6.2.	To align with new SAP template
Amendment 6	10 Jan 2025	Protocol amendment 7 (03 December 2024)	Removed secondary objective related to vaccine efficacy against complicated infections from Section 1.1 Objectives, estimands and endpoints and from section 4.3 Secondary Endpoints Analyses.	To align with protocol amendment 7
			Included at risk sexual contact within 24 hours and 7 days of central NAAT collection as an intercurrent event in Section 1.1 Objectives, estimands and endpoints	To further clarify the intercurrent event handling strategy
			Exact 95% CI for proportions omitted from the descriptive analysis of safety.	Potentially misleading for such descriptive analyses
			Updated the derivation rule of risk time. Individual risk time will stop at the last central NAAT sample collection.	To align with protocol amendment 7 since central NAAT will

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				no longer be required.
			<p>Section 4.2.3. Sensitivity analyses updated to include:</p> <p>Sensitivity analysis to evaluate vaccine efficacy after excluding men having sex with men on pre-exposure prophylaxis.</p> <p>Sensitivity analyses to evaluate vaccine efficacy after censoring participant risk time once at risk sexual contact is reported within 24 hours and within 7 days prior to central NAAT from visit 6 onwards.</p>	To evaluate the sensitivity of the vaccine efficacy estimates to sexual behaviour.
			Other minor corrections and clarifications	

## 1. INTRODUCTION

The purpose of this SAP is to describe the planned statistical analyses for primary and secondary objectives for both Phase I and Phase II parts of the study NGG - 001 (216156). Details of the planned interim analysis, sample size reassessments and other main analyses are provided.

The analyses of tertiary endpoints will be described in a separate SAP.

### 1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Phase I – 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)	<ul style="list-style-type: none"> <li>• 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).</li> <li>• 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).</li> <li>• Number and percentage of participants reporting unsolicited AEs during the 30-day follow-up period after each dose (Day 1 and Day 61).</li> <li>• Number and percentage of participants reporting SAEs from Day 1 after the first dose up to study end (Day 241).</li> <li>• Number and percentage of participants reporting AEs leading to withdrawal from Day 1 after the first dose up to study end (Day 241).</li> <li>• 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.</li> </ul>

Objectives	Endpoints
<p style="text-align: center;">Phase II – Efficacy PoC</p> <p style="text-align: center;">Primary</p>	
To demonstrate the efficacy of the NgG vaccine in preventing gonorrhea cases. <sup>1</sup>	<ul style="list-style-type: none"> <li>Incidence rates of confirmed gonorrhea cases from 1 month (Day 91) to 13 months post-Dose 2 (Day 451).</li> </ul>
To evaluate safety and reactogenicity following administration of the NgG vaccine. <sup>2</sup>	<ul style="list-style-type: none"> <li>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).</li> <li>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).</li> <li>Number and percentage of participants reporting unsolicited AEs during the 30-day follow-up period after each dose (Day 1 and Day 61).</li> <li>Number and percentage of participants reporting SAEs from Day 1 after the first dose up to study end (Day 451).</li> <li>Number and percentage of participants reporting AEs leading to withdrawal from Day 1 after the first dose up to study end (Day 451).</li> <li>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.<sup>3</sup></li> </ul>

Objectives	Endpoints
Phase II – Efficacy PoC	
Secondary	
To evaluate the efficacy of the NgG vaccine in preventing gonorrhea cases with and without <i>Ct</i> co-infection.	<ul style="list-style-type: none"> <li>Incidence rates of confirmed gonorrhea cases with and without <i>Ct</i> co-infection from 1 month (Day 91) to 13 months post-Dose 2 (Day 451).</li> </ul>
To evaluate the efficacy of the NgG vaccine in preventing symptomatic gonorrhea cases.	<ul style="list-style-type: none"> <li>Incidence rates of symptomatic and confirmed gonorrhea cases from 1 month (Day 91) to 13 months post-Dose 2 (Day 451).</li> </ul>

*Ct* = *Chlamydia trachomatis*, HTD = highest tolerated dose, Ng = *Neisseria gonorrhoeae*, PoC = Proof of Concept

<sup>1</sup>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 objectives, cases from urogenital, anorectal and/or pharyngeal sites will be considered. For the purpose of the case definition only the first confirmed gonococcal infection will contribute.

<sup>2</sup>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

<sup>3</sup>The evaluation of the endpoint will be assessed in the subsets for intensive safety monitoring

### Primary estimand

The primary clinical question of interest is: Is at least one of the two NgG vaccine investigational dosages under investigation efficacious in preventing gonorrhea cases from 1 month (Day 91) to 13 months after the administration of Dose 2 (Day 451) compared to placebo in males and females aged between 18 and 50 years old who are at risk of gonococcus infections based on sexual behavioural characteristics, regardless of concomitant medications or vaccination?

The estimand regarding the HTD is described by the following attributes:

- Population:** males and females aged between 18 and 50 years old who are at risk of gonococcus infections based on sexual behavioural characteristics. See Protocol Section 5 for more details on inclusion and exclusion criteria.
- Treatment condition:** highest tolerated dose (HTD) of the NgG vaccine and placebo, each administered with two scheduled doses at Visit 1 (Day 1) and Visit 4 (Day 61).
- Variable / endpoint:** Incidence rates (IRs) of confirmed gonorrhea cases (urogenital and/or anorectal sites) from 1 month (Day 91) to 13 months (Day 451) after the administration of Dose 2.
- Summary measure:** vaccine efficacy (VE) defined as 1 minus the ratio between IRs of HTD investigational dosage over placebo of confirmed gonorrhea cases (urogenital and/or anorectal sites) from 1 month (Day 91) to 13 months (Day 451) after the administration of Dose 2.

- *Intercurrent events:*
  - Use of concomitant medications or vaccinations – treatment policy strategy (IRs of confirmed gonorrhea cases regardless of use of concomitant medications or vaccinations)
  - Confirmed gonorrhea case (urogenital and/or anorectal sites) prior to 1 month post-Dose 2 – treatment policy strategy (IRs of confirmed gonorrhea cases 1 month post-Dose 2 regardless of intercurrent gonococcal infections).

If such confirmed gonorrhea case is still ongoing after 1 month post-Dose 2 person-time at risk will start after this infection is considered resolved.

- At risk sexual contact within 24 hours of central NAAT collection
- At risk sexual contact within 7 days of central NAAT collection

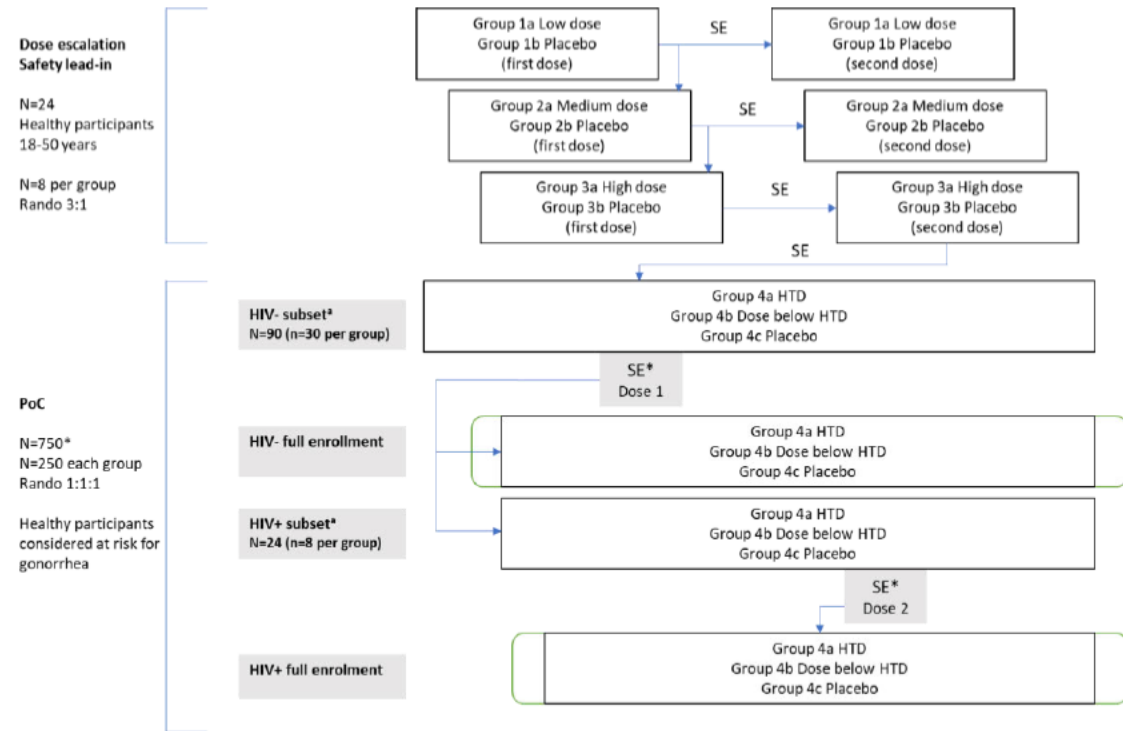
*Rationale for estimand:* Interest lies in the VE after administration of the full treatment course regardless of using concomitant medications or vaccinations, intercurrent gonococcal infections prior to 1 month post-Dose 2, and regardless of at risk sexual contact. The use of a treatment policy strategy is motivated by the interest in vaccine efficacy under the ITT principle, emulating which would be the impact of the investigational product once delivered on the market.

The same definition of estimand will also apply for the dose below the HTD (bHTD) - if any- which will be evaluated in case of demonstrated HTD efficacy.

## 1.2. Study Design

### Overview of Study Design and Key Features

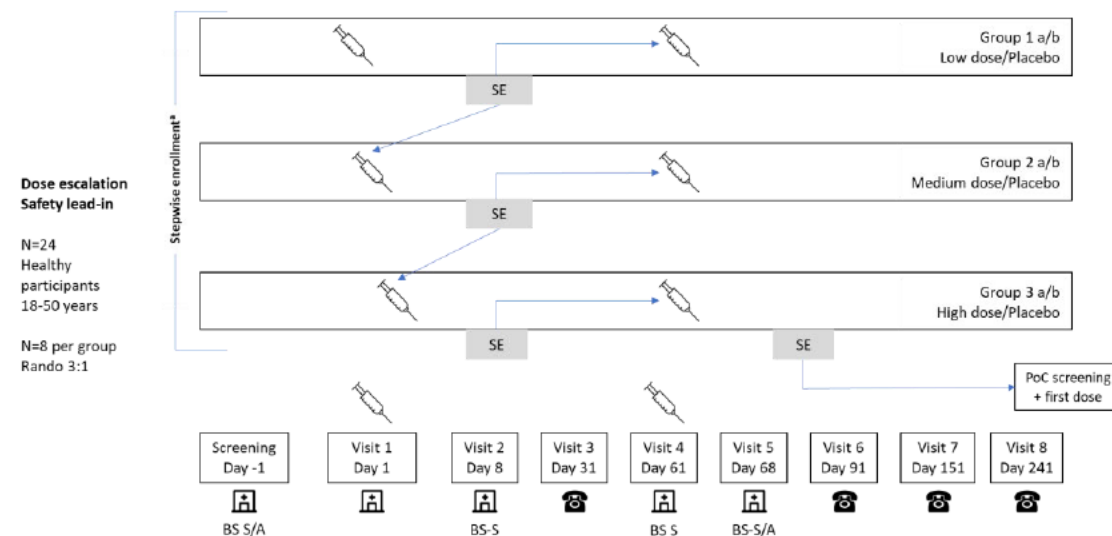
**Figure 1 Overall design**



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

## Overview of Study Design and Key Features

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



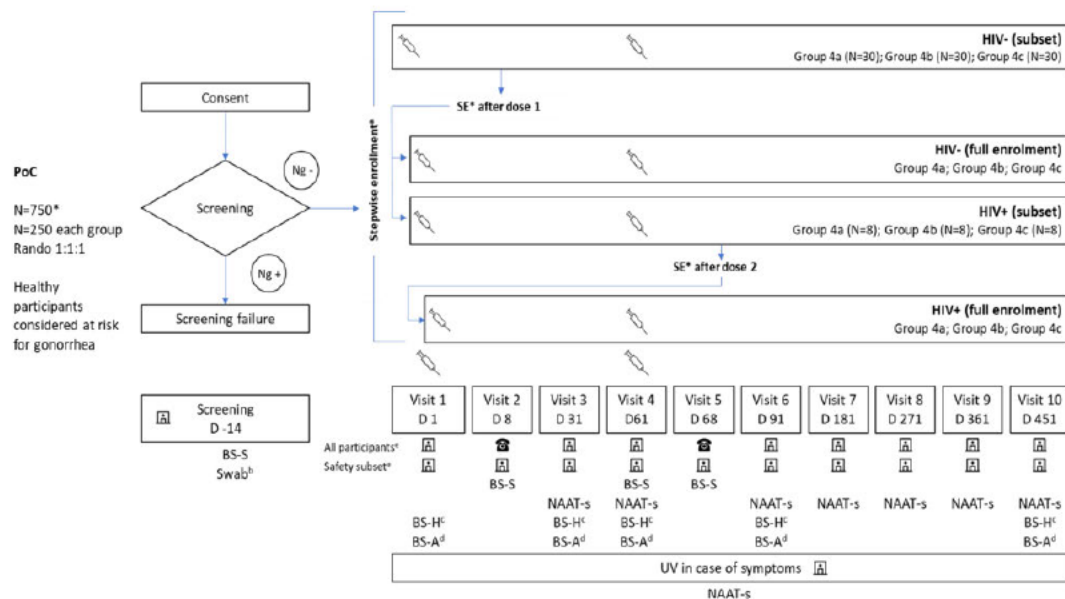
Grp = Group; a/b = vaccine/placebo; Rando = Randomization; SE = Safety evaluation by SRT/ iSRC chair (blinded review) or iSRC (unblinded review); PoC = Proof of Concept; BS-S = Blood Sample for Safety evaluation; BS-S/A = Blood Sample for Safety evaluation and assay development.

<sup>a</sup>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 Protocol Section 4.1.1 for more information

Vaccine/Placebo administration Phone contact. Clinic visit.

## Overview of Study Design and Key Features

**Figure 3 Study design overview of efficacy Proof of Concept (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 only<sup>e</sup>); 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 Protocol Section 9.5 or Section 5 for sample size determination.

<sup>a</sup>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 Protocol Section 4.1.2, for more information

<sup>b</sup>Screening for gonorrhea can be done as per local standard practice

<sup>c</sup>BS-H: Blood sample for humoral immune response from all participants: testing strategy is described in Protocol Section 8.1.1

<sup>d</sup>BS-A: Blood sample for assay development from all participants

<sup>e</sup>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.

Vaccine/Placebo administration Phone contact. Clinic visit.

### Design Features

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).

Overview of Study Design and Key Features	
	<ul style="list-style-type: none"> <li>Phase 2 - Efficacy PoC in healthy participants considered at risk for gonorrhea (Figure 3).</li> </ul> <p>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 into 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.</p> <p>An analysis for the primary and secondary endpoints will be performed when all data up to Day 451 are available. The conclusion of the vaccine efficacy will be based on the primary endpoint analysis. If HTD efficacy is not demonstrated, then the comparison of bHTD vs placebo groups may be reported as a descriptive analysis.</p>
<b>Study intervention</b>	<p>For the safety lead-in part, study treatments are:</p> <ul style="list-style-type: none"> <li><b>Control:</b> placebo control</li> <li><b>Vaccination schedule(s):</b> <ul style="list-style-type: none"> <li><b>Group 1 Low dose</b> (first group), 2 parallel groups: <ul style="list-style-type: none"> <li><b>Group 1a Low dose:</b> 2 doses of NgG investigational vaccine 12.5 µg at Day 1 and Day 61</li> <li><b>Group 1b Placebo:</b> 2 doses of placebo (saline) at Day 1 and Day 61</li> </ul> </li> <li><b>Group 2 Medium dose</b> (second group), 2 parallel groups: <ul style="list-style-type: none"> <li><b>Group 2a Medium dose:</b> 2 doses of NgG investigational vaccine 25 µg at Day 1 and Day 61</li> <li><b>Group 2b Placebo:</b> 2 doses of placebo (saline) at Day 1 and Day 61</li> </ul> </li> <li><b>Group 3 High dose</b> (third group), 2 parallel groups: <ul style="list-style-type: none"> <li><b>Group 3a High dose:</b> 2 doses of NgG investigational vaccine 50 µg at Day 1 and Day 61</li> <li><b>Group 3b Placebo:</b> 2 doses of placebo (saline) at Day 1 and Day 61</li> </ul> </li> </ul> </li> </ul> <p>For the PoC part, study treatments are:</p> <ul style="list-style-type: none"> <li><b>Control:</b> placebo control</li> </ul>

Overview of Study Design and Key Features	
	<ul style="list-style-type: none"> <li>• <b>Vaccination schedule(s):</b> <ul style="list-style-type: none"> <li>– <b>Group 4a Vaccine:</b> A series of 2 doses of NgG highest tolerated dose* given approximately 2 months apart (Days 1 and 61)</li> <li>– <b>Group 4b Vaccine:</b> A series of 2 doses of NgG dose below highest tolerated dose* given approximately 2 months apart (Days 1 and 61)</li> </ul> </li> </ul> <p>* 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</p> <ul style="list-style-type: none"> <li>– <b>Group 4c Placebo:</b> A series of 2 doses of placebo (saline) given approximately 2 months apart (Days 1 and 61)</li> </ul>
<b>Study intervention Assignment</b>	<p>For both parts of the study, subjects will be randomised to a study group using an automated, electronic System Built for Internet Randomization (SBIR).</p> <p>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.</p> <p>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 a 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.</p> <p>For each stratum, in the safety lead-in part, the randomisation ratio is 3:1 while, in the PoC part, the randomisation ratio is 1:1:1.</p>
<b>Interim Analysis</b>	<p>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.</p>

## 2. 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 favour 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 [ $\lambda_{HTD}$ ,  $\lambda_{bHTD}$ ] over placebo [ $\lambda_{PLACEBO}$ ]). Family-wise type I error (FWER) is set at 7.5% (1-sided).

The global null hypothesis ( $H_0$ ) is given by the intersection of the following null hypotheses  $H_{0HTD}$  and  $H_{0bHTD}$ , while the global alternative one ( $H_1$ ) is given by the union of  $H_{1HTD}$  and  $H_{1bHTD}$ :

$$\begin{aligned} H_0: H_{0HTD} \cap H_{0bHTD} &= VE_{HTD} \leq 0 \cap VE_{bHTD} \leq 0 \\ H_1: H_{1HTD} \cup H_{1bHTD} &= VE_{HTD} > 0 \cup VE_{bHTD} > 0 \end{aligned}$$

$$VE_{\bullet} = 1 - \frac{\lambda_{\bullet}}{\lambda_{PLACEBO}}$$

With

The hypothesis testing follows a sequential procedure: HTD is tested first and then, if the HTD efficacy is demonstrated, bHTD is tested. An analysis for the primary and secondary endpoints will be performed when all data up to Day 451 are available. If HTD efficacy is demonstrated, then the comparison of bHTD vs placebo groups will be tested in an analogous way to the first comparison. Otherwise, the comparison of bHTD vs placebo groups may only be reported as a descriptive analysis.

### 2.1. Multiplicity Adjustment

As the hypothesis testing follows a sequential procedure – bHTD testing is conditional upon rejecting HTD - each test (HTD, bHTD) is carried out without a multiplicity adjustment, i.e. the same  $\alpha$ -level is used for both tests, and FWER is controlled.

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

The futility assessment at interim analysis requires no  $\alpha$ -adjustment and has no major detrimental effect on the study power.

No multiplicity adjustment will be performed for primary safety and secondary efficacy endpoints.

### 3. ANALYSIS SETS

#### 3.1. Definition

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	<ul style="list-style-type: none"> <li>All participants who were screened for eligibility</li> </ul>	<ul style="list-style-type: none"> <li>Study Population</li> </ul>
Enrolled	<ul style="list-style-type: none"> <li>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-randomised" group.</li> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>Study Population</li> </ul>
Randomised	<ul style="list-style-type: none"> <li>All participants who were randomly assigned to study intervention in the study.</li> <li>Note: screened, enrolled and randomised populations must be nested, i.e. the enrolled population must be a subset of the screened population, the randomised population must be a subset of the enrolled population.</li> </ul>	<ul style="list-style-type: none"> <li>Study Population</li> </ul>
Exposed	<ul style="list-style-type: none"> <li>All participants who received at least one dose of study intervention.</li> <li>Analysis per group using the exposed set is based on the administered intervention.</li> </ul>	<ul style="list-style-type: none"> <li>Safety</li> </ul>
Full Analysis – Efficacy (Intention-To-Treat population)	<ul style="list-style-type: none"> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>Efficacy (PoC only)</li> </ul>
Modified Full Analysis Efficacy Set (mFAS)	<ul style="list-style-type: none"> <li>All randomized participants who received full study treatment course (2 doses) and have post-vaccination efficacy data.</li> <li>The allocation in a group will be done in function of the randomized intervention.</li> </ul>	<ul style="list-style-type: none"> <li>Efficacy (PoC only)</li> </ul>

Analysis Set	Definition / Criteria	Analyses Evaluated
Per-Protocol (PP)	<ul style="list-style-type: none"> <li>All eligible participants who received all doses as per protocol, had post-vaccination efficacy data (mFAS), complied with dosing intervals, without intercurrent conditions that may interfere with immune response and without prohibited concomitant medications/vaccinations.</li> </ul>	<ul style="list-style-type: none"> <li>Efficacy (PoC only)</li> </ul>
Solicited Safety	<ul style="list-style-type: none"> <li>All participants who received at least 1 dose of the study intervention (Exposed Set) who have solicited safety with onset from 60 minutes up to 7 days after the vaccination.</li> <li>Analysis per group using the solicited safety set is based on the administered intervention.</li> </ul>	<ul style="list-style-type: none"> <li>Safety</li> </ul>
Solicited Safety 60m	<ul style="list-style-type: none"> <li>All participants who received at least 1 dose of the study intervention (Exposed Set) who have solicited safety data with onset within 60 minutes after the vaccination.</li> <li>Analysis per group using the solicited safety 60m set is based on the administered intervention.</li> </ul>	<ul style="list-style-type: none"> <li>Safety</li> </ul>
Unsolicited Safety	<ul style="list-style-type: none"> <li>All participants who received at least 1 dose of the study intervention (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs.</li> <li>Analysis per group using the unsolicited set is based on the administered intervention.</li> </ul>	<ul style="list-style-type: none"> <li>Safety</li> </ul>

### 3.2. Criteria for eliminating data from Analysis sets

Elimination codes are used to identify participants to be eliminated from analysis. Details are provided below for each set. Subcategories are specified only when multiple elimination codes are used for the same category.

#### 3.2.1. Elimination from the Enrolled Set

The following codes are used to eliminate participants from the Enrolled Set:

- 700 (Screening failure)

### 3.2.2. Elimination from the Exposed Set (ES)

The following codes are used to eliminate participants from the ES:

Code	Category and subcategory	Visit (timepoints) where the code is applicable
800	Fraudulent data	All
900	Informed Consent	All
1030	Study vaccine not administered at all	All

### 3.2.3. Elimination from the Full Analysis Set (FAS)

All the elimination codes used for ES are applicable. Additionally, for all subjects not withdrawing before 30 days after first vaccination of the PoC phase, the following code is used:

- 1501a (No scheduled and unscheduled swabs are performed at any timepoint after first vaccination)

### 3.2.4. Elimination from the Modified Full Analysis Set (mFAS)

All the elimination codes used for FAS are applicable. Additionally, for all subjects not withdrawing before 30 days after second vaccination of the PoC phase, the following codes are used:

- 1501b (No scheduled and unscheduled swabs are performed at any timepoint after second vaccination)
- 1070a (Incomplete treatment course).

### 3.2.5. Elimination from the Per Protocol Set (PP)

All the elimination codes used for mFAS are applicable. Additionally, the following codes are used:

Code	Category and subcategory	Visit (timepoints) where the code is applicable
2040	Excluded medication, vaccine or device: <ul style="list-style-type: none"> <li>• Medication, excluded by protocol, was administered</li> <li>• Device, excluded by protocol, was administered</li> </ul>	Visits after the use of concomitant medication(s)/device(s)

Code	Category and subcategory	Visit (timepoints) where the code is applicable
1040	Excluded medication, vaccine or device: <ul style="list-style-type: none"> <li>Vaccine, excluded by protocol, was administered</li> </ul>	Visits after the use of concomitant vaccine(s)
1050	Study procedures: <ul style="list-style-type: none"> <li>Randomization procedures, e.g. subject assigned to wrong stratum, subject randomized out of order</li> </ul>	All
1060	Study procedures: <ul style="list-style-type: none"> <li>Study blinding/unblinding procedures</li> </ul>	All
1070	Wrong study treatment/administration/dose: <ul style="list-style-type: none"> <li>Study treatment not administered per protocol</li> <li>Study treatment administered while contraindication</li> <li>Wrong study treatment or assignment administered</li> <li>Study treatment not prepared as per protocol (e.g. reconstitution)</li> <li>Study treatment not available at site for administration</li> </ul>	Study treatment administration visit, and subsequent visits
1080	Wrong study treatment/administration/dose: <ul style="list-style-type: none"> <li>Use of study treatment impacted by a temperature excursion which was not reported or approved or which was disapproved for further use</li> </ul>	Study treatment administration visit, and subsequent visits
1090	Wrong study treatment/administration/dose: <ul style="list-style-type: none"> <li>Expired study treatment administered</li> </ul>	Study treatment administration visit, and subsequent visits
2010	Eligibility criteria not met	All
2050	Not withdrawn after developing withdrawal criteria: <ul style="list-style-type: none"> <li>Not withdrawn from study</li> <li>Not discontinued from study treatment</li> <li>Other deviation of not being withdrawn after developing withdrawal criteria</li> </ul>	All
2080	Assessment or time point completion: <ul style="list-style-type: none"> <li>Out of Window treatment administration</li> </ul>	Study treatment administration visit, and subsequent visits

### **3.2.6. Elimination from the unsolicited and solicited safety sets**

#### **3.2.6.1. Unsolicited safety set**

All the elimination codes used for the ES are applicable. Additionally, Code 1150 – Study procedures, Other deviation from study procedures, is used.

For safety lead-in, code 1150 will be attributed to participants if all the following conditions are met:

- subject did not perform phone contact at any of the following visits: Visit 3, Visit 6, Visit 7 and Visit 8;
- subject did not return for any post-vaccination visits;
- subject did not report any unsolicited AE.

For PoC, code 1150 will be attributed to participants if all the following conditions are met:

- subject did not perform phone contact at Visit 2 and Visit 5. This is not applicable for PoC safety subsets;
- subject did not return for any post-vaccination visits;
- subject did not report any unsolicited AE.

#### **3.2.6.2. Solicited safety set**

All the elimination codes used for the ES are applicable. Additionally, the following code is used:

- 1160 – Study procedures, Diary procedures (no post-vaccination solicited safety data after 60 minutes, during 7 days of follow up)

#### **3.2.6.3. Solicited safety 60m set**

All the elimination codes used for the ES are applicable. Additionally, the following code is used:

- 1160b – Study procedures, Post study treatment observation not done (no post-vaccination solicited safety data during 60 minutes after the vaccination)

## **4. STATISTICAL ANALYSES**

### **4.1. General Considerations**

#### **4.1.1. General Methodology**

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

#### **4.1.2. Baseline Definition**

For all safety lab endpoints, the baseline value will be the latest pre-dose assessment with a non-missing value; in particular, for both dose-escalation safety lead-in and PoC (safety subsets) parts:

- Visits 2 and 4 have Screening visit as baseline;
- Visit 5 has Visit 4 as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed; baseline and baseline-derived values (e.g. change from baseline) will be set to missing.

#### **4.1.3. 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 as described in Section 6.3.3 and Section 6.3.5.

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 central NAAT sample.
- In case a confirmed gonococcal infection is diagnosed prior to 1 month post-Dose 2 and is considered 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.

#### **4.1.4. Sequence of analyses**

Following completion of the dose-escalation safety lead-in part, all data collected in this part (up to Day 241) will be analysed. However, a CSR will not be generated at the time of this analysis.

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 by an Independent Data Analysis Centre (IDAC). The futility assessment results will be reviewed by an internal Data Review Committee (iDRC) independent from the study team to maintain study integrity and keep the study team blinded. The composition and responsibilities of the iDRC as well as type of results disclosed will be described in a dedicated charter. At the time of the futility assessment, key safety data will also be evaluated as well by the iSRC and iDRC.

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. The conclusion of vaccine efficacy will be based on the final analysis.

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Full unblinding will occur:

- for dose-escalation safety lead-in, when all participants belonging to this phase reach study conclusion;
- for PoC, at the time of the final analysis i.e., when all data up to study end (Day 451) are available.

## **4.2. Primary Endpoint(s) Analyses**

### **4.2.1. Phase I – Dose-escalation safety lead-in analysis**

The analysis of primary endpoints will include analyses of safety lead-in data based on the Exposed, Solicited Safety, Solicited Safety 60m and Unsolicited Safety sets, depending on the specific endpoint under evaluation for Phase 1 – Dose-escalation safety lead-in.

#### 4.2.1.1. Solicited AEs

The analyses for solicited AEs, with onset from 60 minutes up to 7 days after vaccination, will be performed on the Solicited Safety Set by dose.

The 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, after any dose, for each dose and overall doses. The same calculations will be performed for solicited AEs rated as Grade 3.

The number and percentages of each solicited AE maximum intensity during the 7-day follow-up solicited period will be tabulated by study group, after any dose, for each dose and overall doses, using mutually exclusive intensity categories (mild, moderate and severe).

Compliance in completing solicited AEs information will be reported by symptom for each day of the 7-day solicited follow-up period. Calculations will be performed after any dose, for each dose and overall doses.

The duration, number of days from first day with a specific solicited symptom with Grade  $\geq 1$  to last day with the same symptom with Grade  $\geq 1$ , reported during the 7-day solicited follow-up period, will be tabulated for each solicited AE, after each dose and overall doses using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same calculation will be performed for Grade 3 solicited AEs.

The above analyses, excluding compliance and duration, will be repeated for solicited AEs with onset within 60 minutes after vaccination on the Solicited Safety 60m Set by visit.

Solicited AEs still ongoing after the 7-day solicited follow-up period will be listed with starting and end dates, maximum intensity and their outcomes.

Administration site solicited AEs will be summarized according to the following grading categories:

Administrative site AE	Grading
Pain at injection site	0: None 1: Mild 2: Moderate 3: Severe
Redness at injection site	0: < 25 mm diameter 1: $\geq 25$ mm to $\leq 50$ mm diameter 2: > 50 mm to $\leq 100$ mm diameter 3: > 100 mm diameter
Swelling at injection site	0: < 25 mm diameter 1: $\geq 25$ mm to $\leq 50$ mm diameter 2: > 50 mm to $\leq 100$ mm diameter 3: > 100 mm diameter

Systemic solicited AEs will be summarized according to the following grading categories:

Systemic AE	Grading
Headache	0: None 1: Mild 2: Moderate 3: Severe
Myalgia (muscle pain)	0: None 1: Mild 2: Moderate 3: Severe
Arthralgia (joint pain)	0: None 1: Mild 2: Moderate 3: Severe
Fatigue (tiredness)	0: None 1: Mild 2: Moderate 3: Severe
Fever	0: < 38°C 1: ≥38°C to <39°C 2: ≥39.0°C to <40°C 3: ≥40.0°C

Please refer to Table 20 of the study protocol for more details on the grading of solicited AEs.

#### 4.2.1.2. Unsolicited AEs and SAEs

All analyses related to unsolicited adverse events with onset within 30 days from any/each dose will be performed on the Unsolicited Safety Set (overall and by visit); while analyses related to SAEs and unsolicited adverse events leading to premature withdrawal will be performed on the Exposed Set.

A summary of the number and proportion of subjects experiencing:

- at least one unsolicited AE
- at least one Grade 3 unsolicited AE
- at least one causally related unsolicited AE
- at least one causally related Grade 3 unsolicited AE,

with onset within 30 days of any dose will be tabulated by study group and overall.

The incidence of any unsolicited AE, by MedDRA System Organ Class (SOC) and by Preferred Term (PT) during the 30-day (Day 1-30) follow-up post-vaccination period will be tabulated per study group, after any dose and after each dose. 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.

A summary of the number and proportion of subjects experiencing:

- at least one SAE
- at least one related SAE
- a fatal SAE
- a related fatal SAE
- at least one SAE leading to hospitalization
- at least one unsolicited adverse event leading to premature withdrawal

after any vaccination will be tabulated by study group and overall.

The incidence of subjects who experienced at least one SAE, by dose and after any dose, during the entire study period will be reported. This analysis will be performed by MedDRA SOC and PT.

The incidence of subjects who experienced any SAEs related to study vaccine, any fatal SAEs and any AEs leading to withdrawal from the study during the entire study period will be reported in listings and tabulated.

SAEs related to study participation or concurrent GSK medication/vaccine reported from the time informed consent is signed until study end will be listed.

When an unsolicited AE occurs more than once for a participant, the maximum severity grade and strongest relationship to the vaccine group will be counted. This approach will be used both separately after each vaccination and overall after any vaccination.

#### **4.2.1.3. Other safety lead-in analyses**

For all subjects in each group and for each haematology and biochemistry parameter:

- The number and percentage of subjects having haematology and biochemistry results below or above the local laboratory normal ranges will be tabulated as post-vaccination versus pre-vaccination values: Visit 2 versus screening; Visit 5 versus Visit 4.
- Post-vaccination versus pre-vaccination values (Visit 2 versus screening; Visit 5 versus Visit 4) will be tabulated according to FDA Guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007) [[FDA](#), 2007], see Table 23 in Protocol Section 10.9 for details.

## **4.2.2. Phase II – PoC**

### **4.2.2.1. Primary case definition**

For the primary efficacy analyses, a case is defined as the first Ng infection confirmed by a urogenital and/or anorectal sample positive for Ng by central NAAT from 1 month up to 13 months post-dose 2. The date of the case is the sample collection date.

In case of an early Ng infection confirmed by central NAAT from a urogenital and/or anorectal sample collected prior to 1 month post-dose 2, this early infection will be considered ongoing until the earliest of:

- Treatment end date + 7 days, if a highly effective antibiotic treatment is administered to treat this infection.
- Date of subsequent test of cure negative for Ng at the affected anatomical location(s) if an alternative treatment is administered to treat this infection.
- Sample collection date of a subsequent central NAAT negative for Ng at the affected anatomical location(s)

Any central NAAT positive for Ng from a sample collected while an early infection is considered ongoing will not be counted as a new case.

If an early Ng infection is considered ongoing at 1 month post-dose 2, individual person-time at risk will start only after this early infection is considered resolved. Otherwise, individual person-time at risk will start at 1 month post-dose 2.

Any Ng infection (including early infections) that is not confirmed by a urogenital and/or anorectal sample positive for Ng by central NAAT will not be considered in the derivation of cases in the primary efficacy analyses.

In protocol amendment 5, ad-hoc central NAAT samples were introduced to explore the Ng infection status at the time of antibiotic treatment in participants with a confirmed gonorrhea case. These ad-hoc central NAAT samples will not be considered in the derivation of cases in the primary efficacy analyses.

### **4.2.2.2. Vaccine efficacy**

The primary analysis for VE will be based on the Modified Full Analysis Set.

The primary endpoint for vaccine efficacy (VE) is defined as the IRs of confirmed gonorrhea cases from 1 month (Day 91) to 13 months after administration of Dose 2 (Day 451). For efficacy primary endpoint, only cases from urogenital and/or anorectal sites will be considered.

The NgG will be declared efficacious if the global null hypothesis of  $VE = 0$  for both investigational product dosages (HTD and dose below the HTD) will be rejected in favour of the alternative hypothesis of  $VE > 0$  in at least one investigational dose at a family-wise type 1 error of 7.5% (1-sided).

VE will be estimated as:

$$VE = 1 - IRR$$

Where *IRR* is the ratio between  $IR_1$ , i.e. the IR of confirmed gonorrhea cases in the investigational group (HTD or bHTD), and  $IR_0$ , i.e. the IR of confirmed gonorrhea cases in the placebo group. IRs will be estimated as  $y/PT$ , where  $y$  is the number of confirmed gonorrhea cases, defined as the first confirmed occurrence of gonococcus infection experienced by a participant in the relevant follow-up period (from 1 month up to 13 months post-Dose 2), and  $PT$  is the sum of the individual person-times at risk of infections. For participants with gonococcus infections, individual  $PT$  is defined as the time from 1 month after the administration of Dose 2 to date of first confirmed gonococcus infection; whereas, it is the time from 1 month after administration of Dose 2 to the earliest of withdrawal date, data cut-off date (applicable only for the interim analysis) or date of last central NAAT sample, for other participants. Therefore, participants who will not have a confirmed gonococcus infection will be censored at either time of withdrawal, data cut-off date or date of last central NAAT sample. In case a confirmed gonococcal infection 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. The individual  $PT$  will be calculated in days as the time between date of gonorrhea case/censoring and the start date of the follow-up period: gonorrhea case/censoring date – start date + 1. This will be expressed in person-years at risk (number of days/365.25).

The occurrence of infected cases in each treatment group will be assumed to follow a homogeneous Poisson process. Hence, IRs and (85% CI) will be estimated using a generalized linear model (GLM) with Poisson family and a logarithmic link function. An indicator of treatment status (placebo or HTD, denoted as “ARM”) will be used as covariate. To account for differences in individual  $PT$ s between participants, the logarithm of individual  $PT$  will be entered in the right-hand side of the model’s equation as an offset term (LOG\_FU\_TIME). The *IRR*, used to derive *VE*, will be estimated by exponentiating the model’s coefficient of the treatment. The following SAS code will be used to estimate IR in each treatment group and *IRR*:

```
proc genmod data=<dataset>;
  class ARM / param = ref;
  model EVENT=ARM / dist=Poisson offset=LOG_FU_TIME;
  estimate "IR0" intercept 1 ARM 1 0 / alpha=0.15;
  estimate "IR1" intercept 1 ARM 0 1 / alpha=0.15;
  estimate "IRR" intercept 0 ARM 1 -1 / alpha=0.15;
run;
```

Since the number of cases in each treatment condition is assumed to be a realization from a Poisson distribution, the number of confirmed gonorrhea cases in the HTD group is binomially distributed, conditional on  $n$  total confirmed gonorrhea cases (the sum of cases in HTD and placebo groups), as  $\text{Binom}(n, \pi)$  [Nauta, 2020], where:

$$\pi = \frac{PT_1 IR_1}{PT_1 IR_1 + PT_0 IR_0}$$

And  $PT_0$  and  $PT_1$  are the person-times in the placebo and investigational groups, respectively. The parameter  $\pi$  can be defined equivalently as:

$$\pi = \frac{r(1 - VE)}{r(1 - VE) + 1}$$

where  $r = \frac{PT_1}{PT_0}$

Exact 85% lower and upper confidence limits ( $LCL_{VE}$  and  $UCL_{VE}$ ) for VE will be derived from the exact confidence limits of  $\pi$  as follows:

$$LCL_{VE} = 1 - \frac{UCL_{\pi}}{r(1 - UCL_{\pi})}$$

$$UCL_{VE} = 1 - \frac{LCL_{\pi}}{r(1 - LCL_{\pi})}$$

The following SAS code will be used to derive exact 85% lower and upper confidence limits for VE:

```
data ci_ve;
  x = <cases vaccine>;          /*number of cases in vaccine group*/
  n = <overall cases>; /*total number of cases*/
  r = <person-time vaccine/person-time placebo>; /*ratio of the total
person-time in vaccine and placebo groups*/
  alpha = 0.15;
  lower_pi = betainv(alpha/2,x,n-x+1);
  upper_pi = betainv(1-alpha/2,x+1,n-x);
  lower_ve = 1 - (upper_pi/(r * (1 - upper_pi)));
  upper_ve = 1 - (lower_pi/(r * (1 - lower_pi)));
  put lower_ve= upper_ve= ;
run;
```

Because of the discrete nature of the assumed binomial distribution, coverage of the exact confidence interval will exceed the 85% level, leading to a conservative estimate of the confidence interval of VE.

The null statistical hypothesis will be evaluated with exact binomial test on the proportion of cases in the vaccine group, i.e.  $\pi$ . One side p-value will be derived

assuming a null hypothesis of  $\pi = \frac{PT_1}{PT_1 + PT_0}$ , which reflects a VE equal to 0 ( $IR_1 = IR_0$ ), with the following SAS function:

$$\text{CDF}\left(\text{'BINOM'}, x, \frac{PT_1}{PT_1 + PT_0}, n\right),$$

with x, cases in the HTD group, and n, total confirmed gonorrhea cases.

The HTD will be declared to be efficacious if p-value < 0.075.

If VE is shown for the HTD, then the bHTD will be tested, following the same steps mentioned above for HTD. Otherwise, bHTD VE results will be presented only for descriptive purposes.

#### **4.2.2.3. Safety and reactogenicity**

The analysis of safety and reactogenicity endpoints will be based on the Exposed, Solicited Safety, Solicited Safety 60m and Unsolicited Safety sets, depending on the specific endpoint under evaluation for Phase II – PoC safety.

##### **4.2.2.3.1. Solicited AEs**

The analyses for solicited AEs, with onset from 60 minutes up to 7 days after vaccination, will be performed on the Solicited Safety Set by visit.

The 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, after any dose, for each dose and overall doses. The same calculations will be performed for solicited AEs rated as Grade 3.

The number and percentages of each solicited AE maximum intensity during the 7-day follow-up solicited period will be tabulated by study group, after any dose, for each dose and overall doses, using mutually exclusive intensity categories (mild, moderate and severe). Compliance in completing solicited AEs information will be reported by symptom for each day of the 7-day solicited follow-up period. Calculations will be performed after any dose, for each dose and overall doses.

The duration, number of days from first day with a specific solicited symptom with Grade  $\geq 1$  to last day with the same symptom with Grade  $\geq 1$ , reported during the 7-day solicited follow-up period will be tabulated for each solicited AE, after each dose and overall doses using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same calculation will be performed for solicited AEs of Grade 3.

The above analyses, excluding compliance and duration, will be repeated for solicited AEs with onset within 60 minutes after vaccination on the Solicited Safety 60m Set by visit.

Solicited AEs still ongoing after the 7-day solicited follow-up period will be listed with starting and end dates, maximum intensity and their outcomes.

Grading of administration site and systemic solicited AEs will be summarized using categories depicted in the tables of the previous section.

#### **4.2.2.3.2. *Unsolicited AEs, SAEs and DREs***

All analyses related to unsolicited adverse events with onset within 30 days from any/each dose will be performed on the Unsolicited Safety Set (overall and by visit); while analyses related to SAEs and unsolicited adverse events leading to premature withdrawal will be performed on the Exposed Set.

A summary of the number and proportion of subjects experiencing:

- at least one unsolicited AE
- at least one Grade 3 unsolicited AE
- at least one causally related unsolicited AE
- at least one causally related Grade 3 unsolicited AE,

with onset within 30 days of any dose will be tabulated by study group and overall.

The occurrence and the incidence of any unsolicited AE, by MedDRA System Organ Class (SOC) and by Preferred Term (PT) during the 30-day (Day 1-30) follow-up post-vaccination period will be tabulated per study group, after any dose and after each dose. 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.

A summary of the number and proportion of subjects experiencing:

- at least one SAE
- at least one related SAE
- a fatal SAE
- a related fatal SAE
- at least one SAE leading to hospitalization
- at least one unsolicited adverse event leading to premature withdrawal

after any vaccination will be tabulated by study group and overall.

The occurrence and the incidence of subjects who experienced at least one SAE, by dose and after any dose during the entire study period will be reported. These analyses will be performed by MedDRA SOC and PT.

The occurrence and the incidence of subjects who experienced any SAEs related to study vaccine, any fatal SAEs and any AEs leading to withdrawal from the study during the entire study period will be reported in listings and tabulated.

SAEs related to study participation or concurrent GSK medication/vaccine reported from the time informed consent is signed until study end will be listed.

Gonococcal infections (either asymptomatic or symptomatic) are considered DREs and are captured in dedicated forms in the eCRF.

The occurrence and incidence of DREs, after each dose and after any dose, until end of study will be summarized. The summaries will be provided for the following DRE categories:

- Gonococcal infections, overall
  - Asymptomatic gonococcal infections
  - Symptomatic gonococcal infections
    - Overall and by symptom
- Complicated gonococcal infections
  - Overall and by symptom (including uncomplicated symptoms, if any)

For all DREs, the event date is the date of the positive gonorrhoea test. A complicated gonococcal infection is any gonococcal infection linked to at least one complicated symptom, as described in [Table 1](#). A symptomatic gonococcal infection can be linked to more than one symptom.

**Table 1 Complicated and uncomplicated Ng infections**

Presentations of Ng infection	Complicated? (Y/N)
Conjunctivitis	Y
Disseminated gonococcal infection (arthritis dermatitis syndrome or localized septic arthritis)	Y
Epididymo - orchitis	Y
Perihepatitis	Y
Pelvic inflammatory disease (PID)	Y
Other extragenital complicated infections	Y
Proctocolitis	N
Proctitis	N
Urethritis	N
Vulvo-Vaginitis/Cervicitis	N
Other symptoms of non-complicated infections	N

#### 4.2.2.3.3. Other safety PoC analyses

The following calculations will be performed separately for HIV- and HIV+ safety subsets to account for the different grading classification in haematology and biochemistry parameters. The analysis of safety laboratory parameters will be performed only for HIV- and HIV+ safety subsets.

For all subjects in each group and for each haematology and biochemistry parameter:

- The number and percentage of subjects having haematology and biochemistry results below or above the local laboratory normal ranges will be tabulated as post-vaccination versus pre-vaccination values: Visit 2 versus screening; Visit 5 versus Visit 4.
- Post-vaccination versus pre-vaccination values (Visit 2 versus screening; Visit 5 versus Visit 4) will be tabulated, for HIV- participants, according to FDA Guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007) [FDA, 2007] and, for HIV+ participants, 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]. See Table 22 (for HIV+ participants) and Table 23 (for HIV- participants) in section 10.9 of protocol for details.

#### 4.2.3. Sensitivity analyses

##### 4.2.3.1. Handling of early gonococcal infections

For all vaccine efficacy estimands, interest lies in the VE 1 month post-dose 2, regardless of intercurrent gonococcal infections prior to 1 month post-dose 2. Early gonococcal infections are handled using the treatment policy strategy.

For each efficacy endpoint, sensitivity analyses will be performed to estimate the VE after excluding participants with a case prior to 1 month post-dose 2.

The same statistical method described in Section 4.2.2.2 will be used in these sensitivity analyses.

#### **4.2.3.2. Handling infections confirmed at Visit 6 (Day 91)**

In the primary vaccine efficacy analysis, urogenital and/or anorectal gonococcal infections confirmed by a central NAAT collected at Visit 6 are included in the case count.

A sensitivity analysis will be performed where cases are only counted starting from 1 day after central NAAT collection date at Visit 6. Cases identified at Visit 6 will be handled as early infections, hence eliminated from this sensitivity analysis.

Participants with an out of window or missing sample for central NAAT at Visit 6 (Day 91) will be excluded from this analysis.

The same statistical method described in Section 4.2.2.2 will be used.

#### **4.2.3.3. Exclusion of MSM participants on PrEP**

The primary vaccine efficacy analysis described in Section 4.2.2.2 will be repeated after exclusion of men having sex with men (MSM) on pre-exposure prophylaxis (PrEP).

MSM participants on PrEP will be identified based on demographics and risk factors collected at screening.

#### **4.2.3.4. Handling of at risk sexual contact prior to NAAT**

The primary vaccine efficacy analysis described in Section 4.2.2.2 will be repeated after right censoring the risk time of participants reporting at risk sexual contact within 24 hours from central NAAT sample collection, from Visit 6 onwards.

Risk time and case count derivation rules described in Section 4.2.2.2 will be applied, additionally, if a participant reports at risk sexual contact within 24 hours from central NAAT at a certain visit, risk time will be censored on Visit Date – 1 Day.

A similar sensitivity analysis will be performed right censoring the risk time of participants reporting sexual intercourse in the 7 days period prior to any visit from Visit 6 onwards.

#### 4.2.3.5. Permutation test

A permutation test [Hasegawa, 2009; Ernst, 2004], based on the covariate-adaptive assignment algorithm (see Section 6.1.2), will be performed as a sensitivity analysis on the primary efficacy endpoint, if efficacy is demonstrated. The sensitivity analysis will be performed at the final analysis (see Section 4.1.4 for details) based on the mFAS.

Participants will be re-randomized to treatment groups according to the original assignment algorithm while keeping all the covariates, the time-to-event, the censoring indicator and the entry order as observed. Assuming both the HTD and bHTD will be advanced in the efficacy PoC part, the procedure will be as follows:

1. Using the procedure previously described in Section 4.2.2.1, obtain the test statistic  $T^*$  on the observed dataset for the HTD vs placebo comparison;
2. Obtain the distribution of the corresponding test statistic under the null hypothesis of  $VE = 0$  for HTD by repeating the following steps  $R$  times, with  $R$  ranging from a minimum of 5000 to a maximum of 10000:

Re-randomize participants to either HTD, bHTD or placebo groups following the original assignment algorithm;

Re-estimate the test statistic  $T$  for HTD comparison using the procedure previously described;

3. Derive the permutation  $p$ -value associated with the observed test statistic for HTD (from Step 1) based on the empirical distribution under the null hypothesis (Step 2) as  $p\text{-value} = \frac{M+1}{R+1}$ , where  $M$  is the number of times  $T \leq T^*$ .

#### 4.2.4. Additional estimands

None.

### 4.3. Secondary Endpoint(s) Analyses

#### 4.3.1. Secondary endpoint(s)

The analyses of secondary endpoints will further evaluate VE including:

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

The above endpoints will be evaluated for overall cases and by each anatomical site (urogenital, anorectal, and pharyngeal).

The secondary analyses for VE will be based on the Modified Full Analysis Set.

#### 4.3.1.1. Definition of endpoint(s)/estimands

The focus is on evaluating whether at least one of the two NgG vaccine investigational dosages is efficacious in preventing the following:

- Confirmed gonorrhea cases with and without *Ct* co-infection from 1 month (Day 91) to 13 months (Day 451) after the administration of Dose 2;
- Symptomatic and confirmed gonorrhea cases from 1 month (Day 91) to 13 months (Day 451) after the administration of Dose 2: all confirmed gonorrhea cases with at least one related symptom from 1 month (Day 91) to 13 months (Day 451) after the administration of Dose 2;

Investigational dosages will be compared to placebo in males and females aged between 18 and 50 years old who are at risk of gonococcus infections based on sexual behavioural characteristics regardless of concomitant medications or vaccination.

The estimand regarding the HTD is described by the following attributes:

- *Population*: males and females aged between 18 and 50 years old who are at risk of gonococcus infections based on sexual behavioural characteristics. See Section 5 in the protocol for more details on inclusion and exclusion criteria.
- *Treatment condition*: highest tolerated dose (HTD) of the NgG vaccine and placebo, each administered with two scheduled doses at Visit 1 (Day 1) and Visit 4 (Day 61).
- *Variable / endpoint*: Incidence rates (IRs) from 1 month (Day 91) to 13 months (Day 451) after the administration of Dose 2 of the following:
  - gonorrhea cases with and without *Ct* co-infection
  - symptomatic and confirmed gonorrhea cases
- *Summary measure*: vaccine efficacy (VE) defined as 1 minus the ratio between IRs of HTD investigational dosage over placebo of infections as previously defined from 1 month (Day 91) to 13 months (Day 451) after the administration of Dose 2.
- *Intercurrent events*:
  - Use of concomitant medications or vaccinations – treatment policy strategy (IRs of infections as previously defined regardless of use of concomitant medications or vaccinations)
  - Gonorrhea case (according to the endpoint definition) prior to 1 month post-Dose 2 – treatment policy strategy (IRs of confirmed gonorrhea cases 1 month post-Dose 2 regardless of intercurrent gonococcal infections).  
If such confirmed gonorrhea case is still ongoing after 1 month post-Dose 2 person-time at risk will start after this case is considered resolved.

*Rationale for estimand*: Interest lies in the VE after administration of the full treatment course regardless of using concomitant medications or vaccinations, and regardless of intercurrent gonococcal infections prior to 1 month post-Dose 2. The use of a treatment policy strategy is motivated by the interest in vaccine efficacy under the ITT principle,

emulating which would be the impact of the investigational product once delivered on the market.

The same definition of estimand will also apply for the dose below the HTD.

#### **4.3.1.2. Case Definitions**

##### **Confirmed gonorrhea cases with and without Ct co-infection**

A confirmed gonorrhea case with Ct co-infection is defined as the first Ng infection confirmed by a urogenital and/or anorectal and/or pharyngeal sample simultaneously positive for both Ng and Ct by central NAAT from 1 month up to 13 months post-dose 2.

Conversely, a confirmed gonorrhea case without Ct co-infection is defined as the first Ng infection confirmed by a urogenital and/or anorectal and/or pharyngeal sample positive for Ng where none of the anatomical locations positive for Ng are simultaneously positive for Ct by central NAAT from 1 month up to 13 months post-dose 2.

For both case definitions above, the date of the case is the sample collection date. In case of an early gonorrhea case (regardless of Ct co-infection) confirmed by central NAAT from a urogenital and/or anorectal and/or pharyngeal sample collected prior to 1 month post-dose 2, individual person-time at risk will start only after this early infection is considered resolved as described in Section 4.2.2.1.

For the analysis of gonorrhea cases with Ct co-infection, if a gonorrhea case without Ct co-infection occurs first (according to the case definition above), subsequent cases will not be included in the analysis and individual person-time at risk will be censored on the date of that case.

For the analysis of gonorrhea cases without Ct co-infection, if a gonorrhea case with Ct co-infection occurs first (according to the case definition above), subsequent cases will not be included in the analysis and individual person-time at risk will be censored on the date of that case.

Infections not confirmed by central NAAT and ad-hoc central NAAT results will not be considered in the derivation of cases.

##### **Symptomatic and confirmed gonorrhea cases**

A symptomatic and confirmed gonorrhea case is defined as the first Ng infection confirmed by a urogenital and/or anorectal sample positive for Ng by central NAAT from 1 month up to 13 months post-dose 2 with at least one related symptom as follows:

- Urine sample positive for Ng by central NAAT and a related symptom of urethritis and/or Epididymo-orchitis
- Vulvo-Vaginal/Cervical sample positive for Ng by central NAAT and a related symptom of vulvovaginitis/cervicitis and/or PID

- Anorectal sample positive for Ng by central NAAT and a related symptom of proctitis and/or proctocolitis

The date of the case is the later of sample collection date and related symptom onset date.

In this trial all pharyngeal infections will be considered asymptomatic.

In case an early symptomatic Ng infection confirmed by central NAAT from a urogenital and/or anorectal and/or pharyngeal sample with sample collection and symptom onset prior to 1 month post-dose 2, individual person-time at risk will start only after this early infection is considered resolved as described in Section [4.2.2.1](#).

Asymptomatic infections, infections not confirmed by central NAAT and ad-hoc central NAAT results will not be considered in the derivation of cases.

#### **4.3.1.3. Main analytical approach**

VE for secondary endpoints will be estimated using the same analytical approach described in Section [4.2.2.1](#). IRs, IRR and VE will be evaluated separately for each of the three previously described secondary endpoints.

### **4.4. Other Safety Analyses**

#### **4.4.1. Adverse Events**

For details related to the safety analyses, refer to Section [4.2.1](#) and Section [4.2.2.3](#).

##### **4.4.1.1. Adverse Events of Special Interest (AESIs)**

No AESIs will be collected for this study.

##### **4.4.1.2. Laboratory Data**

See Section [4.2.1.3](#) and Section [4.2.2.3.3](#) for the analysis of laboratory data, respectively, in the dose-escalation safety lead-in and PoC parts.

##### **4.4.1.3. Vital Signs**

Vital signs are only recorded at Visit 1 and will only be listed.

### **4.5. Other Analyses**

#### **4.5.1. Subgroup analyses**

Subgroup analysis by HIV status at enrolment (HIV- and HIV+) may be performed for relevant safety and reactogenicity analyses described in section [4.2.2.3](#).

## 4.6. Interim Analyses

An interim futility assessment will be performed to evaluate potential significant evidence of lack of efficacy; however, there will be no related clinical study report (CSR) for the interim analysis.

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.

Lack of benefit (futility) will be declared if the conditional power for the first efficacy analysis (HTD vs placebo) 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 (i.e., study team may decide not to stop the trial if futility is shown).

To help support a well informed decision, the interim futility assessment will evaluate the VE of the HTD and bHTD at interim, and supportive analyses such as VE using sensitivity case definitions and estimates of the (cumulative) incidence of gonorrhea cases in each vaccine group may also be generated. Such interim estimates will be produced by IDAC and reviewed by an iDRC independent from the study team to maintain study integrity.

From Section 4.2.2.1, the number of confirmed gonorrhea cases in the HTD group is binomially distributed, conditional on the number of total confirmed gonorrhea cases between HTD and placebo groups.

The conditional power of the first efficacy analysis (HTD vs placebo) will be evaluated based on the observed number of cases at interim and the expected total number of cases at the end of the study in the HTD + Placebo groups. The expected total number of cases (HTD and placebo groups) by study end,  $E(\text{cases}_{\text{Final}})$ , will be estimated based on the observed incidence rate in the placebo group assuming a  $50\%$  VE.

The critical value of HTD hypothesis test ( $H_{0\text{HTD}}: \pi = 0.5$ , supposing  $PT_1=PT_0$ ) at the first efficacy analysis, given an  $\alpha$ -level of  $7.5\%$ , will be determined as the maximum number of HTD cases fulfilling the below condition:

$$P(\text{Binom}(E(\text{cases}_{\text{Final}}), 0.5) \leq \text{Critical value}) \leq 7.5\%.$$

Therefore, the conditional power for the first efficacy analysis (HTD vs placebo), calculated at the interim analysis, will be equal to the power of the HTD hypothesis test given the information collected at the interim analysis and the expected total cases at study end:

$$P(\text{Binom}(E(\text{cases}_{\text{Final}}) - \text{cases}_{\text{interim}}, 0.33) \leq \text{Critical value} - \text{cases}_{\text{HTD}}),$$

where  $\text{cases}_{\text{interim}}$  is the total number of cases observed at interim in HTD and placebo groups,  $0.33$  is  $\pi$  value under  $H_{1\text{HTD}}$  and  $\text{cases}_{\text{HTD}}$  is the number of cases in the HTD group seen at the interim analysis.

At the time of the interim analysis the above quantity will be calculated with the following SAS function:

`CDF('BINOM', Critical value- casesHTD, 0.33, E(casesFinal)-casesInterim);`

and it will be compared to the 17% threshold. As stated above, if the conditional power is <17%, futility will be declared.

At the time of the interim futility assessment, key safety data will be evaluated as well by the iSRC and iDRC.

#### **4.7. Changes to Protocol Defined Analyses**

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 02 December 2024).

### **5. 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 of the protocol. 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 2), 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% incidence rate (IR) in the placebo group and a 50% true efficacy. The sequential testing procedure requires no  $\alpha$ -adjustment. An approximate 15% drop-out rate is accounted.

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

#### **5.1. Sample size adaptation**

The sample size adaptation 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 in the placebo group. The sample size adaptation will be performed following these steps:

- 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 an IR 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%, see the below formula - is greater than 20%), the sample size for each arm will be increased:  

$$\text{likelihood} = 1 - \text{CDF}(\text{'POISSON'}, \text{placebo\_cases}, \text{assumed\_IR} * \text{tot\_PT\_placebo}),$$
 where placebo\_cases is the number of cases in the placebo group at the time of the assessment and PT\_placebo is the sum of individual person-times in the placebo group until the time of the assessment. Individual person-time is calculated as time from Day 1 until:
  - time of case/withdrawal/last visit, if subject experienced a case/withdrawal/completed the study before time of assessment;
  - time of assessment, otherwise;
- the increase consists of a fixed number of 50 subjects per group;
- whenever a sample size increase is triggered, the assumed placebo IR will be updated to the value needed to have 31 cases (expected number) in the placebo group with the new increased sample size:  

$$\text{assumed\_IR} = 31 / (\text{current\_sample\_size} + 50),$$
 where current\_sample\_size is the current number of subjects in the placebo group before the increase;
- Using the newly assumed IR, the probability of observing a higher number of cases than the one observed will be re-assessed and the steps above will be repeated until this probability is smaller than 20%.
- sample size may be updated until a maximum of 400 participants per group is reached. Thus, according to the initial sample size of 250 subjects per group, sample size can be updated no more than 3 times. The maximum number of potential participants randomized to the study will therefore be limited to 1200 participants in total.

At every interim estimate of the placebo IR, the same computations will be performed as detailed above and, in order to guarantee the blinding, this assessment will be performed by IDAC.

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

## **6. SUPPORTING DOCUMENTATION**

### **6.1. Appendix 1 Study Population Analyses**

Study populations are specified in Section 4 together with the related analyses.

Consort tables, providing subject eliminations and withdrawals from one global study population to another one, will be provided for:

- Screened Set to Enrolled Set;
- Exposed Set to Unsolicited Safety Set;
- Exposed Set to Solicited Safety Set;
- Exposed Set to Solicited 60m Set;
- Exposed Set to Full Analysis Set;
- Full Analysis Set to Modified Full Analysis Set;
- Modified Full Analysis Set to Per Protocol Set.

In case the Enrolled Set is different from the Exposed Set, an additional consort table from Enrolled Set to Exposed Set will be added. The sample applies for the Randomised Set.

#### **6.1.1. Participant Disposition**

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized.

A summary of the number and percentage of participants who attended scheduled study visits will be provided.

All the above summaries will be provided by study phase, i.e. dose-escalation safety lead-in and PoC, and on the Exposed Set.

#### **6.1.2. Minimization algorithm**

Subjects are randomised using a centralised randomisation system on internet (SBIR) at first dose. The system incorporates a minimization algorithm based on White SJ and Freedman LS method [White, 1978] and it is described below:

Notations:

- $K = 5$  input values (sex, site, age group, race, and MSM under pre-exposure prophylaxis for HIV vs others) to be used for minimization, each with a weight  $w_k = 1$  ( $k = 1, \dots, K$ ) &  $s_k$  variants and 4 strata (HIV- subset, HIV- full enrollment, HIV+ subset, HIV+ full enrollment). Overall, 90 participants will be enrolled in the HIV- subset (30 per group) and 24 subjects in the HIV+ subset (8 per group). Overall, 250 participants per group are expected to be enrolled. The number of enrolled participants might be increased depending on whether sample size adaptation rule is triggered.
- $I = 3$  treatment groups (HTD, bHTD, and Placebo) with the following randomization ratio in each stratum:  $[a_1:a_2:a_3] = [1:1:1]$

### Algorithm

For a new subject belonging to a given stratum (HIV- subset, HIV- full enrollment, HIV+ subset, HIV+ full enrollment) with input value variants  $s_1, \dots, s_k$ :

#### 1. Minimization computation

##### 1.1: Initialize Problem flag to 0

For each input value variant  $s_k$ , compute the number of subjects already enrolled in each treatment group in the identified stratum.

Let  $b_{ik}$  the total number of subjects already randomized in treatment  $i$  and with variant  $s_k$  in the identified stratum.

1.2: For each treatment  $i$ : compute  $A_i = \frac{1}{a_i} \sum_k w_k b_{ik}$ , where  $a_i$  is the randomization ratio previously defined

#### 2. Determine whether the algorithm is random or deterministic:

Generate  $R$ , a random number within  $[0 - 1]$  from a uniform distribution

#### 3. Check determinism

If  $R < 0.9$  (deterministic factor), go to 4. Determinism else go to 5. Random

#### 4. Determinism

4.1: Identify all treatments with the lowest value  $A_i$

4.2: Select randomly one of the treatments identified in 4.1 and let it be  $T$ .

Go to 6., if no more treatment then randomization failed

#### 5. Randomization

Select one of the treatments, let it be  $T$ , according to the randomization ratio applicable to the subject stratum.

Go to 6., if no more treatment then randomization failed.

## 6. Treatment allocation

Assign one of the treatments nr. related to treatment  $T$  in the subject's center.

If no treatment nr. related to treatment  $T$  is available in the subject's center, then go & repeat 4. Determinism or 5. Randomization while dropping treatment  $T$  (set problem flag=1).

### 6.1.3. Demographic and Baseline Characteristics

The demographic characteristics including age at first vaccination, age group (18–30 years of age, 31–50 years of age), sex, site, specific risk group participants belong to (i.e. men having sex with men under pre-exposure prophylaxis for HIV vs others), gender, sexual orientation, ethnicity and race will be summarized with descriptive statistics. These summaries will be provided for Enrolled Set, Exposed Set, Modified Full Analysis Set and Per Protocol Set.

### 6.1.4. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior and post unblinding before freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Protocol deviations which result in exclusion from the analysis set will also be summarized. Data will be reviewed prior and post unblinding before freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADaM dataset.

If relevant, a table with protocol deviations by site will be provided.

### 6.1.5. Prior and Concomitant Medications

Prior and concomitant medications and vaccinations will be summarized separately and listed by vaccine group on Exposed Set and modified Full Analysis Set by WHO Drug dictionary. The number and percentage of participants with concomitant DoxyPEP use will be included in this summary.

Concomitant DoxyPEP use is defined as at least one Doxycycline treatment course with an end date on or after first vaccination date and with a duration of 3 days or less (medication end date – medication start date + 1  $\leq$  3 days).

**6.1.6. Medical history**

Summary of adverse events in medical history will be performed on the Exposed Set by study group and by System Organ Class and Preferred Term according to Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

**6.1.7. Study Intervention Compliance**

A summary of the number and percentage of participants receiving the first (i.e., only the first) and the second doses will be provided on the Exposed Set.

**6.1.8. Participants listings**

The following list of individual listings will be provided:

- Listing of Reasons for Study Withdrawal
- Listing of Important Protocol Deviations
- Listing of Subjects Excluded from Any Population
- Listing of Inclusion/Exclusion criteria violations
- Listing of Demographic Characteristics
- Listing of Treatment data
- Listing of Serious Adverse Events
- Listing of All Laboratory Data for Subjects Outside Normal Range and/or Toxicity grade > 0;
- Listing of Concomitant Medications and Vaccinations
- Listing of Vital signs (if needed)

If other listings will be deemed as relevant, they will be added.

## 6.2. Appendix 2 Electronic Clinical Outcome Assessment Compliance

### 6.2.1. eDiary compliance

The study protocol defines a 7-day solicited AE follow-up period. Overall eDiary compliance is calculated as:

$$\frac{\text{Total number of complete daily eDiaries}}{\text{Expected number of complete daily eDiaries}} \times 100$$

An eDiary is considered complete for a given day if there is no missing data within that day. The eDiary compliance will be reported overall and for each treatment group.

In this study, eDiary compliance targets were defined based on quality tolerance limits (QTLs) that are reviewed on a regular basis. These QTLs are based on different metrics than the ones reported in this section.

No predefined compliance targets were set for the study based on the metrics described in this section, however an overall eDiary compliance level around 70% is considered acceptable.

A participant is compliant with eDiary if at least 80% of their eDiaries are complete (have no missing data), i.e., a participant is eDiary compliant if they meet the following criteria:

$$\frac{\text{Total number of complete daily eDiaries}}{\text{Expected number of complete daily eDiaries}} \times 100 \geq 80\%$$

The number of participants who are 0-<50% compliant, 50-<80% compliant and  $\geq 80\%$  compliant with eDiary assessments will be summarized.

In terms of compliance for each of Days 1-7, and for each solicited symptom, the number/percentage of completed eDiaries by either a participant or the investigator/study staff will be summarized by study group and by dose, using a frequency table. The denominator will be the number of expected completed eDiaries (i.e., the number of participants).

For compliance of each day beyond Day 7, the number/percentage of completed eDiaries by either a participant or the investigator/study staff will be summarized by study group and dose, using a frequency table. In this summary the denominator will be the number of expected completed diaries (i.e., the number of participants with the symptom on the previous day) and the numerator will be the number of participants with the symptom data among the participants contributing to the denominator. An overall compliance summary will also be provided across symptoms and days in which the numerator and denominator will be the sum of numerators and denominator respectively of the previously described daily and symptom compliance specific summaries.

If available, the number/percentage of daily recordings from the investigator/study staff due to missed entries or due to erroneous participant entries will be summarized by study group using a frequency table. In these summaries, the denominator will be the sum of all entries by either the participants or investigator.

### **6.3. Appendix 3 Data Derivations Rule**

#### **6.3.1. Laboratory data and criteria for Potential Clinical Importance**

Missing laboratory results (including immunological data) will not be replaced.

Haematology/chemistry laboratory data requiring grading as per FDA Guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007) [FDA, 2007] (Table 23 in protocol) and, for HIV+ participants, 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] (Table 22 in protocol) may have more decimals than expected or may require conversion to the unit associated to the grade, leading to more decimals than expected.

In order to determine the grading, the following rule will be used

1. In case a conversion is needed, the original results will be used for the conversion without a previous rounding.
2. In case an approximation is needed to determine the grading, the result (or the result divided by the upper limit of the normal range (ULN), depending on the test) expressed in the expected units will be rounded to the number of decimals used for the grading.

If the original result is expressed as  $< x$  or  $> x$ , then, for grading purpose, it is imputed to  $x$  and converted to expected units, if needed.

#### **6.3.2. Study Period**

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the CRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

### 6.3.3. Study Day and Reference Dates with Partial Dates

Partial dates will be displayed as captured in participant listing displays. However, partial dates may be imputed for 'slotting' data to study phases (vaccination epochs).

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 1
- A missing day and month will be replaced by January 1<sup>st</sup>

The following exceptions apply:

- Birth dates:
  - A missing day will be replaced by 15
  - A missing month will be replaced by June 30<sup>th</sup>
- Adverse event start dates with missing day:
  - If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected or missing, the imputed start date will match the first (or only) study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.
- Adverse event start dates with missing day and month:
  - If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year. Adverse event end dates with missing day:
  - If the event ends in the same month and year as the end of study date (if it exists) then the imputed end date will match the end of study date;
  - Otherwise, day will be imputed to the last day of the month.
- Adverse event end dates with missing day and missing month:
  - If the event ends in the same year as the end of study date (if it exists) then the imputed end date will match the end of study date
  - Otherwise, day and month will be imputed to the last day and month of the year i.e. 31<sup>st</sup> December

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

#### **6.3.4. Studies with electronic diaries**

As the study foresees the use of electronic diaries for the collection of solicited adverse events, a solicited adverse event will be considered present only when a daily recording of grade 1 or more is present. Missing or unevaluable measurements will not be replaced. Therefore, the analysis of the solicited symptoms will include only subjects/doses with documented safety data (i.e., symptom screen completed).

By definition, solicited adverse events are considered related to the study intervention.

#### **6.3.5. Unsolicited adverse events**

Unsolicited adverse event summaries include serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' in all statistical outputs.

#### **6.3.6. Multiple measurements at One Analysis Time Point**

For gonorrhea lab tests on a study day, if more than one assessment is taken per anatomical site on the same day, the last test performed on the study day coming from the central lab will be considered for the analyses.

#### **6.3.7. Treatment of gonococcal infections**

In the eCRF, treatments of gonococcal infections are recorded in the concomitant medication form and are linked to the corresponding gonococcal infection.

A gonococcal infection can either be treated with a highly effective antibiotic treatment or with an alternative treatment.

A gonococcal infection is considered as treated with a highly effective antibiotic treatment if at least one treatment course containing one of the following treatments (including combinations) was administered:

- Ceftriaxone
- Azithromycin
- Cefixime
- Spectinomycin

If the administered treatments do not contain any the above (alone or in combination), the infection will be considered treated with an alternative treatment.

**6.3.8. Data derivation****6.3.8.1. Weight**

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

$$\text{Weight in kilograms} = \text{Weight in pounds} / 2.2$$

**6.3.8.2. Height**

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

$$\text{Height in centimeters} = \text{Height in inches} \times 2.54$$

**6.3.8.3. Body mass index (BMI)**

BMI will be calculated as follows:

$$\text{BMI} = (\text{Weight in kilograms}) / (\text{Height in meters})^2$$

**6.3.8.4. Temperature**

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

$$\text{Temperature (Celsius)} = ((\text{Temperature (Fahrenheit)} - 32) \times 5) / 9$$

**6.3.8.5. Onset day**

The onset day for an event (e.g. AE, medication, vaccination) is the number of days between the last study vaccination and the start date of the event. This is 1 for an event occurring on the same day as a vaccination (and reported as starting after vaccination).

**6.3.8.6. Duration of events**

The duration of an event with a start and end date will be the number of days between the start and end dates plus one day, i.e. an event that starts on 03MAR2022 and ends on 12MAR2022 has a duration of 10 days.

**6.3.8.7. Counting rules for combining solicited and unsolicited adverse events**

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered general events since the administration site flag is not included in the expedited adverse event CRF pages.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

#### **6.3.8.8. Counting rules for occurrences of solicited adverse events**

When the occurrences of solicited adverse events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs.

### **6.3.9. Display of decimals**

#### **6.3.9.1. Percentages**

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group
  - Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

<b>n/N</b>	<b>Displayed percentage</b>
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

- The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
- Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

#### **6.3.9.2. Differences in percentages**

Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual

percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

#### **6.3.9.3. Demographic/baseline characteristics statistics**

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (BMI), pre-vaccination body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maximum and minimum of transformed height/weight variables will be displayed with no decimals.

The maximum and minimum of transformed body temperatures will be displayed with one decimal.

#### **6.3.10. Trademarks**

<b>Trademarks of the GlaxoSmithKline Group of Companies</b>
None

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#### 6.4. Appendix 4 Calculations for sample size adaptation

In the following table it is shown how the sample size adaptation strategy can mitigate the risk of having an IR in the placebo group lower than expected.

Following the same approach described in Section 5.1, if placebo IR checks are performed until 16 months from PoC start of enrolment (with an enrolment rate of 31.25 participants per month), simulations lead to the following results:

True IR in placebo	Probability $\geq 31$ cases in placebo with 250 subjects (without reassessment)	Probability $\geq 31$ cases in placebo with 250 subjects (with reassessment)	Probability $\geq 1$ sample size increase
15%	80%	90%	41%
14%	66%	88%	52%
13%	50%	85%	67%
12%	32%	82%	78%
11%	17%	80%	86%
10%	7.8%	75%	95%

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