Protocol Amendment 6

Study ID: 208833

Official Title of Study: A Phase I/II, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK S. aureus candidate vaccine when administered to healthy adults (dose escalation) and to adults 18 to 64 years of age with a recent S. aureus skin and soft tissue infection (SSTI)

NCT number: NCT04420221

Date of Document: 11-Oct-2022

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'Institut 89,
1330 Rixensart, Belgium

Primary Study vaccine	• GlaxoSmithKline (GSK) Biologicals *Staphylococcus aureus* candidate vaccine (*S. aureus* candidate vaccine [Sa-5Ag adjuvanted]) CCI [redacted]
Other Study vaccine(s)	• Placebo (Saline) • GlaxoSmithKline (GSK) Biologicals Sa-5Ag half dose non-adjuvanted • GlaxoSmithKline (GSK) Biologicals Sa-5Ag non-adjuvanted • GlaxoSmithKline (GSK) Biologicals Sa-5Ag half dose adjuvanted
eTrack study number and abbreviated title	208833 (STAPH AUREUS BIOCONJ-001 STG)
Investigational New Drug (IND) number	IND 19408
EudraCT number	2021-006215-29
Date of protocol	Final Version 1: 4 September 2019
Date of protocol amendment	Amendment 1 Final: 26 May 2020 Amendment 2 Final: 2 April 2021 Amendment 3 Final: 15 June 2021 Amendment 4 Final: 30 November 2021 Amendment 5 Final: 22 June 2022 Amendment 6 Final: 6 October 2022
Short title	Safety, immunogenicity and efficacy of GSK *S. aureus* candidate vaccine (GSK3878858A) when administered to healthy adults (dose-escalation) and to adults 18 to 64 years of age with a recent *S. aureus* skin and soft tissue infection (SSTI).

eTrack study number and abbreviated title	208833 (STAPH AUREUS BIOCONJ-001 STG)
Investigational New Drug (IND) number	IND 19408
EudraCT number	2021-006215-29
Title	A Phase I/II, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK S. aureus candidate vaccine when administered to healthy adults (dose-escalation) and to adults 18 to 64 years of age with a recent S. aureus skin and soft tissue infection (SSTI).
Co-ordinating author(s) ***(Amended 6 October 2022)***	PPD (Scientific Writer ***for GSK***)
Contributing authors ***(Amended 6 October 2022)***	• PPD (***CSL***) • PPD (SDL) • PPD (***DMQL***) • PPD (Study Statistician) • PPD (Lead Statistician) • PPD (CLS CRT-L) • PPD (Safety Physician) • PPD (Safety Scientist) • PPD (GRA)

GSK Protocol WS v 16.0.1

Protocol Amendment 6 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	208833 (STAPH AUREUS BIOCONJ-001 STG)
Investigational New Drug (IND) number	IND 19408
EudraCT number	2021-006215-29
Date of protocol amendment	Amendment 6 Final: 6 October 2022
Title	A Phase I/II, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK S. aureus candidate vaccine when administered to healthy adults (dose-escalation) and to adults 18 to 64 years of age with a recent S. aureus skin and soft tissue infection (SSTI).
Sponsor signatory ***(Amended 6 October 2022)***	Michele Pellegrini Clinical Project Lead
Signature	
Date	

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

Protocol Amendment 6 Investigator Agreement

I agree:

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

Hence, I:

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

eTrack study number and Abbreviated Title	208833 (STAPH AUREUS BIOCONJ-001 STG)
Investigational New Drug (IND) number	IND 19408
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Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA
Rue de l'Institut 89, 1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 12.5.9.3

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

5. GSK Central Safety Physician On-Call Contact information for Emergency Unblinding

GSK Central Safety Physician and Back-up Phone contact: refer to protocol Section 7.3.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1 Document history

Document	Date
Amendment 6	6 October 2022
Amendment 5	22 June 2022
Amendment 4	30 November 2021
Amendment 3	15 June 2021
Amendment 2	2 April 2021
Amendment 1	26 May 2020
Original Protocol	4 September 2019

Amendment 6: 6 October 2022

Overall Rationale for the Amendment: The aim of this protocol amendment is to **ensure consistency across the different protocol sections related to the interim efficacy analysis, with reference to the possibility to continue the enrolment up to the planned number of events needed for the key efficacy endpoint evaluation (i.e.** CCI [redacted] **In addition, correction of typographical errors, and minor edits for clarification have been made (refer to Section 12.8.1 for information).**

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Synopsis; Section 5.2.2	Update to clarify that "CCI [redacted] of the targeted total number of culture confirmed cases of recurrent *S. aureus* SSTIs are observed…"	To ensure consistency across the different protocol sections related to the interim efficacy analysis
Section 10.1.1 Hypotheses related to primary and secondary objectives	Update to text linked to hypotheses related to primary and secondary objectives	To ensure consistency across the different protocol sections related to the interim efficacy analysis
Section 10.1.2 Sample size calculation	Update to text linked to sample size calculation and clarification for the basis of assumptions	To ensure consistency across the different protocol sections related to the interim efficacy analysis
Section 10.3.7 Interim analyses	Update to text linked to interim analyses	To ensure consistency across the different protocol sections related to the interim efficacy analysis

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1. SYNOPSIS

Indication:

Active immunisation for the prevention of *S. aureus* infection (SSTI/Surgical Site Infection [SSI]/ Blood Stream Infection [BSI]) in adults aged 18 years or older.

Rationale:

The purpose of this seamless Phase I/II, first time in human - proof of principle (FTIH-PoP) study is to assess safety and reactogenicity, to perform a preliminary evaluation of clinical efficacy and to explore immunogenicity of GSK Biologicals' *S. aureus* vaccine compared to placebo (saline), both administered in a 2-dose schedule on Day 1 and Day 61.

There are no established correlates of protection for immunity against *S. aureus* infections, and therefore trials aimed at evaluating only safety and immunogenicity cannot currently predict vaccine efficacy. For this reason, an early evaluation of the efficacy of the candidate vaccine in this FTIH clinical trial is intended to provide an early reliable PoP that will serve to better guide future vaccine development. CCI [redacted]

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Descriptive: • To assess safety and reactogenicity of investigational *S. aureus* vaccine	• Occurrence and intensity of solicited local and general AEs during 7 days after each dose (i.e. day of vaccination and the 6 subsequent days) in all subjects by vaccination group. • Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days after each dose (i.e. day of injection and the 29 subsequent days) in all subjects by vaccination group. • Occurrence, intensity and relationship to vaccination of all SAEs in all subjects by vaccination group: – Groups 1 to 3 from Day 1 (day of vaccination) until Day 366. – Groups 4 and 5 from Day 1 (day of vaccination) until Day 426. • Occurrence, intensity and relationship to vaccination of all potential immune-mediated disease (pIMDs) during in all subjects by vaccination group. – Groups 1 to 3 from Day 1 (day of vaccination) until Day 366. – Groups 4 and 5 from Day 1 (day of vaccination) until Day 426. • Occurrence of haematological and biochemical laboratory abnormalities, and changes from the baseline values after vaccination: – In all subjects of Groups 1 to 3 on Day 8. – In all subjects of Group 4 on Days 8 and 68 (i.e. 7 days after dose 1 and dose 2), respectively. – Subjects in Group 5 Step 1 (i.e. first 40 subjects enrolled in the PoP) on Days 8 and 68 (i.e. 7 days after dose 1 and dose 2), respectively.

Objectives	Endpoints
Secondary	
Confirmatory: • To evaluate vaccine efficacy (VE) in the prevention of recurrent culture confirmed *S. aureus* SSTIs compared to placebo	• Key secondary endpoint: Number of subjects with at least one culture confirmed case of recurrent *S. aureus* SSTI starting from Day 75 (i.e.14 days after the second dose) up to 12 months after the second dose • Secondary endpoint: Number of subjects with at least one culture confirmed case of recurrent *S. aureus* SSTI starting from Day 15 (i.e. 14 days after the first dose) up to 12 months after the second dose
CCI [redacted]	

Ab = Antibody; AE = Adverse Event; CD = Cluster of Differentiation EAP = Exploratory Analysis Plan; CCI [redacted]

CCI [redacted]

pIMDs = potential Immune-Mediated Disease; SAE = Serious Adverse Events; CCI SSTI = Skin and Soft Tissue Infection; VE = Vaccine Efficacy; CCI

Overall Design:

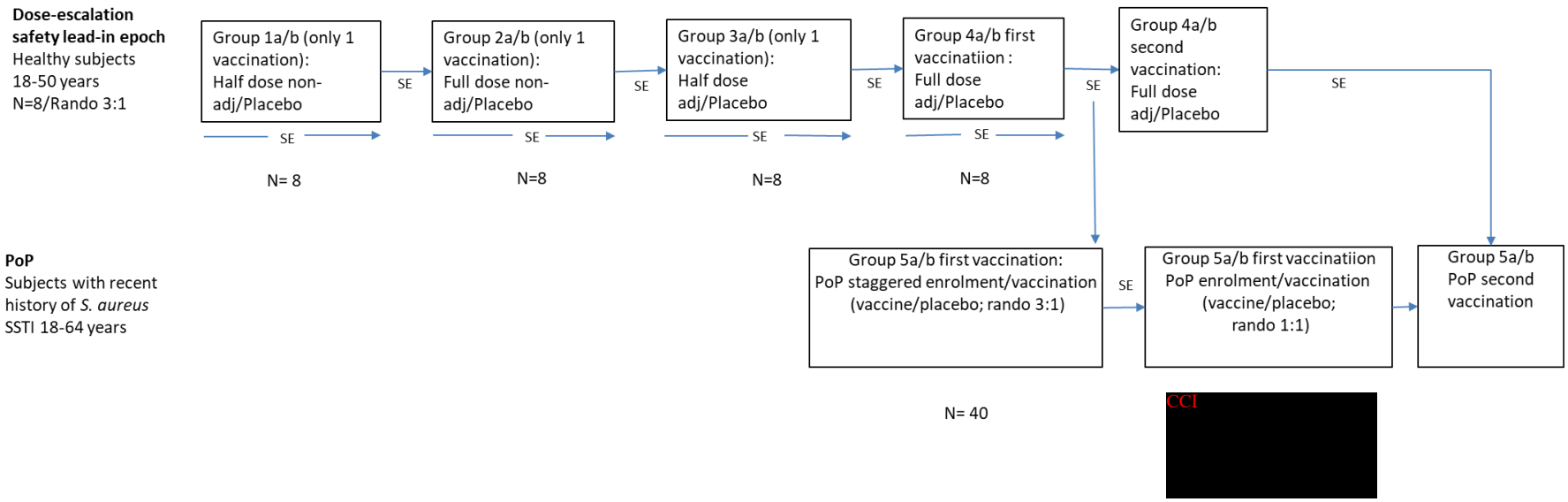
This is a Phase I/II, placebo-controlled, observer-blind, randomised, multi-centric study.

Figure 1 presents a high-level overview of the whole study design. More detailed figures are provided in the respective subsections for dose-escalation safety lead-in and PoP.

The study will include the following epochs (see also Figure 2 and Figure 3):

- Dose-escalation safety lead-in in healthy subjects
  - Screening epoch
  - Vaccination epoch
- PoP in subjects with a recent *S. aureus* SSTI
  - Screening epoch
  - Vaccination epoch

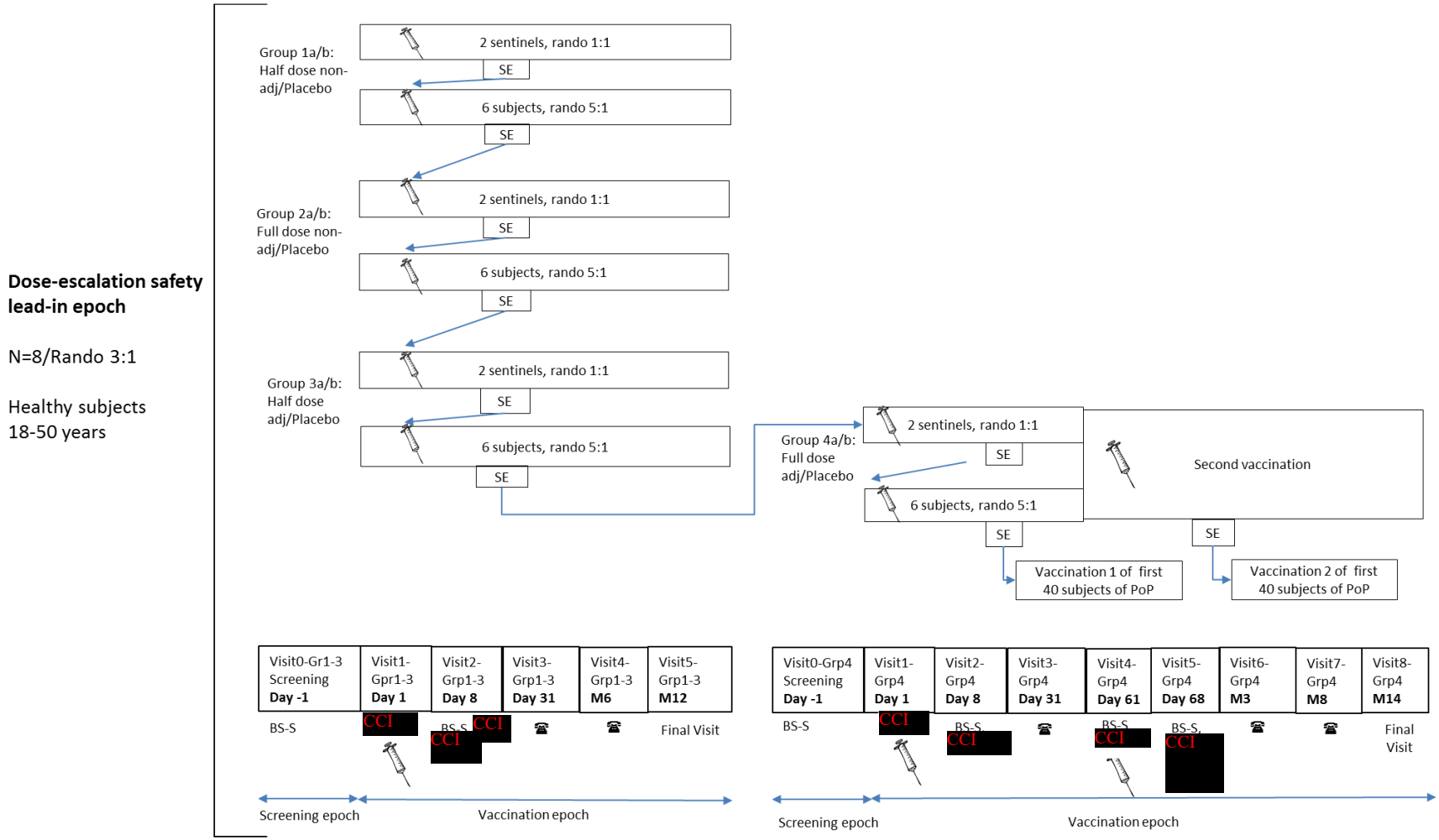
Figure 1 Overall design



Grp = Group
a/b = vaccine/placebo.
Rando = Randomisation
adj = adjuvanted
SE = Safety evaluation by SRT/ iSRC chair (blinded review) or iSRC (unblinded review), for details refer to Section 8.6
PoP = Proof of Principle

Dose-Escalation safety lead-in healthy subjects

Figure 2 Study design overview dose-escalation safety lead-in healthy subjects Groups 1-4a/b



CDISC is not calculating with Day 0, i.e. interval between Day –1 and Day 1 is 1 day.
Grp = Group
a/b =vaccine/placebo
Rando = Randomisation
adj = adjuvanted
SE = Safety evaluation by SRT/ iSRC chair (blinded review) or iSRC (unblinded review), for details refer to Section 8.6
PoP = Proof of Principle
M = Month
V = Vaccination
BS-S = Blood Sample for Safety evaluation

CCI

Groups in dose-escalation safety lead-in epochs:

- **Group 1 Half dose non-adjuvanted** (first group), 2 parallel groups:
  - **Group 1a Half dose non-adj**.: 1 dose of Sa-5Ag half dose, non-adjuvanted at Day 1
  - **Group 1b Placebo**: 1 dose of placebo (saline) at Day 1
- **Group 2 Full dose non-adjuvanted** (second group), 2 parallel groups:
  - **Group 2a Full dose non-adj**.: 1 dose of Sa-5Ag full dose, non-adjuvanted at Day 1
  - **Group 2b Placebo**: 1 dose of placebo (saline) at Day 1
- **Group 3 Half dose adjuvanted** (third group), 2 parallel groups:
  - **Group 3a Half dose adj**.: 1 dose of Sa-5Ag half dose, adjuvanted at Day 1
  - **Group 3b Placebo**: 1 dose of placebo (saline) at Day 1
- **Group 4 Full dose adjuvanted** (fourth group), 2 parallel groups:
  - **Group 4a Full dose adj**.: A series of 2 doses of Sa-5Ag full dose, adjuvanted (*S. aureus* candidate vaccine, target vaccine formulation) given approximately 2 months apart (Days 1 and 61)
  - **Group 4b Placebo**: A series of 2 doses of placebo (saline) given approximately 2 months apart (Days 1 and 61)

For each group, the enrolment of 8 subjects is planned as follows:

- 1 vaccinated subject + 1 subject receiving placebo (sentinel subjects). The 2 sentinel subjects in each group should be vaccinated on 2 different days. All the available safety data collected up to the Day 8 after vaccination visit from both subjects (including laboratory assessments at Day 8) will be evaluated. The Safety Review Team (SRT) and the internal Safety Review Committee (iSRC) Chair will evaluate safety data and confirm the start of the step below. Conditionally; unblinded data may be evaluated by iSRC and only after positive opinion of iSRC the next step can be started.
- 5 vaccinated subjects + 1 subject receiving placebo. All the available safety data collected up to the Day 8 after vaccination visit for the last vaccinated subject (including laboratory assessments at Day 8) will be evaluated. The SRT and the iSRC Chair will evaluate all the safety data available and confirm the start of the next step (subsequent group). Conditionally; unblinded data may be evaluated by iSRC and only after positive opinion of iSRC the next step can be started.
  All the unblinded data collected up to Day 8 after vaccination Visit 1 of the fourth group will be reviewed by iSRC.

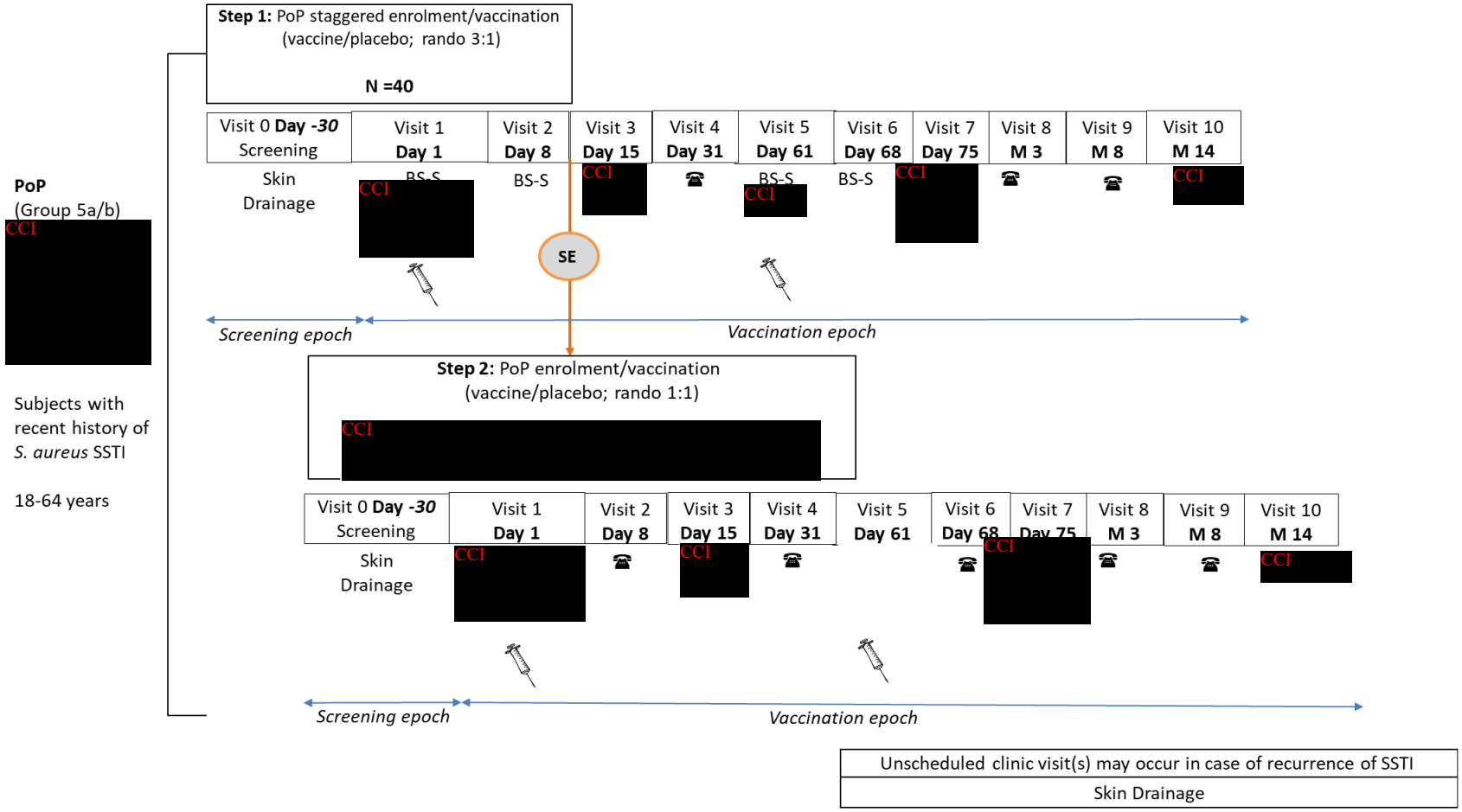
In addition to the above described steps, the fourth group (Full dose adjuvanted) will receive a second dose with an interval of approximately 2 months and subjects of all the groups will be followed until study end (i.e. for each subject approximately 12-14 months).

After the iSRC review of the unblinded data collected up to the Day 8 after vaccination Visit 1 of the fourth group and prior to administering the second dose in that fourth group, the staggered enrolment for the PoP epochs of the first approximately 40 subjects in the vaccine target population (subjects with a recent *S. aureus* SSTI) can start. Vaccination will be performed with a staggered approach limited to approximately 40 subjects (30 subjects receiving GSK *S. aureus* candidate vaccine and 10 receiving placebo) followed by an iSRC evaluation of the unblinded safety data up to Day 8 after vaccination (including laboratory assessments).

For both the dose-escalation safety lead-in and the staggered enrolment for PoP of the first approximately 40 subjects, the investigator will not be permitted to start the administration of Dose 1 for the next group until receipt of the favourable outcome of the safety assessment committees evaluation (SRT/iSRC). In case more than 1 subject is to be vaccinated on the same day per site, subjects should be vaccinated sequentially at this site and at least 60 minutes apart as acute adverse reactions, such as anaphylactic shock, typically occur within 1 hour of vaccination (for holding rules refer to Section 8.6.3 and Table 26). Therefore, not vaccinating subjects in parallel and leaving at least 60 minutes between vaccinations of 2 consecutive subjects will ensure that, in the event of an acute adverse reaction, the site will be able to provide the required medical attention. The 2 sentinel subjects of Groups 1 to 4 dose-escalation safety lead in should be vaccinated on 2 different days.

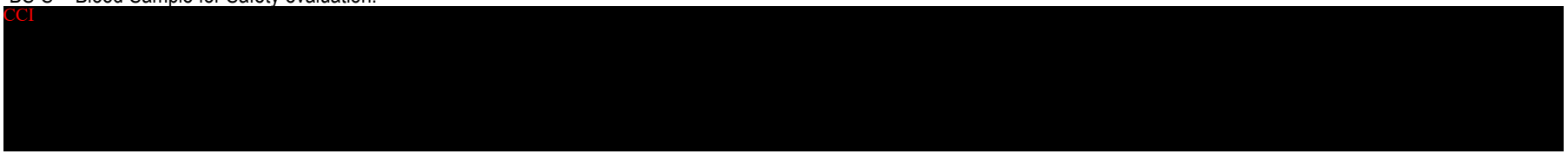
PoP in subjects with recent *S. aureus* SSTI

Figure 3 Study design overview PoP in subjects with a recent *S. aureus* SSTI Group 5a/b



Note: CDISC is not calculating with Day 0, i.e. interval between Day –30 and Day 1 is 30 days.

a/b = vaccine/placebo
SE = Safety evaluation by iSRC (unblinded review), for details refer to Section 8.6
Rando = Randomisation
PoP = Proof of Principle
SSTI = Skin and Soft Tissue Infection
Vac = Vaccine
Plac = Placebo
M = Month
V = Vaccination
BS-S = Blood Sample for Safety evaluation.
CCI



In the PoP screening epoch, study subjects can be selected according to the following ways:

1. Subjects with signs and symptoms of an ongoing skin infection and purulent lesion, i.e. SSTI, suspected to be caused by *S. aureus* will be enrolled after signing an informed consent form (ICF). Subjects with surgical site infections are not eligible for entry in this study. After demonstration of *S. aureus* positive culture, performed as a study procedure, and confirmation by investigator that *S. aureus* is the most likely cause of SSTI, subjects will continue in the study. Diagnosis (e.g. abscess or cellulitis) and body location will be collected in the eCRF. In addition, data related to *S. aureus* CCI [redacted] and recorded in the eCRF. Specific treatment will be given in compliance with the standard medical practice for the management of *S. aureus* SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures. After conclusion of the specific treatment for the skin lesion and after clinical resolution of the SSTI (e.g. no signs of ongoing infection such as swelling, erythema, pain or drainage), the first dose of *S. aureus* candidate vaccine or placebo will be administered.
2. Subjects with an ongoing *S. aureus* SSTI (i.e. *S. aureus* is the most likely cause), as confirmed by positive culture performed outside the study procedures and not earlier than 30 days prior to ICF signature. Subjects with surgical site infections are not eligible for entry in this study. Diagnosis (e.g. abscess or cellulitis) and body location will be collected in the eCRF. In addition, *S. aureus* CCI [redacted] and recorded in the eCRF. These subjects will be enrolled whether they have or have not already started specific treatment of the infection. In case they have not started the treatment, this will be then given in compliance with the standard medical practice for the management of *S. aureus* SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures. After conclusion of the specific treatment for the skin lesion and after clinical resolution of the SSTI (e.g. no signs of ongoing infection such as swelling, erythema, pain or drainage), the first dose of *S. aureus* candidate vaccine or placebo will be administered.

The enrolment in the PoP phase will also follow a staggered approach. Enrolment will be stopped as soon as 40 subjects have been vaccinated with the first dose of the GSK *S. aureus* candidate vaccine or placebo. Only subjects who already signed the ICF and entered the screening phase, at the time of enrolment hold, will be allowed to continue the study; therefore, approximately 40 subjects (30 subjects receiving GSK *S. aureus* candidate vaccine and 10 receiving placebo) will be evaluated for safety. After the iSRC evaluation of unblinded safety data collected up to the Day 8 after first dose (including laboratory assessments) for the last vaccinated subject of this staggered subset has shown lack of safety issues, the full enrolment of the remaining subjects in the PoP epochs will continue with a randomisation of a 1:1 ratio either to the GSK *S. aureus* candidate vaccine or to the placebo group. The study will follow a group sequential design with two analyses. CCI [redacted]

CCI [redacted]

The subjects of the PoP vaccination and PoP follow-up epoch of the study will be evaluated in 2 parallel groups:

- **Group 5a Vaccine**: A series of 2 doses of *S. aureus* candidate vaccine (Sa-5Ag full dose adjuvanted) given approximately 2 months apart (Days 1 and 61)
- **Group 5b Placebo**: A series of 2 doses of placebo (saline) given approximately 2 months apart (Days 1 and 61)

The investigator will not be permitted to start the administration of the second dose in the staggered PoP subset (approximately 40 subjects) until receipt of the favourable outcome of the safety assessment performed by SRT and iSRC Chair, which needs to evaluate all the safety data available up to Day 68 (including laboratory assessments) related to the subjects of the fourth group (Full dose adjuvanted) of the dose-escalation safety lead-in step. Conditionally; unblinded data may be evaluated by iSRC and only after positive opinion of iSRC the next step (i.e. second dose of staggered PoP subset) can be started.

Subjects in the PoP vaccination epoch will be followed with an overall duration of participation for each subject of approximately 14 months.

Subjects will be monitored:

- For safety for the entire duration of the study.
- For recurrence of SSTI starting from Day 1 up to 12 months after last dose.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 2 Schedule of activities (dose-escalation safety lead-in epochs, Groups 1-3a/b)

Epoch		Dose-escalation safety lead-in screening	Dose-escalation safety lead-in vaccination				
Type of contact	Group 1a/b Half dose non-adjuvanted Group 2a/b Full dose non-adjuvanted Group 3a/b Half dose adjuvanted	**V0-Grp1-3 Screening**	**V1-Grp1-3**	**V2-Grp1-3**	**V3-Grp1-3 phone call**	**V4-Grp1-3 phone call**	**V5-Grp1-3**
Time points		**Day –1***	**Day 1**	**Day 8**	**Day 31**	**Day 181 (M 6)**	**Day 366 (M 12)**
Sampling time points			**Pre-Vac1**				
Informed consent by subjects		●					
Check inclusion/exclusion criteria		●					
Physical examination		O	●				
Collect demographic data		●					
Vaccine(s)/Product(s)							
Study group and treatment number allocation			O				
Recording of administered treatment number			●				
Vaccine administration			●				
CCI [redacted]							
Safety assessments							
Medical history		●					
History of administration of adjuvanted vaccine		●					
Urine pregnancy test		●					
Check contraindications and warnings and precautions to vaccination		O	O				
Pre-vaccination body temperature			●				
Blood sampling for safety laboratory evaluation (~6 mL)		●		●			
Record any concomitant medication/vaccination		●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●	●
Distribution of eDiaries and training			O				
Review of eDiary data			O	O			
Return of eDiaries to the sites				O			
Phone contact					●	●	
Recording of solicited adverse events			O				

Epoch		**Dose-escalation safety lead-in screening**	**Dose-escalation safety lead-in vaccination**				
Type of contact	Group 1a/b Half dose non-adjuvanted Group 2a/b Full dose non-adjuvanted Group 3a/b Half dose adjuvanted	**V0-Grp1-3 Screening**	**V1-Grp1-3**	**V2-Grp1-3**	**V3-Grp1-3 phone call**	**V4-Grp1-3 phone call**	**V5-Grp1-3**
Time points		**Day –1***	**Day 1**	**Day 8**	**Day 31**	**Day 181 (M 6)**	**Day 366 (M 12)**
Sampling time points			**Pre-Vac1**				
Recording of unsolicited adverse events			●	●	●		
Occurrence of solicited AEs at the investigator's site within 30 minutes post-vaccination observation			●				
Reporting of pIMDs			●	●	●	●	●
Reporting of SAEs, pregnancies and pregnancy outcomes		●	●	●	●	●	●
Study Conclusion							●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
*CDISC is not calculating with Day 0, i.e. interval between Day –1 and Day 1 is 1 day.
a/b = vaccine/placebo
pIMDs = potential Immune-Mediated Diseases
SAE = Serious Adverse Event
Vac = Vaccination
M = Month
V = Visit

Table 3 Schedule of activities (dose-escalation safety lead-in epochs, Group 4a/b)

Epoch		Dose-escalation safety lead-in screening	Dose-escalation safety lead-in vaccination							
Type of contact	Group 4a/b Full dose adjuvanted	**V0-Grp4 Screening**	**V1-Grp4**	**V2-Grp4**	**V3-Grp4 phone call**	**V4-Grp4**	**V5-Grp4**	**V6-Grp4 phone call**	**V7-Grp4 phone call**	**V8-Grp4**
Time points		**Day –1***	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 68**	**Day 91 (M 3)**	**Day 241 (M 8)**	**Day 426 (M 14)**
Sampling time points			**Pre-Vac1**			**Pre-Vac2**				
Informed consent by subjects		●								
Check inclusion/exclusion criteria		●								
Physical examination		O	●			●				
Collect demographic data		●								
Vaccine(s)/Product(s)										
Study group and treatment number allocation			O							
Treatment number allocation for subsequent doses						O				
Recording of administered treatment number			●			●				
Vaccine administration			●			●				
CCI [redacted]										
Safety assessments										
Medical history		●								
History of administration of adjuvanted vaccine		●								
Urine pregnancy test		●				●				
Check contraindications and warnings and precautions to vaccination		O	O			O				
Pre-vaccination body temperature			●			●				
Blood sampling for safety laboratory evaluation (~6 m*L)*		●		●		●	●			
Record any concomitant medication/vaccination		●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●	●
Distribution of eDiaries and training			O			O***				
Review of eDiary data			O	O		O	O			
Return of eDiaries to the sites							O			
Phone contact					●			●	●	

Epoch		**Dose-escalation safety lead-in screening**	**Dose-escalation safety lead-in vaccination**							
Type of contact	Group 4a/b Full dose adjuvanted	**V0-Grp4 Screening**	**V1-Grp4**	**V2-Grp4**	**V3-Grp4 phone call**	**V4-Grp4**	**V5-Grp4**	**V6-Grp4 phone call**	**V7-Grp4 phone call**	**V8-Grp4**
Time points		**Day –1***	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 68**	**Day 91 (M 3)**	**Day 241 (M 8)**	**Day 426 (M 14)**
Sampling time points			**Pre-Vac1**			**Pre-Vac2**				
Recording of solicited adverse events			O			O				
Recording of unsolicited adverse events			●	●	●	●	●	●		
Occurrence of solicited AEs at the investigator's site within 30 minutes post-vaccination observation			●			●				
Reporting of pIMDs			●	●	●	●	●	●	●	●
Reporting of SAEs, pregnancies and pregnancy outcomes		●	●	●	●	●	●	●	●	●
Study Conclusion										●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
*CDISC is not calculating with Day 0, i.e. interval between Day –1 and Day 1 is 1 day.
CCI .
***Remind subjects that the device is now ready to collect after Dose 2 data
a/b = vaccine/placebo
CCI
pIMDs = potential Immune-Mediated Diseases
SAE = Serious Adverse Event
Vac = Vaccination
M = Month
V = Visit

Table 4 Schedule of activities (Group 5a/b, PoP screening epoch, PoP vaccination epochs)

Epoch	PoP screening	PoP vaccination										
Type of contact	**V0**	**V1**	**V2 Clinic visit or Phone call[e]**	**V3**	**V4 Phone call**	**V5**	**V6 Clinic visit or Phone call [e]**	**V7**	**V8 Phone call**	**V9 Phone call**	**V10**	**Unscheduled visit[h]**
Time points	**Day –30[a]**	**Day 1**	**Day 8**	**Day 15**	**Day 31**	**Day 61**	**Day 68**	**Day 75**	**Day 91 (M 3)**	**Day 241 (M 8)**	**Day 426 (M 14)**	
Sampling time points		**Pre-Vac1**				**Pre-Vac2**						
Informed consent by subjects	●											
Check inclusion/exclusion criteria	●	●										
Physical examination	O	●				●						
Verification of clinical resolution of SSTI		●										
Collect demographic data	●											
Vaccine(s)/Product(s)												
Study group and treatment number allocation		O										
Treatment number allocation for subsequent doses						O						
Recording of administered treatment number		●				●						
Vaccine administration		●				●						
CCI [redacted]												
Clinical Specimens for microbiology assessments												
Sampling of drainage for cultures performed in the study	●											●[c]
Check of culture test report for SA-SSTI confirmation	●											●
CCI [redacted]												
Safety assessments												
Medical history	●	●										
History of administration of adjuvanted vaccine	●	●										
Urine pregnancy test	●	●				●						

Epoch	**PoP screening**	**PoP vaccination**										
Type of contact	**V0**	**V1**	**V2 Clinic visit or Phone call[e]**	**V3**	**V4 Phone call**	**V5**	**V6 Clinic visit or Phone call [e]**	**V7**	**V8 Phone call**	**V9 Phone call**	**V10**	**Unscheduled visit[h]**
Time points	**Day –30[a]**	**Day 1**	**Day 8**	**Day 15**	**Day 31**	**Day 61**	**Day 68**	**Day 75**	**Day 91 (M 3)**	**Day 241 (M 8)**	**Day 426 (M 14)**	
Sampling time points		**Pre-Vac1**				**Pre-Vac2**						
Check contraindications and warnings and precautions to vaccination	O	O				O						
Pre-vaccination body temperature		●				●						
Blood sampling for safety laboratory evaluation (~6 mL) (PoP Step 1 subjects only)[g]		●	●			●	●					
Phone contact (PoP Step 2 subjects only)			●				●					
Record any concomitant medication/vaccination		●	●	●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●	●	●	●
Distribution of eDiaries and training		O				O[f]						
Review of eDiary data		O	O				O					
Return of eDiaries to the sites								O				
Phone contact (all subjects)					●				●	●		
Recording of solicited adverse events		O				O						
Recording of unsolicited adverse events		●	●	●	●	●	●	●	●			
Occurrence of solicited AEs at the investigator's site within 30 minutes post-vaccination observation[i]		●				●						
Reporting of pIMDs		●	●	●	●	●	●	●	●	●	●	●
Reporting of SAEs, pregnancies and pregnancy outcomes	●	●	●	●	●	●	●	●	●	●	●	●
Study Conclusion											●	

● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
[a] CDISC is not calculating with Day 0, i.e. interval between Day –30 and Day 1 is 30 days.
CCI
[c] SSTI must be amenable to microbiological culturing per standard clinical practice.

CCI [redacted]

[e] Visit 2 and 6: Clinical visit for PoP Step 1 subjects (i.e. first 40 subjects enrolled in the PoP) where 6 m***L*** of whole blood for safety laboratory evaluation will be collected; Phone call for PoP Step 2 subjects (i.e. all those following subjects after the first 40 enrolled in the PoP Step 1).
[f] Remind subjects that the device is now ready to collect after Dose 2 data.
[g] The blood sampling for safety lab evaluation only (~6 mL to be drawn from PoP Step 1 subject only) should occur on Day 1 and Day 61 but, as an alternative, can be performed up to 1 day before vaccine administration.
[h] Unscheduled visits can occur at any time after first study vaccination and should happen as soon as possible after signs/symptoms onset
[i] Occurrence of solicited AEs within 30 minutes post vaccination observation must be recorded in the eCRF
a/b = vaccine/placebo

CCI [redacted]

CCI [redacted]

pIMDs = potential Immune-Mediated Diseases
SAE = Serious Adverse Event
Vac = Vaccination
M = Month
V = Visit

Whenever possible, the investigator should arrange study visits within the intervals described in Table 5 and Table 6.

Table 5 Intervals between study visits (dose-escalation safety lead-in epochs)

Groups	Interval	Optimal Length of interval	Allowed interval
Group 1a/b Group 2a/b Group 3a/b	V0-Grp1-3 (Day -1)→ V1-Grp1-3 (Day 1)	1 days	0 - 3 days *
	V1-Grp1-3 (Day 1)→ V2-Grp1-3 (Day 8)	7 days	7 - 8 days
	V1-Grp1-3 (Day 1)→ V3-Grp1-3 (Day 31)	30 days	30 - 33 days
	V1-Grp1-3 (Day 1)→ V4-Grp1-3 (Month 6, Day 181)	180 days	180 - 190 days
	V1-Grp1-3 (Day 1)→ V5-Grp1-3 (Month 12, Day 366)	365 days	365 - 380 days
Group 4a/b	V0-Grp4 (Day –1)→ V1-Grp4 (Day 1)	1 days	0 - 3 days *
	V1-Grp4 (Day 1)→ V2-Grp4 (Day 8)	7 days	7 - 8 days
	V1-Grp4 (Day 1)→ V3-Grp4 (Day 31)	30 days	30 - 33 days
	V1-Grp4 (Day 1)→ V4-Grp4 (Day 61)	60 days	60 - 67 days
	V4-Grp4 (Day 61)→ V5-Grp4 (Day 68)	7 days	7 - 9 days
	V4-Grp4 (Day 61)→ V6-Grp4 (Month 3, Day 91)	30 days	30 - 40 days
	V4-Grp4 (Day 61)→ V7-Grp4 (Month 8, Day 241)	180 days	180 - 190 days
	V4-Grp4 (Day 61→ V8-Grp4 (Month 14, Day 426)	365 days	365 - 380 days

a/b = vaccine/placebo; GRP = Group; V = Visit
Note: CDISC is not calculating with Day 0, i.e. interval between Day –1 and Day 1 is 1 day.
*The minimum interval of 0 days means that screening and vaccination is on the same day and automatically the screening is then for this subject on Study Day 1.

Table 6 Intervals between study visits (PoP epochs)

Group 5a/b	Interval	Length of interval	Allowed interval
All subjects	V0 (Day -30 up to Day 1)→ V1 (Day 1)	up to 30 days	0 - 30 days*
	V1 (Day 1)→V2 (Day 8)	7 days	7 - 9 days
	V1 (Day 1)→V3 (Day 15)	14 days	14 - 21 days
	V1 (Day 1)→V4 (Day 31)	30 days	30 - 37 days
	V1 (Day 1)→V5 (Day 61)	60 days	60 - 67 days
	V5 (Day 61)→V6 (Day 68)	7 days	7 - 9 days
	V5 (Day 61)→V7 (Day 75)	14 days	14 - 21 days
	V5 (Day 61)→V8 (Month 3, day 91)	30 days	30 - 40 days
	V5 (Day 61)→V9 (Month 8, day 241)	180 days	180 - 190 days
	V5 (Day 61)→V10 (Month 14, day 426)	365 days	365 - 380 days

a/b = vaccine/placebo; PoP = Proof of Principle; V = Visit
Note: CDISC is not calculating with Day 0, i.e. interval between Day –30 and Day 1 is 30 days.
* Vaccination should occur after clinical resolution of culture confirmed SSTI caused by *S. aureus* and must occur within 30 days from the date of skin drainage for microbiology assessment (done either outside or in the study)

3. INTRODUCTION

3.1. Study rationale

The purpose of this seamless Phase I/II first time in human - proof of principle (FTIH-PoP) study is to evaluate safety and reactogenicity, to perform a preliminary evaluation of clinical efficacy and to explore immunogenicity of GSK Biologicals' *S. aureus* vaccine compared to placebo (saline), both administered in a 2-dose schedule on Day 1 and Day 61.

There are no established correlates of protection for immunity against *S. aureus* infections, and therefore trials aimed at evaluating only safety and immunogenicity cannot currently predict vaccine efficacy. For this reason, an early evaluation of the efficacy of the candidate vaccine in this FTIH clinical trial is intended to provide an early reliable PoP that will serve to better guide future vaccine development. CCI [redacted]

3.2. Background

3.2.1. Skin and soft tissue infections caused by *S. aureus*

S. aureus is a gram-positive bacterium causing a spectrum of illnesses varying from mild to life-threatening diseases and it is considered as a major cause of morbidity and mortality despite the availability of several anti-staphylococcal antibiotics. The clinical pattern of *S. aureus* infections includes:

- SSTI (impetigo, cellulitis, furuncles, and abscesses)
- Surgical wound infections
- Bacteraemia including sepsis and septic shock
- Respiratory tract infections (pneumonia including necrotizing pneumonia)
- Musculoskeletal infections (arthritis, osteomyelitis, pyomyositis, necrotizing fasciitis)
- Endocarditis
- Device-related infections
- Toxin-mediated illnesses

There is a high medical need worldwide for a vaccine against *S. aureus* infections. It is a leading cause of surgical site infections (SSI), bloodstream infections (BSI), hospital-acquired pneumonia (HAP), and community-acquired skin and soft tissue infections (CA-SSTI) [Pozzi, 2017], [Lowy, 1998], [Knox, 2015]. It is among the species with highest antibiotic resistance and currently no vaccine is available on the market.

The World Health Organization [WHO, 2017] and the Centre for Disease Control and Prevention [CDC, 2013] recently listed human pathogens with threatening drug-resistance patterns with respectively global relevance or more specifically for the US: *S. aureus* is included in both lists. A recent assessment made by the European Medicines Agency (EMA) includes *S. aureus* as one of the major indicators as regards surveillance of antimicrobial resistance and antimicrobial consumption in humans [EFSA, 2017]. Standard of care for most infections is based on antibiotic therapy, which is not always sufficiently effective and leaves a considerable unmet medical need. CCI [redacted] causes more than 11, 000 deaths per year in the US and more than 5,400 deaths in EU [Pozzi, 2017].

Infections significantly increase length of hospital stay. In EU 1,050,000 extra days of hospitalization, with extra costs of € 380 million annually have been reported [Kock, 2010]. Recently bundle measures that included screening, decolonization, and targeted antibiotic prophylaxis of patients prior to surgery were shown to slightly, but significantly, reduce *S. aureus* post-operative infection rate in US hospitals [Schweizer, 2015].

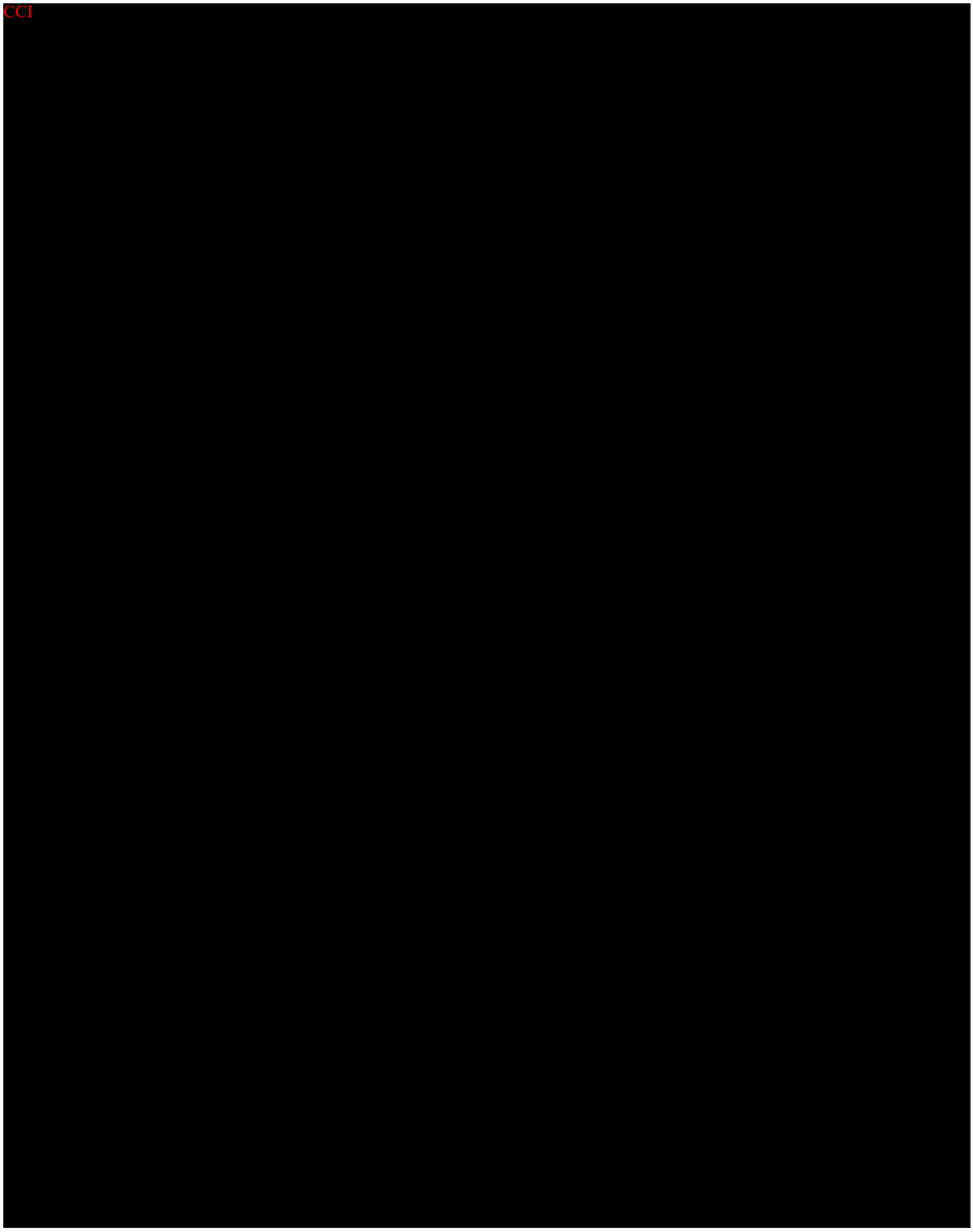
An efficacious vaccine would reduce the significant costs associated with bundle measures, could prevent the further increase of antibiotic resistance as well as all the infections not prevented by the bundles.

The virulence of *S. aureus* involves the coordinated expression of a large number of surface and secreted proteins implicated in different aspects of pathogenesis [Cheng, 2011], [Pozzi, 2015]. The ability of *S. aureus* to cause a wide variety of infections depends on the expression of numerous virulence factors. Moreover, *S. aureus* has evolved immune escape mechanisms as well as strategies to survive on inert surfaces (e.g., medical devices) and to persist in biofilms.

In view of the complexity of *S. aureus* virulence mechanisms and of failed *S. aureus* vaccine attempts that targeted only one single virulence factor, a multi-component vaccine approach is considered essential [Daum, 2012].

CCI [redacted]

CCI



CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

3.3. Benefit/Risk assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of *S. aureus* candidate vaccine.

The following section outlines the risk assessment and mitigation strategy for this study protocol.

3.3.1. Risk assessment

Important/Potential/Identified/Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
GSK *S. aureus* candidate vaccine		
Theoretical risk of acquiring a vaccine-induced immune-mediated disease after vaccination.	No confirmed signals related to this potential risk have been identified to date.	Close monitoring of potential immune-mediated diseases (pIMDs) in clinical development programs using adjuvants systems (AS). The potential risk of events of possible immune aetiology occurring is mentioned in the ICF. In addition, the ICF advises subjects to contact the study doctor or the study staff immediately, should they get any symptoms that they feel may be serious.
Study Procedures		
Risk of blood sampling.	Blood sampling associated risk of syncope, dizziness, infection at the site after or during venipuncture.	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the subject's health (see Table 2, Table 3, Table 4 and Section 8.4.2.2).
Other		
Potential increase of mortality after *S. aureus* infection in subjects with low IL-2 and IL-17A before vaccination	An increased mortality rate was seen in a vaccine study [McNeely, 2014] in subjects with low IL-2 and IL-17A before vaccination with iron-regulated surface determinant B (IsdB) staphylococcal vaccine who subsequently underwent cardio-thoracic surgery and experienced a *S. aureus* infection post-surgery.	The composition of the GSK *S. aureus* candidate vaccine is different from the composition used in the study [McNeely, 2014], i.e. IsdB is not a component. Baseline values of IL-2 and IL17A will be measured and assessed together with safety data.
Risk to receive placebo	Subjects will have the risk of local reactions due to an injection without the benefit of efficacy. Placebo (saline) cannot be expected to have any effect on SSTI recurrences.	Injection will be given by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation, swelling, redness or other injection site reactions is explained in the ICF.

3.3.2. Benefit assessment

- Administration of the vaccine may reduce the risk of recurrences of *S. aureus* SSTIs.
- Contribution to the process of developing a vaccine against treatment/antibiotic resistant *S. aureus* infections.
- Medical evaluations/assessments associated with study procedures (i.e. physical examination).

3.3.3. Overall Benefit: Risk conclusion

The investigational GSK *S. aureus* candidate vaccine is currently in an early stage of clinical development with no vaccine efficacy demonstrated. With the measures taken to minimize the risks to subjects participating in this study, the potential risks are justified by the potential benefits linked to development of this vaccine.

4. OBJECTIVE(S) AND ENDPOINT(S)

Table 9 Study objectives and endpoints

Objectives	Endpoints
Primary	
Descriptive: • To assess safety and reactogenicity of investigational *S. aureus* vaccine	• Occurrence and intensity of solicited local and general AEs during 7 days after each dose (i.e. day of vaccination and the 6 subsequent days) in all subjects by vaccination group. • Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days after each dose (i.e. day of injection and the 29 subsequent days) in all subjects by vaccination group. • Occurrence, intensity and relationship to vaccination of all SAEs in all subjects by vaccination group: – Groups 1 to 3 from Day 1 (day of vaccination) until Day 366. – Groups 4 and 5 from Day 1 (day of vaccination) until Day 426. • Occurrence, intensity and relationship to vaccination of all potential immune-mediated disease (pIMDs) during in all subjects by vaccination group. – Groups 1 to 3 from Day 1 (day of vaccination) until Day 366. – Groups 4 and 5 from Day 1 (day of vaccination) until Day 426. – Occurrence of haematological and biochemical laboratory abnormalities, and changes from the baseline values after vaccination: – In all subjects of Groups 1 to 3 on Day 8. – In all subjects of Group 4 on Days 8 and 68 (i.e. 7 days after dose 1 and dose 2), respectively. – Subjects in Group 5 Step 1 (i.e. first 40 subjects enrolled in the PoP) on Days 8 and 68 (i.e. 7 days after dose 1 and dose 2), respectively.

Objectives	Endpoints
Secondary	
Confirmatory: • To evaluate vaccine efficacy (VE) in the prevention of recurrent culture confirmed *S. aureus* SSTIs compared to placebo	• Key secondary endpoint: Number of subjects with at least one culture confirmed case of recurrent *S. aureus* SSTI starting from Day 75 (i.e.14 days after the second dose) up to 12 months after the second dose • Secondary endpoint: Number of subjects with at least one culture confirmed case of recurrent *S. aureus* SSTI starting from Day 15 (i.e. 14 days after the first dose) up to 12 months after the second dose
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	[redacted]

Ab = Antibody; AE = Adverse Event; CD = Cluster of Differentiation EAP = Exploratory Analysis Plan; CCI [redacted] CCI [redacted]
pIMDs = potential Immune-Mediated Disease; SAE = Serious Adverse Events; CCI [redacted]; SSTI = Skin and Soft Tissue Infection; VE = Vaccine Efficacy; CCI [redacted]

5. STUDY DESIGN

5.1. Scientific rationale for study design

The rationale for the vaccine composition and dosage is provided in Section 3.2.2.

This is a seamless Phase I/II self-contained study comprising of 2 phases: the study design comprises a combined FTIH evaluation and PoP demonstration aiming to provide an agile pathway from the concept to the clinical PoP.

CCI [redacted] the *S. aureus* vaccine candidate is a FTIH, considering that any new combination of antigens/adjuvants and vaccine technology are always considered as a new product from a safety perspective. For this reason, the study begins with a dose-escalation safety lead-in phase in healthy subjects (Phase I). The dose-escalation safety lead-in phase will investigate half dose and full dose non-adjuvanted and adjuvanted vaccine with a staggered vaccination approach and includes safety review checkpoints by safety assessment committees (SRT/ iSRC). For details of study design refer to Section 5.2; details about the internal safety evaluation by iSRC will be described in the iSRC Charter.

The primary objective of this FTIH study is the assessment of safety and reactogenicity of the investigational *S. aureus* vaccine.

Endpoints and statistical considerations of the secondary objective “vaccine efficacy (VE) in the prevention of recurrent culture confirmed *S. aureus* SSTIs compared to placebo” are based on the results of a study (207908 [EPI-STAPH-006 BOD DB]) which retrospectively reviewed the databases of three hospitals in the US that had available data on SSTI. The retrospective review focused on adult outpatients attending the outpatient and emergency departments and that were diagnosed with SSTI with the purpose of investigating the frequency of *S. aureus* SSTIs.

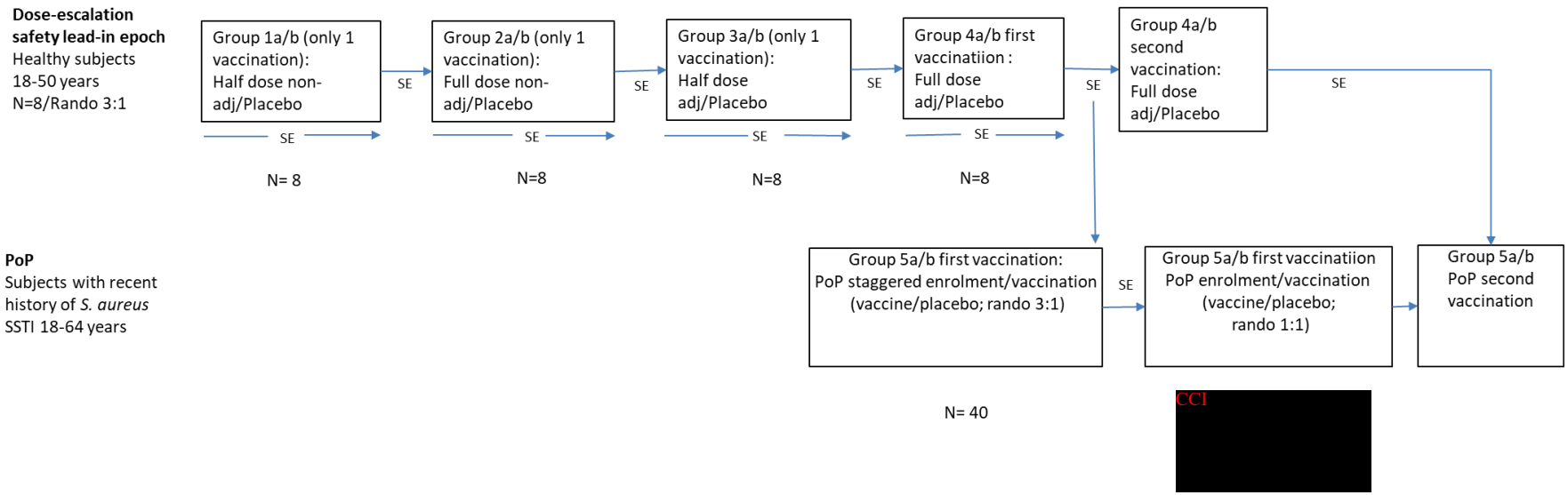
CCI [redacted]. Since there is currently no licensed vaccine against *S. aureus* infections the comparator group will receive placebo (saline).

In the protocol ahead, Phase I is called as the dose-escalation safety lead-in or safety lead-in phase and Phase II is called as PoP phase.

5.2. Overall design

Figure 4 presents a high-level overview of the whole study design. More detailed figures are provided in the respective subsections for dose-escalation safety lead-in (Figure 5) and PoP (Figure 6).

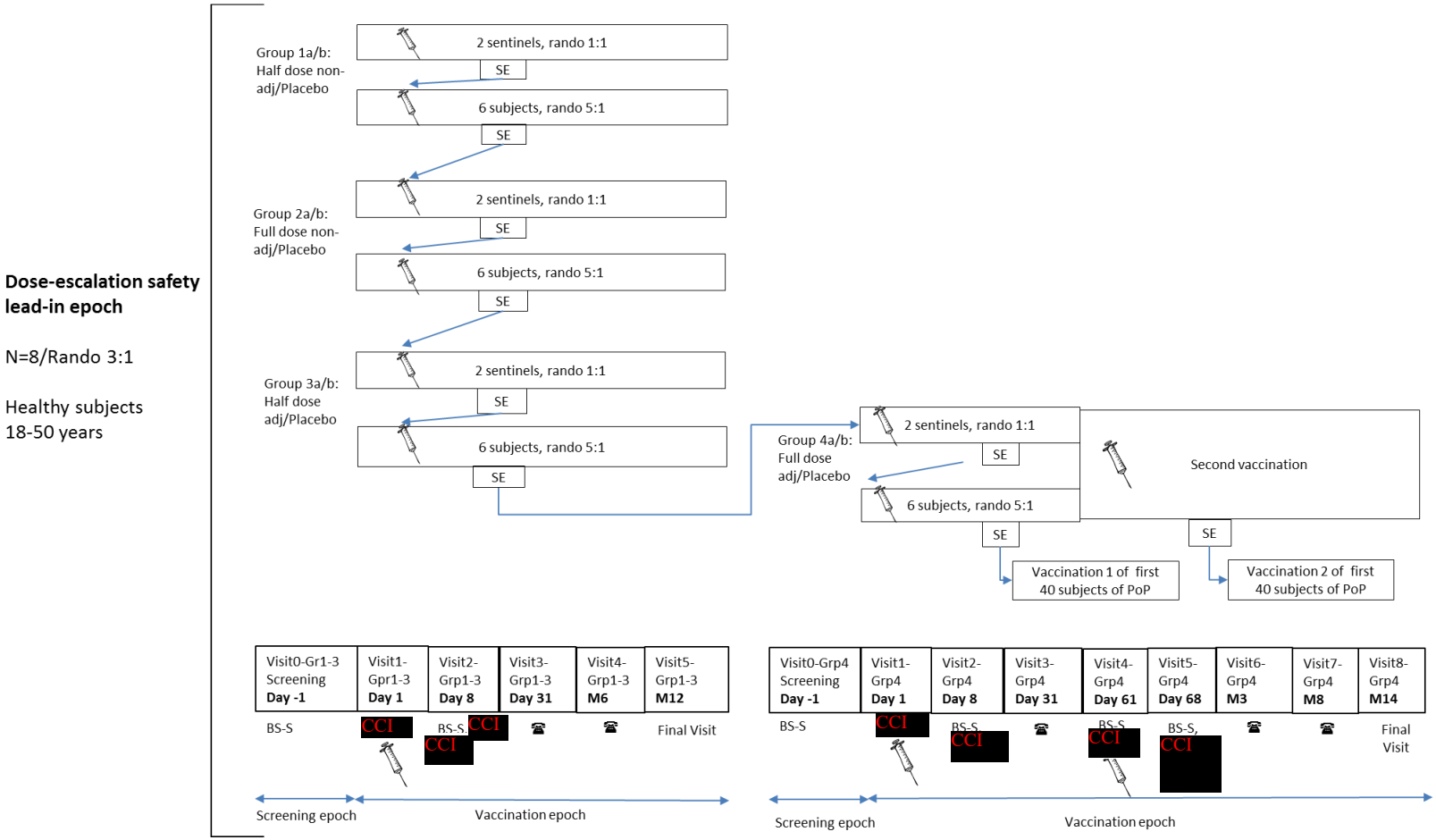
Figure 4 Overall design



adj = adjuvanted
Grp = Group
a/b = vaccine/placebo
Rando = Randomisation
SE = Safety evaluation by SRT/ iSRC chair (blinded review) or iSRC (unblinded review), for details refer to Section 8.6
PoP = Proof of Principle

5.2.1. Dose-Escalation safety lead-in healthy subjects (Phase I)

Figure 5 Study design overview dose-escalation safety lead-in healthy subjects Groups 1-4a/b



CDISC is not calculating with Day 0, i.e. interval between Day –1 and Day 1 is 1 day.
Grp = Group
a/b = vaccine/placebo
adj = adjuvanted
Rando = Randomisation
SE = Safety evaluation by SRT/ iSRC chair (blinded review) or iSRC (unblinded review), for details refer to Section 8.6
PoP = Proof of Principle
M = Month
V = Vaccination
BS-S = Blood Sample for Safety evaluation

CCI [redacted]

- **Type of study:** self-contained
- **Experimental design:** Phase I, observer-blind, randomised, controlled, multi-centric study with staggered enrolment of subjects in 4 groups receiving different vaccine formulations in the dose-escalation safety lead-in epochs.
- **Duration of the study:**
  - Dose-escalation safety lead-in screening epoch: Groups 1 to 4 screening starting at Visit 0 (Day –1) and ending just before the Visit 1 (Day 1).
  - Dose-escalation safety lead-in vaccination epoch: Groups 1 to 3 starting with vaccination at Visit1-Grp1-3 (Day 1) and ending just before the Visit5-Grp1-3 (Month 12 [Day 366]). Group 4 starting with vaccination at Visit1-Grp4 (Day 1) and ending just before the Visit8-Grp4 (Month 14 [Day 426]).
- **Study groups:** Table 10

Table 10 Study groups, treatment and epochs foreseen in the study (dose-escalation safety lead-in)

Study Groups	Number of healthy subjects	Age (Min-Max)	Treatment name	Epochs (Blinding)	
				Dose-escalation safety lead-in screening (N/A)	Dose-escalation safety lead-in vaccination (observer-blind)
Group 1a Half dose non-adj	6	18 - 50 years	Sa-5Ag half dose non-adjuvanted	●	●
Group 1b Placebo	2		Placebo	●	●
Group 2a Full dose non-adj	6	18 - 50 years	Sa-5Ag full dose non-adjuvanted	●	●
Group 2b Placebo	2		Placebo	●	●
Group 3a Half dose adj	6	18 - 50 years	Sa-5Ag half dose adjuvanted	●	●
Group 3b Placebo	2		Placebo	●	●
Group 4a Full dose adj	6	18 - 50 years	Sa-5Ag full dose adjuvanted	●	●
Group 4b Placebo	2		Placebo	●	●

N/A = Not Applicable
Note: For details regarding content and quantity of antigens and adjuvants refer to Table 12.

- **Control:** placebo control.
- **Vaccination schedule(s):**
  - **Group 1 Half dose non-adjuvanted** (first group), 2 parallel groups:
    - **Group 1a Half dose non-adj**.: 1 dose of Sa-5Ag half dose, non-adjuvanted at Day 1
    - **Group 1b Placebo**: 1 dose of placebo (saline) at Day 1

- **Group 2 Full dose non-adjuvanted** (second group), 2 parallel groups:
  - **Group 2a Full dose non-adj**.: 1 dose of Sa-5Ag full dose, non-adjuvanted at Day 1
  - **Group 2b Placebo**: 1 dose of placebo (saline) at Day 1
- **Group 3 Half dose adjuvanted** (third group), 2 parallel groups:
  - **Group 3a Half dose adj**.: 1 dose of Sa-5Ag half dose, adjuvanted at Day 1
  - **Group 3b Placebo**: 1 dose of placebo (saline) at Day 1
- **Group 4 Full dose adjuvanted** (fourth group), 2 parallel groups:
  - **Group 4a Full dose adj**.: A series of 2 doses of Sa-5Ag full dose, adjuvanted (*S. aureus* candidate vaccine, target vaccine formulation) given approximately 2 months apart (Days 1 and 61)
  - **Group 4b Placebo:** A series of 2 doses of placebo (saline) given approximately 2 months apart (Days 1 and 61)

For each group, the enrolment of 8 subjects with an overall randomisation of a 3:1 ratio either to the GSK *S. aureus* candidate vaccine or to the placebo group is planned (details are given below in bullet "Safety monitoring").

- **Treatment allocation:** randomised, subjects will be allocated to a study group using an automated, electronic System Built for Internet Randomisation (SBIR).
- **Blinding:** not applicable for screening epoch, vaccination epoch is observer-blind.
- **Sampling schedule:** Blood samples for laboratory safety evaluation and CCI [redacted] will be drawn from all subjects. Blood samples will be collected at the timepoints as detailed in Table 2 and Table 3.
- **Data collection:** standardised Electronic Case Report Form (eCRF). Solicited AEs will be collected using a subject Diary (electronic Diary [eDiary])
- **Safety monitoring:**

  For each group in the dose-escalation safety lead-in, a staggered enrolment of 8 subjects is planned as follows: 1 vaccinated subject + 1 subject receiving placebo (sentinel subjects) followed by 5 vaccinated subjects + 1 subject receiving placebo after safety assessment of safety data collected up to Day 8 (for details refer to Section 8.6). The 2 sentinel subjects in each group should be vaccinated on 2 different days.

  The fourth group (Full dose adjuvanted) will receive a second vaccine/placebo dose with an interval of approximately 2 months and subjects of all the groups will be followed until study end (i.e. for 12 months after last vaccination for each subject).

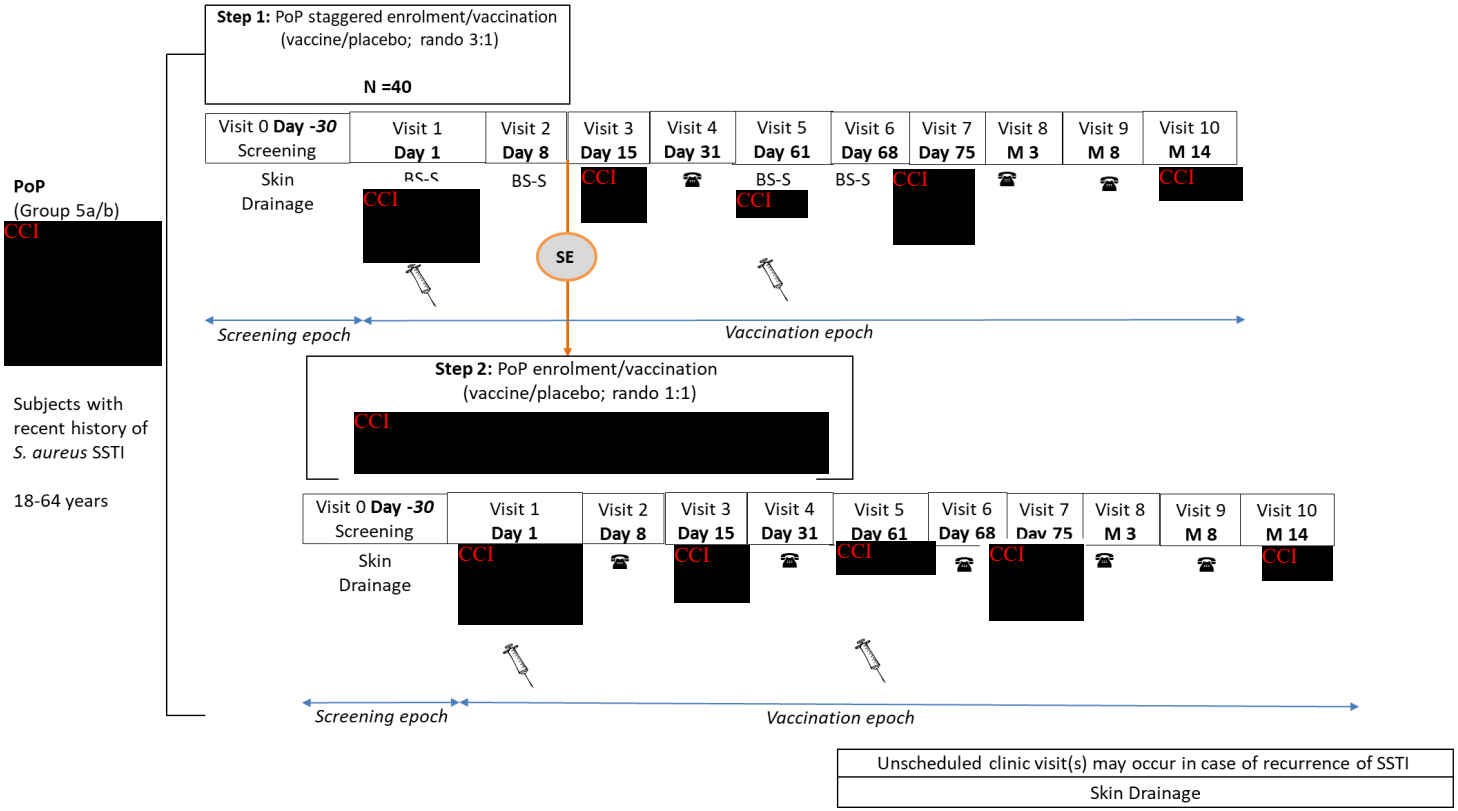
  The investigator is not permitted to start the administration of Dose 1 for the next group and Dose 2 in the fourth group until receipt of the favourable outcome of the safety evaluation as described in Section 8.6.1.

During the whole study period, if the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately (e.g. in case of death or any life-threatening SAEs).

Refer to Section 8.6 for detailed description of holding rules and safety monitoring. Refer to the iSRC Charter for details about the safety assessment committees evaluation.

5.2.2. PoP in subjects with recent S. aureus SSTI Group 5a/b (Phase II)

Figure 6 Study design overview PoP in subjects with a recent *S. aureus* SSTI



a/b = vaccine/placebo
SE = Safety evaluation by iSRC (unblinded), for details refer to Section 8.6
PoP = Proof of rinciple
SSTI = Skin and Soft Tissue Infection
Rando = Randomization
Vac = Vaccine

Plac = Placebo
M = Month
V = Vaccination
BS-S = Blood Sample for Safety evaluation.
CCI

Note: CDISC is not calculating with Day 0, i.e. interval between Day –30 and Day 1 is 30 days.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (Section 2), is essential and required for study conduct.

- **Type of study:** self-contained
- **Experimental design:** Phase II, observer-blind, randomised, controlled, group sequential, multi-centric study with 2 parallel groups in the PoP vaccination epoch.
- **Duration of the study:**
  - PoP screening epoch: starting at Visit 0 and ending just before Visit 1.
  - PoP vaccination epoch: starting with vaccination at Visit 1 and ending just before Visit 10.

In the PoP screening epoch, study subjects can be selected according to the following ways:

1. Subjects with signs and symptoms of an ongoing skin infection and purulent lesion, i.e. SSTI, suspected to be caused by *S. aureus* will be enrolled after signing an informed consent form (ICF). Subjects with surgical site infections are not eligible for entry in this study. After demonstration of *S. aureus* positive culture, performed as a study procedure, and confirmation by investigator that *S. aureus* is the most likely cause of SSTI, subjects will continue in the study. Diagnosis (e.g. abscess or cellulitis) and body location will be collected in the eCRF. In addition, data related to *S. aureus* CCI [redacted] and recorded in the eCRF. Specific treatment will be given in compliance with the standard medical practice for the management of *S. aureus* SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures. After conclusion of the specific treatment for the skin lesion and after clinical resolution of the SSTI (e.g. no signs of ongoing infection such as swelling, erythema, pain or drainage), the first dose of *S. aureus* candidate vaccine or placebo will be administered.
2. Subjects with an ongoing *S. aureus* SSTI (i.e. *S. aureus* is the most likely cause), as confirmed by positive culture, performed outside the study procedures and not earlier than 30 days prior to ICF signature. Subjects with surgical site infections are not eligible for entry in this study. Diagnosis (e.g. abscess or cellulitis) and body location will be collected in the eCRF. In addition, CCI [redacted] and recorded in the eCRF. These subjects will be enrolled whether they have or have not already started specific treatment of the infection. In case they have not started the treatment, this will be then given in compliance with the standard medical practice for the management of *S. aureus* SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures. After conclusion of the specific treatment for the skin lesion and after clinical resolution of the SSTI (e.g. no signs of ongoing infection such as swelling, erythema, pain or drainage), the first dose of *S. aureus* candidate vaccine or placebo will be administered.

The enrolment and vaccination in the PoP phase will also follow a staggered approach. Details are given below in bullet "Safety monitoring" and Section 8.6.1. The study will follow a group sequential design with two analyses. CCI [redacted]). It is estimated that then a total of approximately 500 to 600 subjects will be vaccinated in the PoP CCI [redacted]

- **Primary Completion Date (PCD):** Visit 10 (Month 14 [Day 426])

Refer to glossary of terms for the definition of PCD.

- **End of Study (EoS):** Last subject last visit (LSLV) (Visit 10).

Refer to glossary of terms for the definition of EoS.

- **Study groups:** Table 11

Table 11 Study groups, treatment and epochs foreseen in the study (PoP epochs)

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Epochs (Blinding)	
				PoP screening (N/A)	PoP vaccination (observer-blind)
Group 5a Vaccine	250*	18 - 64 years	Sa-5Ag full dose adjuvanted	•	•
Group 5b Placebo	250*	18 - 64 years	Placebo	•	•

N/A = Not Applicable
*Design of the study is event driven and it can be only estimated that approximately 250 to 300 subjects per study group may be needed. Enrolment may continue until 27 events are reached.

- **Control:** placebo control
- **Vaccination schedule(s):**
  - **Group 5a Vaccine:** A series of 2 doses of *S. aureus* candidate vaccine (Sa-5Ag full dose adjuvanted) given approximately 2 months apart (Days 1 and 61)
  - **Group 5b Placebo:** A series of 2 doses of placebo (saline) given approximately 2 months apart (Days 1 and 61)
- **Treatment allocation:** randomised, subjects will be allocated to a study group using an automated, electronic system (SBIR).
- **Blinding:** not applicable for the screening epoch, and the vaccination epoch is observer-blind

- **Sampling schedule:**
  - Blood samples for laboratory safety evaluation will be drawn from the first 40 subjects enrolled (i.e. subjects belonging to PoP Step 1)

CCI [redacted]

  - Drainage samples will be taken from those subjects performing culture test as study procedures at screening (i.e. Visit 0) and from all subjects with recurrences at the time of recurrence.
- **Data collection:** standardised eCRF. Solicited AEs will be collected using a subject eDiary.
- **Safety monitoring:**

  The enrolment and vaccination in the PoP phase will also follow a staggered approach. After safety assessment (for details refer to Section 8.6.1) of the first vaccination of the first approximately 40 subjects (randomised with a 3:1 ratio either to the GSK *S. aureus* candidate vaccine or to the placebo group) the full enrolment of the remaining subjects in the PoP phase will continue. The remaining subjects will be randomised with a 1:1 ratio either to the GSK *S. aureus* candidate vaccine or to the placebo group.

  Safety of the subjects in the PoP vaccination epoch will be monitored for the entire duration of the study with an overall duration of participation for each subject of approximately 14 months (i.e. 12 months after last vaccination).

  For both, PoP staggered enrolment/vaccination and the PoP full enrolment/vaccination, the investigator is not permitted to start the administration of Dose 1 for the next group and Dose 2 until receipt of the favorable outcome of the safety evaluation as described in Section 8.6.1.

  During the whole study period, if the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately (e.g. in case of death or any life-threatening SAEs).

  Refer to Section 8.6 for detailed description of holding rules and safety monitoring. Refer to the iSRC Charter for details about the safety assessment committees evaluation.

5.3. Number of subjects

Dose-escalation safety lead-in epochs:

Approximately 32 subjects will be screened to achieve 32 randomised and 32 evaluable subjects for an estimated total of 8 evaluable subjects per treatment group. Withdrawals will not be replaced.

PoP epochs:

The design of the PoP phase of the study is event driven. Vaccination of subjects with a randomisation of a 1:1 ratio either to the GSK *S. aureus* candidate vaccine or to the placebo group is planned until [redacted]. It is estimated that a total of approximately 500 to 600 subjects will be vaccinated in the PoP.

Approximately 1000 to 1200 subjects may be screened to achieve 500 to 600 randomised and evaluable subjects for an estimated total of 250 to 300 evaluable subjects per treatment group. Withdrawals will not be replaced.

5.4. Subject and study completion

A subject is considered to have completed the study if he/she returns for the concluding visit as described below:

- **Dose-escalation safety lead-in:**
  - Groups 1 to 3: Visit5-Grp1-3
  - Group 4: Visit8-Grp4
- **PoP:**
  - All groups: Visit 10

Global completion of the study is required in order to provide sufficient subjects as defined in Section 10.1.

6. STUDY POPULATION

6.1. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written or witnessed informed consent obtained from the subject prior to performance of any study specific procedure.
- Subject satisfying screening requirements.
- Subjects who, after the nature of the study has been explained to them, have shown adequate comprehension of the study procedures and knowledge of study.

- A male or female:
  - Dose escalation and safety lead-in phase: Aged between 18 and 50 years of age, inclusive, at the time of first vaccination.
  - PoP phase: Aged between 18 and 64 years of age, inclusive, at the time of first vaccination.
- Female subjects of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause. Refer to Section 12.6.1 for definitions of women of child-bearing potential, menarche and menopause.
- Female subjects of childbearing potential may be enrolled in the study, if the subject (refer to Section 12.6.1.1 for definitions of woman of child bearing potential and adequate contraception):
  - has practiced adequate contraception for 30 days prior to vaccination,
  - has a negative pregnancy test on the day of enrolment, and
  - has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

Additional inclusion criteria only for subjects to be enrolled in the dose-escalation safety lead-in screening epoch:

- Healthy subjects as established by medical history, clinical examination and laboratory assessment.

Additional inclusion criteria only for subjects to be enrolled in the PoP screening epoch:

- Healthy subjects as established by medical history and clinical examination before entering into the study with an ongoing SSTI suspected to be caused by *S. aureus,* as diagnosed by investigator (before randomisation subjects have to be treated until clinical resolution of culture confirmed SSTI caused by *S. aureus*). SSTI must be amenable to microbiological culturing per standard clinical practice (i.e. recovery of drainage sample from abscess or suppurative cellulitis).

  OR

- Healthy subjects as established by medical history and clinical examination before entering into the study with an ongoing *S. aureus* SSTI (i.e. *S. aureus* is the most likely cause), as confirmed by a *S. aureus* positive culture performed outside the study procedures and not earlier than 30 days prior to ICF signature. Before randomisation subjects have to be treated until clinical resolution of the culture confirmed SSTI caused by *S. aureus*. These subjects will be enrolled whether they have or have not already started specific treatment of the infection. In case they have not started the treatment, this will be then given in compliance with the standard medical practice for the management of *S. aureus* SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures.

6.2. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study.

6.2.1. Medical conditions

6.2.1.1. Subjects to be enrolled in the dose-escalation safety lead-in epochs

- Any active or ongoing illness at screening and the time of injection.
- Body mass index (BMI) >40 kg/m^2.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Hypersensitivity to latex.
- Recurrent history of uncontrolled neurological disorders or seizures.
- History of any serious chronic or progressive disease according to the judgment of the investigator (e.g., neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease).
- History of potential immune-mediated disease (pIMD).

  Note: Please refer to Table 33 for a non-exhaustive list of pIMDs. If the subject has any condition on this list, they must be excluded unless the etiology is clearly documented to be non-immune-mediated. The investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin and thus meet the exclusion criteria.
- Clinical conditions that in the investigator's opinion represent a contraindication to intramuscular vaccination and blood draws.
- Known bleeding diathesis or any condition that may be associated with a prolonged bleeding time.
- Any clinically significant* haematological (haemoglobin level, white blood cell, lymphocyte, neutrophil, eosinophil, platelet count and red blood cell count) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine) laboratory abnormality.

  *The investigator should use his/her clinical judgement to decide which abnormalities are clinically significant as follows: all Haematology/ Biochemistry parameters should be within local laboratory normal ranges for the subject to be eligible, unless the laboratory abnormalities are of Grade 1 (Refer to Appendix 7, Section 12.7) and considered not clinically significant by the investigator. See Appendix 2, Section 12.2.2 for examples.

6.2.1.2. Subjects to be enrolled in the proof of principle epochs

Exclusion criteria to be considered at study entry:

- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination, including human immunodeficiency virus (HIV) infection, hyper IgE syndrome and chronic granulomatous disease (no laboratory testing required).
- Hypersensitivity to latex.
- Major congenital defects, as assessed by the investigator.
- Acute or chronic, clinically significant pulmonary, cardiovascular*, hepatic or renal functional abnormality, neoplasm, diabetes type 1 and uncontrolled diabetes type 2*, as determined by physical examination or laboratory screening tests.

  * Note: Well-controlled type 2 diabetes mellitus (HbA1c <7%) and well-controlled arterial hypertension (blood pressure <140/90 mmHg) can be considered for inclusion in the study.
- Body mass index (BMI) >40 kg/m^2.
- Recurrent history of uncontrolled neurological disorders or seizures.
- Any behavioural or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study.
- Clinical conditions that in the investigator’s opinion represent a contraindication to intramuscular vaccination and blood draws.
- Known bleeding diathesis or any condition that may be associated with a prolonged bleeding time.
- Individuals at risk for severe or life-threatening SSTIs (e.g., lymphatic or venous insufficiency, liver and kidney disease, IV drug use, etc.)
- History of potential immune-mediated disease (pIMD).

  Note: Please refer to Table 33 for a non-exhaustive list of pIMDs. If the subject has any condition on this list, they must be excluded unless the etiology is clearly documented to be non-immune-mediated. The investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin and thus meet the exclusion criteria.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.

Exclusion criterion to be considered at time of vaccination:

- Any clinically significant* haematological (haemoglobin level, white blood cell, lymphocyte, neutrophil, eosinophil, platelet count and red blood cell count) and/or biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine) laboratory abnormality at the time of vaccination.

  *The investigator should use his/her clinical judgement to decide which abnormalities are clinically significant as follows. All Haematology/ Biochemistry parameters should be within local laboratory normal ranges for the subject to be eligible, unless the laboratory abnormalities are of Grade 1 (Refer to Appendix 7, Section 12.7) and considered not clinically significant by the investigator. See Appendix 2, Section 12.2.2 for examples.

- Microbiological test results of drainage suggest that the SSTI etiology could be other than infection with *S. aureus* (i.e. culture shows presence of another pathogen that in the investigator's opinion could have caused the SSTI).

6.2.2. Prior/Concomitant therapy

The prior or concomitant therapies below are applicable as exclusion criteria for all subjects:

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine(s) during the period starting 30 days before the first dose of study vaccine(s)/placebo (Day -29 to Day 1), or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first vaccine/placebo dose. For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Cytotoxic therapy (e.g., medications used during cancer chemotherapy).
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study vaccine or planned administration during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 15 days before the first dose and ending 15 days after the last dose of vaccine(s) administration* with the exception of any non-adjuvanted influenza vaccine which may be administered ≥7 days before or after each study vaccination.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine, provided it is licensed and used according to its Product Information.

6.2.3. Prior/Concurrent clinical study experience

The prior or concurrent clinical study experiences below are applicable as exclusion criteria for all subjects:

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device).
- History of having received a vaccine against *S. aureus*.

6.2.4. Other exclusions

The other conditions below are applicable as exclusion criteria for all subjects:

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions before 2 months after completion of the vaccination series.
- History of chronic alcohol consumption and/or drug abuse. Chronic alcohol consumption is defined as: a prolonged period of frequent, heavy alcohol use; the inability to control drinking once it has begun; physical dependence manifested by withdrawal symptoms when the individual stops using alcohol; tolerance, or the need to use more and more alcohol to achieve the same effects; a variety of social and/or legal problems arising from alcohol use.
- Any study personnel or immediate dependants, family, or household member.

6.3. Criteria for temporary delay for enrolment and vaccination

Dose-escalation safety lead-in:

In the dose-escalation safety lead-in epochs time windows for the vaccination visits of first vaccination are too small to allow a delayed vaccination due to reasons mentioned below. They were only planned to allow sufficient time for the availability of results from haematology and chemistry laboratory evaluations before vaccination. For the first vaccination please refer to the exclusion criteria in Section 6.2.

In Group 4a/b the second vaccination may be postponed within the allowed time interval until transient circumstances cited below have been resolved:

- Subjects with haematological/biochemical values out of normal range which are expected to be temporary may be vaccinated at a later date within the allowed time interval.
- Acute disease and/or fever at the time of vaccination. Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity. Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be vaccinated at the discretion of the investigator.

- Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to vaccination.

PoP:

Vaccination for the PoP epochs may be postponed within the allowed time interval until transient circumstances cited below have been resolved:

- Subjects with haematological/biochemical values out of normal range which are expected to be temporary may be vaccinated at a later date within the allowed time interval.
- Acute disease and/or fever at the time of vaccination. Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity. Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be vaccinated at the discretion of the investigator.
- Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to vaccination.
- Initial SSTI is not clinically resolved per medical judgment of the investigator (e.g. signs of ongoing infection are evident such as swelling, erythema, pain or drainage).

6.4. Screen and baseline failures

Screening failures are defined as subjects who sign the ICF but do not enter the vaccination epoch of the study.

Dose-escalation safety lead-in:

Screening failures will be replaced to achieve the planned number of 8 subjects per study group.

PoP:

Screening activities will continue at sites until the target number of events is reached.

The following information will be collected in the eCRF for screening failures (dose-escalation safety lead-in and PoP):

- Informed consent.
- Demographic data.
- Inclusion/exclusion criteria.
- Screening conclusion.
- Concomitant medication/vaccination (if applicable).
- SAEs related to study participation, to concomitant use of GSK products or any fatal SAEs (if applicable).
- Microbiology results (PoP only) (if applicable).

7. TREATMENTS

Study treatment is defined as a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.

7.1. Treatments administered

Table 12 Treatments administered

Study Treatment Name:	Sa-5Ag half dose non-adjuvanted		Sa-5Ag full dose non-adjuvanted		Sa-5Ag half dose adjuvanted		Sa-5Ag full dose adjuvanted *		Placebo
Study intervention name	CCI								
Study intervention formulation:									
Presentation	Powder for solution for injection/ vial	Solution for injection/ vial	Powder for solution for injection/ vial	Solution for injection/ vial	Powder for solution for injection/ vial	Suspension for suspension for injection/ vial	Powder for solution for injection/ vial	Suspension for suspension for injection/ vial	Solution for injection/ vial or prefilled syringe******
Type	Study	Co-administration	Study	Co-administration	Study	Co-administration	Study	Co-administration	Control
Product category	Biological product	Biological product	Biological product	Biological product	Biological product	Biological product	Biological product	Biological product	Combination product
Route of Administration	IM		IM		IM		IM		IM

Study Treatment Name:	Sa-5Ag half dose non-adjuvanted	Sa-5Ag full dose non-adjuvanted	Sa-5Ag half dose adjuvanted	Sa-5Ag full dose adjuvanted *	Placebo
Administration site:					
Location	Deltoid	Deltoid	Deltoid	Deltoid	Deltoid
Directionality	Upper	Upper	Upper	Upper	Upper
Laterality ***	Non-dominant	Non-dominant	Non-dominant	Non-dominant	Non-dominant
Number of doses to be administered:	1	1	1	2****	1 or 2 ****
Volume to be administered *****	0.5 mL	0.5 mL	0.5 mL	0.5 mL	at least 0.5 mL
Packaging and Labelling	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	CCI [redacted]				

CCI [redacted] SPM = Study Procedures Manual

Note: The half dosage and the full dosage derive from the same product obtained by resuspending the lyophilised product with different volumes (NaCl CCI [redacted]

* *S. aureus* candidate vaccine

CCI [redacted]

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

**** The total number of doses is 1 or 2 depending on the study group, i.e. 2 doses only for subjects in group 4 dose-escalation safety lead-in treatment epoch and PoP treatment epoch

***** Refer to the SPM for the volume after reconstitution

****** The volume in the syringe may be between 0.6 mL and 0.8 mL. The full volume is to be injected.

After completing all prerequisite procedures prior to vaccination (refer to Section 7.7 regarding the contraindications to subsequent vaccination), 1 dose of reconstituted study vaccine or placebo will be administered intramuscularly (IM) in the deltoid preferably of the non-dominant arm (refer to Table 12 for details regarding the treatment administered).

If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine/placebo administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 5 and Table 6).

The subjects will be observed closely for at least 60 minutes following the administration of vaccine/placebo, with appropriate medical treatment readily available in case of anaphylaxis and syncope. Occurrence of solicited AEs within 30 minutes post vaccination observation must be recorded in the eCRF (Table 4).

7.2. Method of treatment assignment

7.2.1. Subject identification

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

7.2.2. Randomisation of treatment

7.2.2.1. Treatment allocation to the subject

The treatment numbers will be allocated by component.

7.2.2.1.1. Study group and treatment number allocation

Dose-escalation safety lead-in:

For each group, the enrolment of 8 subjects is planned as follows:

- 1 vaccinated subject + 1 subject receiving placebo (sentinel subjects).
  The 2 sentinel subjects in each group should be vaccinated on 2 different days.
- 5 vaccinated subjects + 1 subject receiving placebo approximately 8 days after vaccination of the sentinel subjects (for safety evaluation and consequence on study progress refer to Section 8.6.1).

PoP:

The target enrolment of subjects is event driven (CCI [redacted]). The enrolment in the PoP phase will also follow a staggered approach:

- The first approximately 40 subjects will be randomised with a 3:1 ratio (30 subjects receiving GSK *S. aureus* candidate vaccine and 10 receiving placebo).
- The remaining subjects in the PoP epochs will be enrolled approximately 8 days after the last of the approximately 40 subjects was vaccinated (for safety evaluation and consequence on study progress refer to Section 8.6.1). The subjects will be randomised with a 1:1 ratio either to receive the GSK *S. aureus* candidate vaccine or placebo until CCI [redacted] (event driven design). It is estimated that a total of approximately 500 to 600 subjects will be vaccinated in the PoP but enrolment may continue until 27 events is reached (see Section 10.1.2).

Allocation of the subject to a treatment number at the investigator site will be performed using a randomisation system on internet (SBIR). The randomisation algorithm will use a minimisation procedure (PoP only) accounting for site and for previous SSTIs yes or no within the last 12 months. Minimisation factors will have equal weight in the minimisation algorithm.

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will determine the study group and will provide the treatment number to be used for the first dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

7.2.2.1.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

7.3. Blinding and unblinding

Subjects will be randomised at Visit 1 (Day 1) before vaccination (dose-escalation safety lead-in and PoP).

From that timepoint onwards, data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine(s) recipient and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity, and efficacy) will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by authorised medical personnel who will not participate in any of the study clinical evaluation assays.

Each study site is responsible for having a blinding plan.

Two teams of study personnel will hence be set up:

- A team of unblinded personnel (responsible for the preparation and the administration of the vaccines/placebo)
- A team of blinded personnel (responsible for the clinical evaluation of the subjects).

  Refer to the SPM for guidance on vaccine preparation and administration while maintaining the blind.
- The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

The SBIR will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' treatment assignment is warranted. Please refer to the Section 7.3.1 for details regarding emergency unblinding.

7.3.1. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency when knowledge of the treatment is essential for the clinical management or welfare of the subject.

The emergency unblinding process consists of the automated Internet-based system (SBIR) that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

As back-up process, the investigator has the option of contacting a GSK Helpdesk (refer to Table 13) if he/she needs support to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Non-investigator physician (e.g. physician from emergency room) or subject/care giver/family member can also request emergency unblinding either via the investigator (preferred option) or via the GSK Helpdesk (back-up process). Contact details of investigator and GSK Helpdesk are reported in the patient/subject card.

Table 13 Contact information for emergency unblinding

GSK Helpdesk 24 hours/7 days availability
The Helpdesk is available by phone, fax and email Phone: +32 2 656 68 04 Fax: +32 2 401 25 75 email: rix.ugrdehelpdesk@gsk.com For US Toll-free number: 1 844 446 3133

GSK policy (which incorporates ICH E2A guidance, EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any SAE which is unexpected and attributable/suspected to be attributable to the study vaccine(s) prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the treatment assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Section 12.5.9.2).

A subject may continue in the study if that subject's treatment assignment is unblinded.

GSK VCSP staff may unblind the treatment assignment for any subject in case of Suspected Unexpected Serious Adverse Reaction (SUSAR) as well as in case of fatal or life-threatening cases. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.4. Handling, storage and replacement of study vaccine(s)/product(s)

7.4.1. Storage and handling of study vaccines

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorised study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines.

A temperature excursion is any temperature that is not in range of the label storage temperature conditions. Temperatures outside the range of label storage temperature conditions must be reported and/or documented. Temperature excursion impacting study vaccines must be reported and/or documented.

In the frame of the reporting, the lack/absence of temperature monitoring documentation from a device meeting GSK requirements has to be considered as a temperature excursion.

Study vaccine(s) that are impacted by a temperature excursion may not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g. Site Monitor).

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine(s).

7.4.2. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 10% additional vaccine/placebo doses will be supplied to replace those that are unusable.

The investigator will use SBIR to obtain the replacement dose number. The replacement numbers will be allocated by component. The system will ensure, in a blinded manner, that the replacement dose matches the formulation the subject was assigned to by randomisation.

7.5. Concomitant medication(s)/product(s) and concomitant vaccinations

7.5.1. Recording of concomitant medications/products and concomitant vaccinations

At each study contact, the investigator or delegate should question the subject about any medications/products taken and vaccinations received by the subject.

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

- All concomitant medications/products, except vitamins and dietary supplements, administered during a period of 30 days following the first (from Day 1 to Day 31) and the second (from Day 61 to Day 91) dose of study vaccine/placebo, as applicable according to the study group.
- Any concomitant vaccination administered during the whole study period.
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  An anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥38.0°C/100.4°F regardless the location of measurement]. The preferred location for measuring temperature in this study will be the oral cavity.

- Any concomitant medications/products/vaccines leading to the withdrawal or non-eligibility of the subject from the study. Please refer to the Section 7.5.2 for further details.
- Any concomitant medications/products/vaccines relevant to an SAE/pIMD to be reported as per-protocol or administered at any time during the study period for the treatment of an SAE/pIMDs. In addition, concomitant medications relevant to SAEs and pIMDs need to be recorded on the expedited Adverse Event report.
- Any concomitant medications/product/vaccines aiming to prevent the occurrence of *S. aureus* SSTI.

7.5.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See Section 10.2 for populations to be analysed.

For withdrawal of subjects from further vaccinations refer to Section 7.7 (contraindications against subsequent vaccination).

- Any investigational or non-registered product (drug or vaccine) other than the study vaccines used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- A vaccine not foreseen by the study protocol administered during the period starting 15 days before the first dose and ending 15 days after the last dose of vaccine(s)/placebo administration*, with the exception of any non-adjuvanted influenza vaccine which may be administered ≥7 days before or after each study vaccination.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine, provided it is licensed and used according to its Product Information.
- Immunoglobulins and/or any blood products administered during the study period.
- Drug and/or alcohol abuse.

7.6. Intercurrent medical conditions that may lead to elimination of a subject from per-protocol analyses

At each study visit subsequent to the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition that may lead to elimination from per-protocol analysis. If it is the case, the condition(s) must be recorded in the eCRF.

Subjects may be eliminated from the per-protocol set for efficacy and immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (e.g. malignancies) or are confirmed to have an alteration of their initial immune status.

7.7. Contraindications to subsequent vaccine(s) administration

Prior to receipt of additional study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination.

If subjects meet any of the original exclusion criteria or the criteria listed below, they should not receive additional vaccinations. However, the subjects should be encouraged to continue other study procedures at the discretion of the investigator (Section 8.5.5).

- Subjects who experience any serious adverse event judged to be possibly or probably related to study vaccine or non-study vaccines, including hypersensitivity reactions.
- Subjects who develop any new condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, exposes the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine(s). Refer to Section 12.5.5.1 for the definition of pIMDs.

7.8. Treatment after completion of the study

Not applicable.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in Section 2, Schedule of Activities.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness, to determine if the subject(s) should discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g. drainage, *S. aureus* confirmation) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

Under special circumstances, modification of specific study procedures may be implemented.

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.
- If the eDiary device was provided to the participant, it may be returned to the site by conventional mail after the end of the relevant data collection period .
- Blood samples for safety assessment may be collected at a different location[1] other than the study site or at participant's home. Blood samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

8.1. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

[1] It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.

8.2. Pre-vaccination procedures

8.2.1. Informed Consent

The signed/witnessed informed consent of the subject must be obtained before study participation (at the screening visit). Refer to Section 12.4.3 for the requirements on how to obtain informed consent.

8.2.2. Collection of demographic data

Record demographic data such as month and year of birth, sex, race and ethnicity in the subject's eCRF.

8.2.3. Medical/vaccination history

Obtain the subject's medical/vaccination history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject at the screening visit and for the PoP also at Visit 1 prior to the first study vaccination in the eCRF. Take note of whether the subject has had a SSTI within 12 months preceding the initial infection at study entry.

8.2.4. Physical examination

At the screening visit and at each vaccination visit a complete physical examination will be performed for all subjects.

Perform a physical examination of the subject, including assessment of resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Physical examination at other visits will be performed only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

Height and weight will be measured pre-vaccination, at visit 1.

Collected information at the pre-vaccination visits needs to be recorded in the eCRF.

If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the allowed time interval for this visit (see Table 5 and Table 6).

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

8.2.5. Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine(s)/placebo may only be administered if the pregnancy test is negative.

Note: Pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

8.2.6. Pre-vaccination body temperature

The oral body temperature of each subjects needs to be measured prior to any study vaccine(s)/placebo administration. If the subject has fever [fever is defined as body temperature ≥38.0°C/100.4°F regardless the location of measurement] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Section 6.3).

8.3. Case definition of recurrent *S. aureus* SSTI

Subjects that report signs or symptoms compatible with an SSTI are invited to present themselves for an *ad-hoc* visit. The investigator will assess whether the subject has an SSTI suspected to be caused by *S. aureus*, and whether the lesion is amenable to microbiological diagnostics (i.e. abscess with drainage or purulent cellulitis). Diagnosis (i.e. abscess or cellulitis) and body location will be collected in the eCRF. Samples for microbiological culture will be obtained whenever possible, and treatment will ensue according to the investigator's clinical judgment. Provided that the episode is a new (recurrent) SSTI, rather than incomplete resolution of a previous SSTI per investigators judgment, the case will be assessed as follows.

- If results from microbiological diagnostics in the investigator's opinion suggest that *S. aureus* is the primary cause of the SSTI, then the case will be considered as a culture confirmed recurrence.
- If results from microbiological diagnostics are inconclusive, or if no microbiological testing was performed, then the case will be considered as a suspected recurrence.
- If results from microbiological diagnostics suggest that another pathogen is the primary cause of the SSTI, or if no microbiological testing was performed and the investigator considers other causes for the lesion to be equally or more probable than infection by *S. aureus*, then the case will not be reported unless it fulfils other reporting requirements (e.g. AE).

Should the subject report an SSTI that has already occurred and resolved, e.g. because medical attention was sought elsewhere or not at all, the investigator will seek permission to obtain clinical records from the managing physician in order to evaluate the case per the above criteria.

8.4. Efficacy *and/or* immunogenicity assessments

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

Samples which will be sent to GSK laboratories or GSK designated laboratories will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

CCI [redacted]

It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

CCI [redacted]

Information on further investigations and their rationale can be obtained from GSK.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

The investigator is not allowed to do extra testing on samples including drainage samples outside of what has been agreed upon by the ethic committees.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK.

8.4.1. Use of specified study materials

When materials are provided by GSK, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the per-protocol analysis (see Section 10.2 for the definition of populations for analyses). The investigator must ensure that his/her personnel and the laboratory(ies)

under his/her supervision comply with this requirement. However, when GSK does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

8.4.2. Biological samples

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

8.4.2.1. Sampling for efficacy assessments

Skin drainage samples will be collected from those subjects in the PoP performing culture test as a study procedure at screening (i.e. Day –30 [Visit 0]) and from all subjects at the time of their recurrence of SSTI (i.e. unscheduled visits).

Drainage samples will not be stored.

Table 14 Biological samples for efficacy assessment (PoP)

Sample type	Quantity	Unit	Timepoint	Subjects
Drainage samples	Depends on availability		Day –30 (V0)	Subjects with SSTI who perform culture test as a study procedure at screening
			Unscheduled*	Subjects with suspected SA-SSTI

V = Visit
* Additionally, subjects with recurrent SSTI at the time of recurrence

8.4.2.2. Blood sampling for immunogenicity response assessments

Refer to the SPM for detailed information on sample collection and storage.

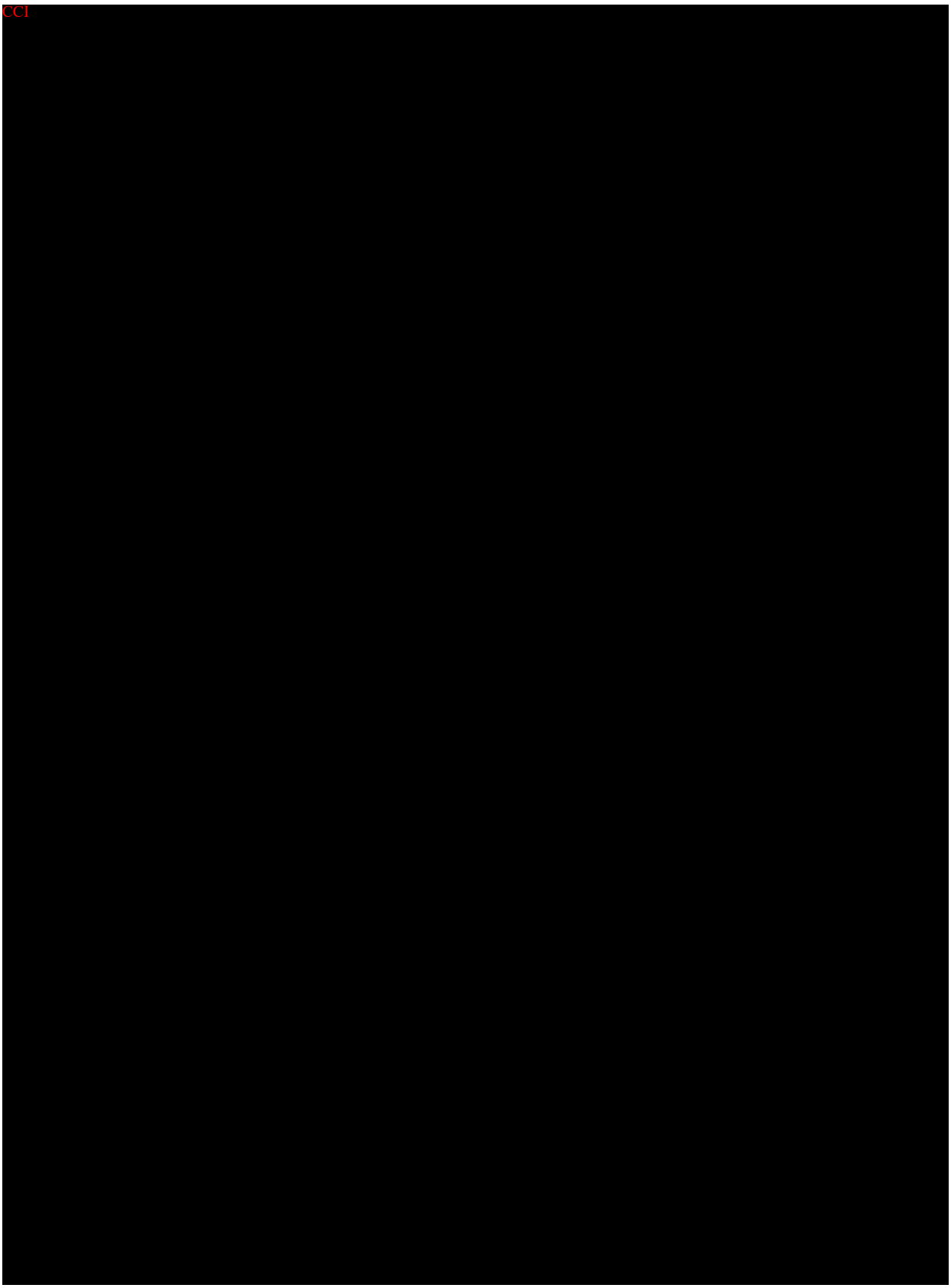
The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 125 mL for subjects participating in the dose-escalation safety lead-in and will not exceed 274 mL for subjects participating in the PoP.

Blood samples will be taken during certain study visits as specified in Section 2 Schedule of Activities (SoA). For more information regarding blood sampling for haematologal and chemistry evaluations refer to Section 8.5.7.

- In the dose-escalation safety lead-in:
  - A volume of at least approximately 10 mL of whole blood (to provide at least 3.3 mL of serum) should be drawn from all subjects for serum preparation at each pre-defined timepoint. After whole blood processing into serum, samples should be kept at –20°C (–4°F) or below until shipment.

CCI [redacted]

CCI



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[redacted]

8.4.3. Laboratory assays

Please refer to Section 12.2 (Appendix 2) for a description of the haematology/chemistry and immunological assays performed in the study. Please refer to Section 12.3 (Appendix 3) for the address of the clinical laboratories used for sample analysis.

8.4.3.1. Microbiology assessment for efficacy

Conventional bacteriological methods at the investigator's institution and/or at a laboratory designated by GSK Biologicals will be used to study the skin infection aetiology, and in particular to demonstrate if *S. aureus* is the leading bacterial cause of the infection. (Table 17). The laboratories that will perform microbiology assessment listed in Table 17 are not yet identified. Each laboratory will be performing the microbiological evaluations according to their own routine clinical practices.

Table 17 Microbiology

System	Component	Method	Laboratory
Skin drainage	*S. aureus* identification CCI [redacted]	Standard bacteriological methods	Investigator's institution and/ or at a laboratory designated by GSK Biologicals

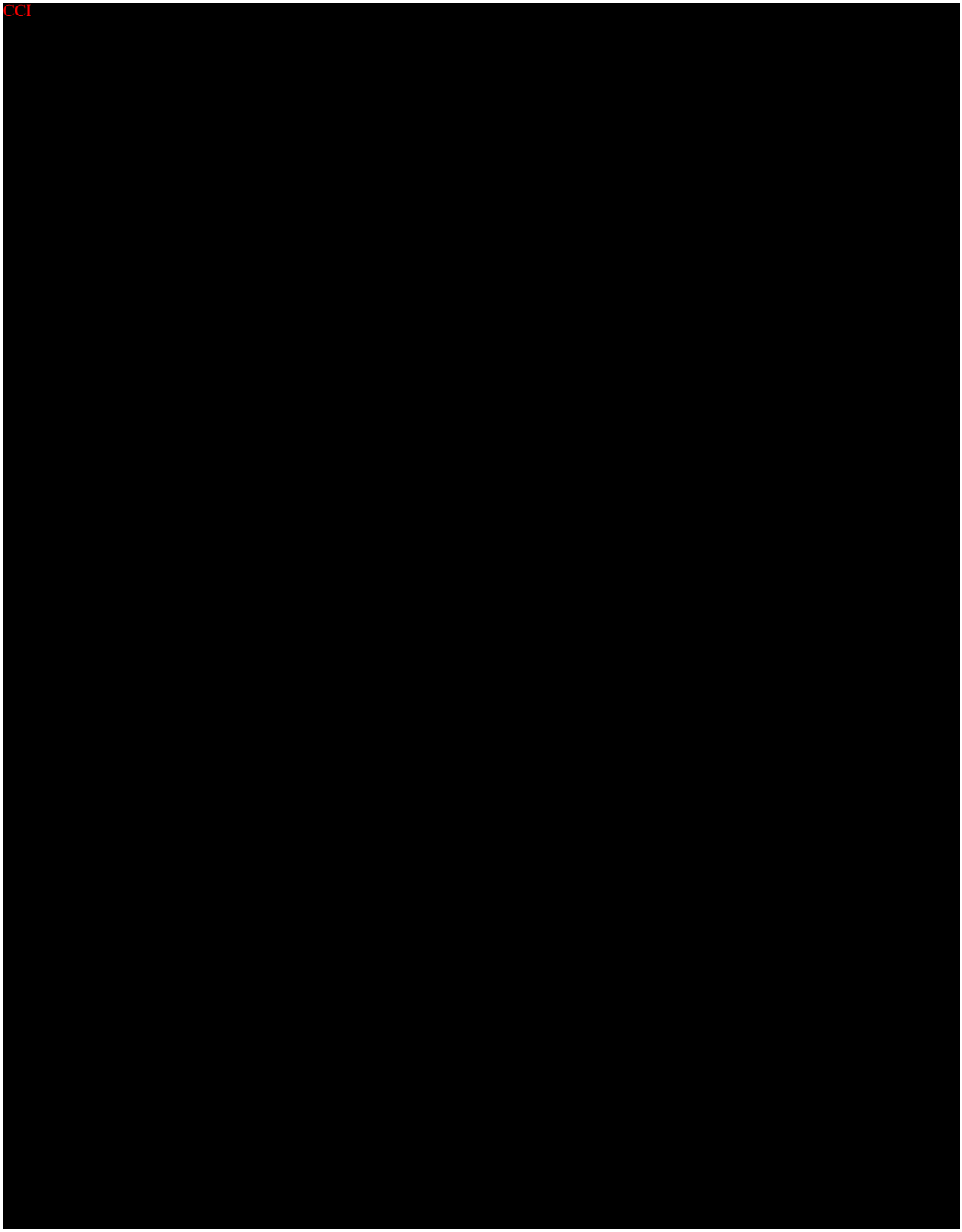
CCI

[redacted]

CCI

[redacted]

CCI



8.4.4. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far for *S. aureus*.

8.5. Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. This includes the assessment of COVID-19 cases per the WHO definition [WHO, 2020]. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue the this study.

8.5.1. Safety definitions

Please refer to Section 12.5 for safety definitions.

8.5.2. Time period and frequency for collecting AE and serious adverse event (SAE) information

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 21 for dose-escalation safety lead-in and Table 22 for PoP. Refer to the Section 12.5.8.1 for details on the time period for recording safety information.

Table 21 Reporting periods for collecting safety information (dose-escalation safety lead-in)

Event	Study group	Pre-Vac	Vac1			Vac2			Study Conclusion
	Half dose non-adjuvanted Full dose non-adjuvanted Half dose adjuvanted	D–1*	D1	D7	D30	NA	NA	NA	D366 M12
	Full dose adjuvanted	D–1*	D1	D7	D30	D61	D67	D90	D426 M14
Solicited local and general AEs									
Unsolicited AEs**									
AEs/SAEs leading to withdrawal from the study									
SAEs**									
SAEs related to the study vaccine(s)									
SAEs related to study participation or concurrent GSK medication/vaccine									
Pregnancies									
pIMDs									

* i.e. consent obtained.
** Unsolicited AEs/SAEs due to COVID-19 will be recorded according to the WHO case definition [WHO, 2020].
AEs = Adverse Events; SAEs = Serious Adverse Events; pIMDs = potential Immune-Mediated Diseases; Pre-Vac = Pre-Vaccination; Vac = Vaccination; D = Day; M = Month

Table 22 Reporting periods for collecting safety information (PoP)

Event	Study group	Pre-Vac	Vac1			Vac2			Study Conclusion
	Vaccine Placebo	D–30*	D1	D7	D30	D61	D67	D90	D426 M14
Solicited local and general AEs			■			■			
Unsolicited AEs**			■			■			
AEs/SAEs leading to withdrawal from the study			■						■
SAEs**			■						■
SAEs related to the study vaccine(s)			■						■
SAEs related to study participation or concurrent GSK medication/vaccine		■							■
Pregnancies			■						■
pIMDs			■						■

* i.e. consent obtained.
** Unsolicited AEs/SAEs due to COVID-19 will be recorded according to the WHO case definition [WHO, 2020].
AEs = Adverse Events; SAEs = Serious Adverse Events; pIMDs= potential Immune-Mediated Diseases; Pre-Vac = Pre-Vaccination; Vac = Vaccination; D = Day; M = Month

All SAEs will be recorded and reported via Expedited AE Reporting Form to the sponsor or designee immediately and under no circumstance should this exceed 24 hours after the investigator became aware of it, as indicated in Section 12.5 (Appendix 5). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 21 and Table 22. Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccine(s), the investigator will promptly notify the Study Contact for Reporting SAEs.

8.5.3. Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing intensity, causality and outcome of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.5.8.

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subjects is the preferred method to inquire about AE occurrence.

8.5.4. Reporting of serious adverse events, pregnancies, and other events

SAEs, pregnancies and pIMDs that occur in the time period defined in Section 8.5.2 will be reported promptly to GSK within the timeframes described in Table 23 once the investigator determines that the event meets the respective protocol definition.

Table 23 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	24 hours*	electronic pregnancy report	24 hours*	electronic pregnancy report
pIMDs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours*	Electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.
‡ The investigator will be required to confirm review of the SAE/pIMD causality within 72 hours of submission of the SAE/pIMD.

8.5.4.1. Contact information for reporting of serious adverse events (SAEs), pIMDs, pregnancies and study holding rules

Table 24 Contact information for reporting of serious adverse events (SAEs), pIMDs, pregnancies and study holding rules

Study contact for questions regarding SAEs, pIMDs, pregnancies and study holding rules Refer to the local study contact information document
Study Contact for Reporting of study holding rules As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the Local Medical Lead (LML).
Back-up Study Contact for Reporting SAEs, pIMDs, pregnancies and study holding rules 24 hours/7 days availability: GSK Clinical Safety & Pharmacovigilance **Outside US sites:** Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: Rix.CT-safety-vac@gsk.com US sites only: Fax: 1-610-787-7053

8.5.4.2. Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential for meeting legal obligations and ethical responsibilities for the safety of subjects and the safety of a study treatment under clinical investigation.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and pIMDs (serious and non-serious), will be followed until the event is resolved, stabilised, otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Section 12.5.11.

8.5.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE/pIMD should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 7.5).

8.5.7. Clinical safety laboratory assessments

In the dose-escalation safety lead-in and in the PoP Step 1 (i.e. first 40 subjects enrolled in the PoP): a volume of approximately 6 mL of whole blood should be drawn from all subjects for each analysis for haematology and chemistry assessments at each pre-defined timepoint (Table 25). Part of the whole blood will be processed into serum and will be managed according to local laboratory practices.

Table 25 Biological samples for haematology and chemistry assessments

Sample type	Quantity	Unit	Study group	Timepoint	Subjects
Blood for haematology and chemistry	~6	m*L*	1a/b Half dose non-adjuvanted 2a/b Full dose non-adjuvanted 3a/b Half dose adjuvanted	Day –1 (V0-Grp1-3) Day 8 (V2-Grp1-3)	All subjects
			4a/b Full dose adjuvanted	Day –1 (V0-Grp4) Day 8 (V2-Grp4) Day 61 (V4-Grp4) Day 68 (V5-Grp4)	All subjects
	~6	m*L*	5a/b vaccine/placebo	Day 1 (V1) Day 8 (V2) Day 61 (V5) Day 68 (V6)	PoP Step 1 (i.e. first 40 subjects enrolled in the PoP)

V = Visit; Grp = Group; a/b = vaccine/placebo

Refer to Section 12.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The tests detailed in Appendix 2, Section 12.2 will be performed by the local laboratory at the investigator's site. Results of tests will be needed before vaccination i.e. on the same of the blood draw day for PoP Step 1 or latest on the next day for dose-escalation safety lead-in (see also Section 6.2 exclusion criteria).

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significant abnormal during participation in the study or within 8 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor. Refer to

the Section 12.5.6 for clinical laboratory abnormal assessments qualified as AEs or SAEs.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory safety assessments, as defined in Section 12.2 (Appendix 2), must be conducted in accordance with the SPM and the SoA.

8.5.8. Subject card

Study subjects must be provided with the address and telephone number of the main site contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject. In an emergency situation, this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects must be instructed to keep subject cards in their possession at all times during the study duration.

8.6. Holding rules and safety monitoring

For both, the dose-escalation safety lead-in and PoP, the investigator will not be permitted to start the administration of Dose 1 for the next group until receipt of the favourable outcome of the safety assessment committees evaluation (SRT/iSRC), documented and provided in writing (scanned and emailed), authorising the investigator to proceed. The same applies for the administration of Dose 2 in the fourth group of the dose-escalation safety lead-in and for the administration of Dose 2 in the staggered enrolment of first 40 subjects of the PoP epoch.

Refer to the iSRC Charter for details about the safety assessment committees evaluation.

During the whole study period (dose-escalation safety lead-in and PoP) if the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately (e.g. in case of death or any life-threatening SAEs).

8.6.1. Staggered vaccination

A staggered enrolment approach of healthy subjects of the dose-escalation safety lead-in epochs is chosen and additionally a staggered enrolment of subjects in PoP epochs. The safety assessment committees (SRT/iSRC) will evaluate safety throughout the study and will decide at different steps about continuation of the study.

Staggered enrolment in dose-escalation safety lead-in epochs:

Four groups receiving 4 different vaccine formulations will be included in the dose-escalation safety lead-in epochs (for details see Section 5.2 and Figure 5). Subjects in the 4 groups will be enrolled in 4 successive steps (see Figure 7), the next group can only be enrolled after safety assessment of the previous group and safety assessment committees (SRT/iSRC) approval. Additionally, for each step/group, a 2-substep staggered design is chosen (see Figure 7):

- Substep a: 1 vaccinated subject + 1 subject receiving placebo (sentinel subjects). The 2 sentinel subjects in each group should be vaccinated on 2 different days. All the available safety data collected up to the Day 8 after vaccination visit from both subjects (including laboratory assessments at Day 8) will be evaluated. The SRT and iSRC Chair will evaluate safety data and confirm the start of the step below. Conditionally; unblinded data may be evaluated by iSRC and only after positive opinion of iSRC the next step can be started.
- Substep b: 5 vaccinated subjects + 1 subject receiving placebo. All the available safety data collected up to the Day 8 after vaccination visit for the last vaccinated subject (including laboratory assessments at Day 8) will be evaluated. The SRT and iSRC Chair will evaluate all the safety data available and confirm the start of the next step (subsequent group). Conditionally; unblinded data may be evaluated by iSRC and only after positive opinion of iSRC the next step can be started.
  All the unblinded data collected up to Day 8 after vaccination Visit 1 of the fourth group will be reviewed by iSRC.

After the iSRC unblinded data review of dose 1 of the fourth group of the dose-escalation safety lead-in and prior to administering the second vaccine/placebo dose in that fourth group, the staggered enrolment of the first approximately 40 subjects in the PoP epochs in the vaccine target population (subjects with a recent *S. aureus* SSTIs) can start.

The fourth group will receive a second vaccine/placebo dose with an interval of approximately 2 months and subjects of all the groups will be followed until study end (i.e. for each subject approximately 12 months after last vaccination).

Staggered enrolment in PoP epochs (for details see Section 5.2 and Figure 6 and Figure 8):

In a first step (PoP step 1) first dose of vaccination will be performed with a staggered approach. Enrolment will be stopped as soon as 40 subjects have been vaccinated with the first dose of the GSK *S. aureus* candidate vaccine or placebo. Only subjects who already signed the ICF and entered the screening phase, at the time of enrolment hold, will be allowed to continue the study; therefore, approximately 40 subjects (30 subjects receiving GSK *S. aureus* candidate vaccine and 10 receiving placebo) will be evaluated for safety. After iSRC evaluation of unblinded safety data collected up to the Day 8 after first dose (including laboratory assessments) for the last vaccinated subject of this staggered subset (step 1) has shown lack of safety issues, the PoP step 2, (full enrolment of the remaining subjects in the PoP epochs) will continue.

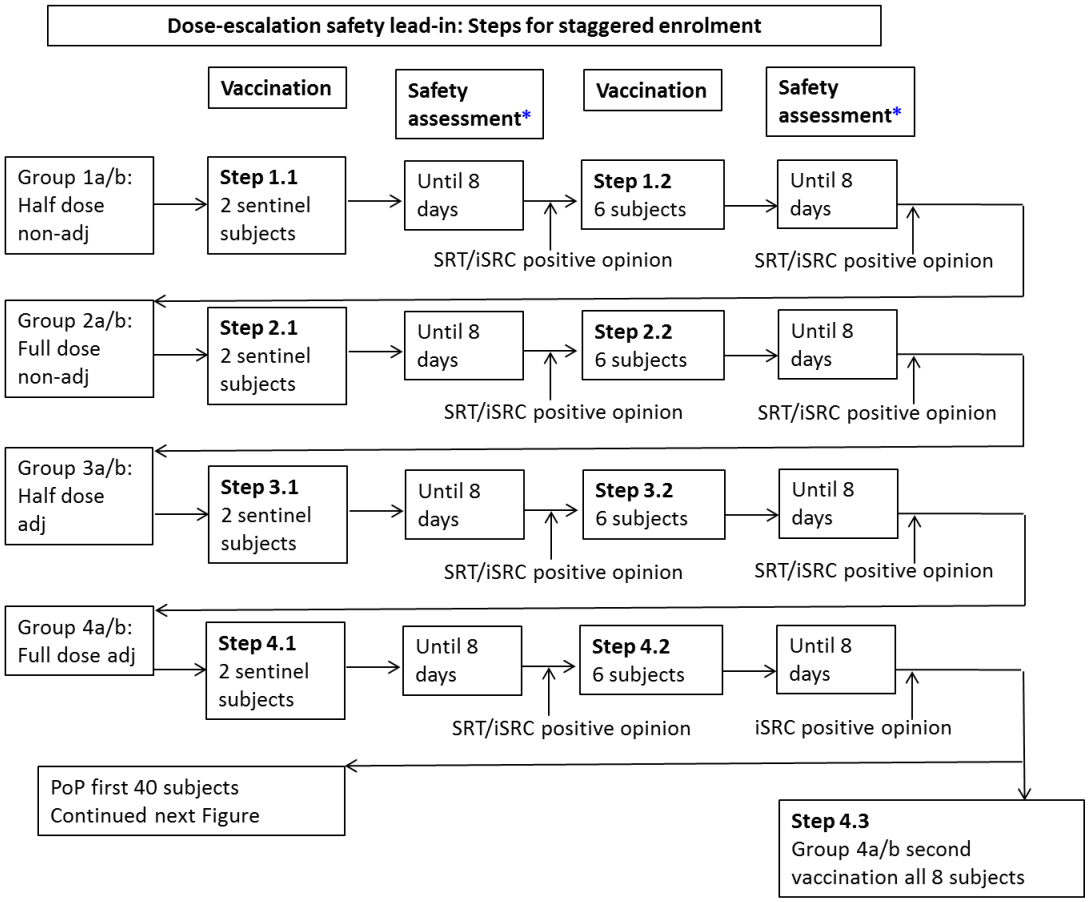
The investigator will not be permitted to start the administration of the second vaccine/placebo dose in the staggered PoP subset from step 1 (approximately 40 subjects) until receipt of the favourable outcome of the SRT and iSRC Chair, which needs to evaluate all the safety data available up to Day 68 (including laboratory assessments) related to the subjects of the fourth group (Full dose adjuvanted) of the last dose-escalation safety lead-in step. Conditionally, unblinded data may be evaluated by iSRC and, only after positive opinion of iSRC, the next step (i.e. second dose of staggered PoP subset) can be started.

All subjects will be closely observed at the site for a minimum of 60 minutes after vaccination. Occurrence of solicited AEs within 30 minutes post vaccination observation must be recorded in the CRF (Table 4).

For both, the dose-escalation safety lead-in and PoP, the investigator is not permitted to start the administration of Dose 1 for the next group until receipt of the favourable outcome of the safety assessment committees evaluation (SRT/iSRC), documented and provided in writing (scanned and emailed), authorising the investigator to proceed (Figure 7 and Figure 8). The same applies for the administration of Dose 2 in the fourth group of the dose-escalation safety lead-in and for the administration of Dose 2 in the staggered enrolment of first 40 subjects of the PoP epoch.

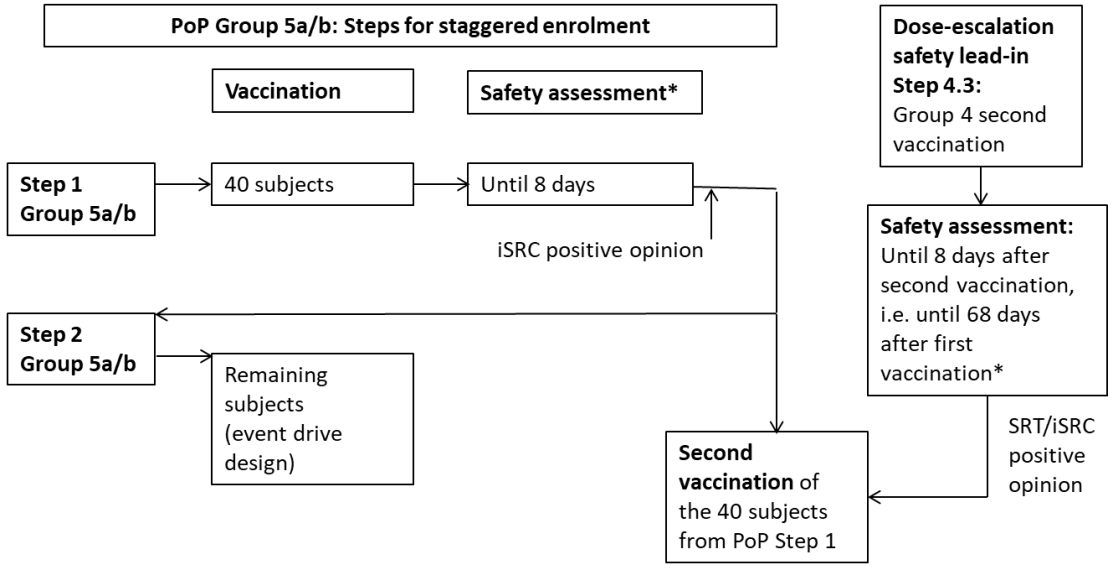
In case more than 1 subject is to be vaccinated on the same day per site, subjects should be vaccinated sequentially at this site and at least 60 minutes apart as acute adverse reactions, like anaphylactic shock, typically occur within 1 hour of vaccination (for holding rules refer to Section 8.6.3 and Table 26). Therefore, not vaccinating subjects in parallel and leaving at least 60 minutes between vaccinations of 2 consecutive subjects will ensure that, in the event of an acute adverse reaction, the site will be able to provide the required medical attention. The 2 sentinel subjects of Groups 1 to 4 of dose-escalation safety lead-in should be vaccinated on 2 different days.

Figure 7 Overview of staggered enrolment and safety evaluation (dose-escalation safety lead-in)



* Safety reviews will take into account all safety data accumulated up to the specified timepoint

Figure 8 Overview of staggered enrolment and safety evaluation (PoP)



* All safety reviews (i.e. SRTs/iSRCs) will take into account all safety data accumulated up to the specified timepoint

8.6.2. Outcome of safety evaluation

- If no safety signal is observed, the favourable outcome of the safety evaluations will be documented and provided in writing (scanned and e-mailed), authorising the investigator to start vaccination of subjects with the subsequent dose as well as enrolment and vaccination of the remaining subjects in the next step of the study, as applicable.
- In case the investigator becomes aware of holding rule(s) 1 is met, he/she should immediately inform GSK of the event (Refer to Table 24 for contact information).
- If a safety signal is observed during the safety evaluations or if any of the holding rules 2a-c is met, the iSRC Chair (or his/her representative) is responsible for the urgent communication to GSK, including the rationale for the decision to put the vaccination on hold or not.
- All site staff will be informed about that final decision (suspend or continue the study) by their local GSK contact. CRDL who is the primary contact will inform the local GSK contact.

8.6.3. Study holding rules

The safety holding rules are defined in Table 26. Holding rules 1 will be assessed by the investigator on a continuous basis irrespective of the number of subjects enrolled and meeting any of these holding rules will trigger a hold of vaccination irrespective of number of subjects enrolled and/or timing of the event relative to vaccination. Holding rules 2 will be assessed by the iSRC during the safety evaluations on unblinded data. Please refer to Appendix 7, Section 12.7 for the definition of the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

These holding rules have been written under the assumption that the safety data from all subjects will be available. If the data from all subjects are not available (i.e. in case a subject is lost to follow-up), then the holding rules will be assessed on a pro-rata basis.

Of note, no formal holding rules will be applied for other safety data such as non-life-threatening SAEs, missed visits due to vaccine-related AEs, Grade 1 and Grade 2 (Refer to Section 12.5.8.2.2) solicited and unsolicited AEs in the 7-day follow-up period and unsolicited AEs collected from Day 8 to Day 30 after vaccination. However, these data, if available, will also be reviewed by the safety assessment committee (SRT/iSRC as applicable) in order to allow for an overall assessment of the benefit/risk ratio of vaccination.

Table 26 Study holding rules

Holding rule	Event	FTIH Dose-escalation Safety Lead-In steps 1-4 Number of subjects needed to trigger the hold	Staggered enrolment step of PoP vaccination epoch (PoP step 1) Number and % of subjects needed to trigger the hold	Full enrolment step of PoP vaccination epoch (PoP step 2) Number of subjects needed to trigger the hold
1a	Death or any life-threatening SAE	≥ 1	≥ 1	≥ 1
1b	Any withdrawal from the study (by investigator or subject request) following a Grade 3 AE that cannot reasonably be attributed to a cause other than vaccination	≥ 1	≥ 1	N/A
1c	Any local or general solicited AE leading to hospitalization, or fever >40°C (104°F) or necrosis at the injection site, within the 7-day (Days 1-7) post-vaccination period	≥ 1	≥ 1	N/A
2a	Any Grade 3 solicited local AE (lasting 48h or more) in an investigational group, within the 7-day (Day 1-7) post-vaccination period	≥ 1	≥ 6/30 or 20%	N/A
2b	Any Grade 3 solicited general AE (lasting 48h or more) in an investigational group, within the 7-day (Day 1-7) post-vaccination period	≥ 1	≥ 6/30 or 20%	N/A
2c	Any Grade 3 unsolicited AE in an investigational group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (Day 1-7) post-vaccination period or any Grade 3 abnormality in pre-specified haematological or biochemical laboratory parameters in an investigational group within the 7-day (Day 1-7) post-vaccination period *	≥ 1	≥ 6/30 or 20%	N/A

AE = Adverse Event; SAE = Serious Adverse Event; FTIH = First Time in Human; PoP = Proof of Principle; N/A = Not Applicable

* Grading of laboratory parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (refer to Appendix 7, Section 12.7). Those laboratory parameters not included in the FDA Toxicity Grading Scale will not be graded.

Holding rules 1a (in all steps), 1b and 1c (during the dose-escalation safety lead-In epoch and the PoP Step 1) will be monitored by the investigators on a continuous basis for as long as vaccination is ongoing in the study. Meeting any of these holding rules will trigger a hold of vaccination irrespective of the number of subjects vaccinated.

Holding rules 2a, 2b and 2c are reviewed during unblinded review in the planned or *ad-hoc* iSRC. These rules will be applied only during the dose-escalation safety lead-In epoch and the staggered enrolment step of PoP vaccination epoch. Also in this case, different cut-offs are considered based on the sample size of the study group.

For both, the dose-escalation safety lead-in and PoP, the investigator will not be permitted to start the administration of Dose 1 for the next group until receipt of the favourable outcome of the safety assessment committees evaluation (SRT/iSRC), documented and provided in writing (scanned and emailed), authorising the investigator to proceed. The same applies for the administration of Dose 2 in the fourth group of the dose-escalation safety lead-in and for the administration of Dose 2 in the staggered enrolment of first 40 subjects of the PoP epoch.

During the whole study period, if the investigator becomes aware of a holding rule being met, he/she will suspend vaccination and will inform GSK immediately.

The below flow of communication has to be followed:

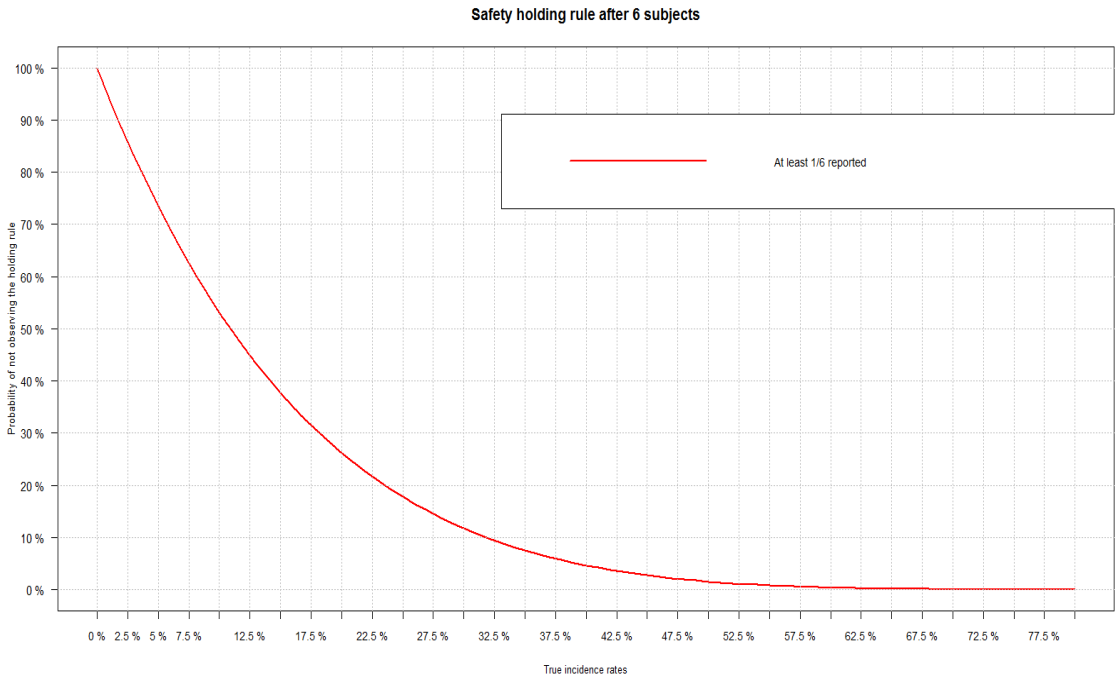
- The concerned site staff must suspend the vaccination.
- The concerned site staff must immediately inform their local contact defined in the Table 24.
- Local Medical Lead (LML) will inform the other sites of his/her country, LMLs of other countries and the Clinical Research & Development Lead (CRDL).
- All informed site staff will send back an e-mail to their local contact to acknowledge receipt of the information.
- GSK Central will further evaluate the case with the iSRC and will take the decision to stop or to restart the vaccination. CRDL who is the primary contact will inform the local GSK contact. All site staff will be informed about that final decision by their local GSK contact.

The detailed flow of communication will be described in the iSRC Charter.

8.6.4. Risk assessment

Figure 9, Figure 10 and Figure 11 give the probability of not meeting each holding rule 1 and 2 for the subjects in 1 vaccine group.

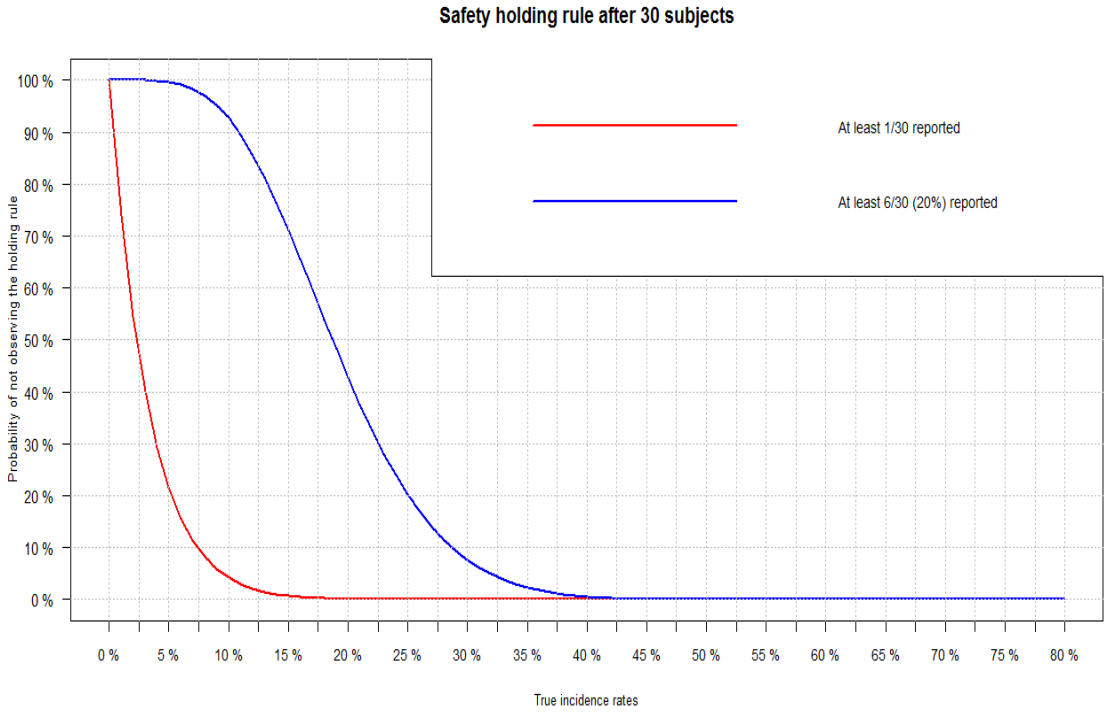
Figure 9 Evaluations based on 6 subjects per group – Risk assessment curve for 1 formulation based on the proposed safety holding rules (dose-escalation safety lead-in steps)



The Figure 9 illustrates that, with 6 subjects per study group:

- Each holding rule 1a-c and 2a-c has more than 82% chance of being met for vaccination with a true incidence rate above 25% and has more than 53% chance of not being met for vaccination with a true incidence rate below 10%.

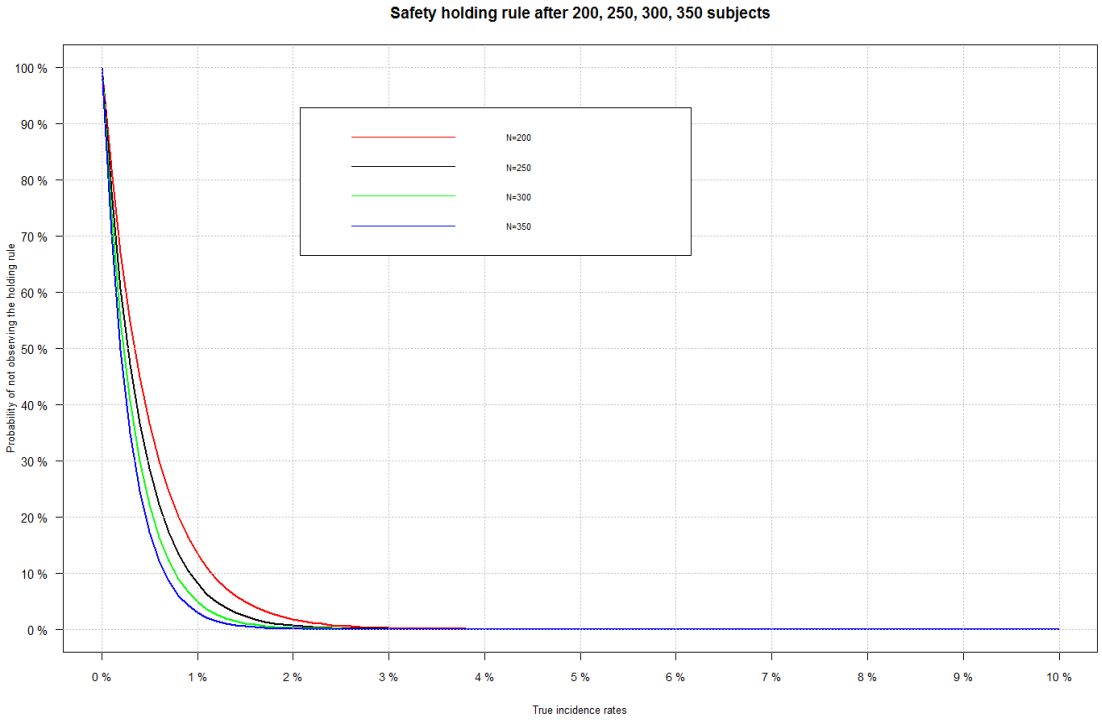
Figure 10 Evaluations based on 30 subjects per group – Risk assessment curve for 1 formulation based on the proposed safety holding rules (staggered step)



The Figure 10 illustrates that, with 30 subjects per study group:

- Each holding rule 1a-c has more than 78% chance of being met for vaccination with a true incidence rate above 5% and has more than 74% chance of not being met for vaccination with a true incidence rate below 1%.
- Each holding rule 2a-c has more than 80% chance of being met for vaccination with a true incidence rate above 25% and more than 93% chance of not being met for vaccination with a true incidence rate below 10%.

Figure 11 Evaluations based on 200, 250, 300, 350 subjects per group – Risk assessment curve for 1 formulation based on the proposed safety holding rules (PoP full enrolment step)



The Figure 11 illustrates that, with 200-350 subjects per study group:

- The holding rule 1a has a chance ranging from 3% (with 350 subjects) to 13% (with 200 subjects) of not being met for vaccination with a true incidence rate below 1% and has more than 98% chance of being met for vaccination with a true incidence rate above 2%.

8.6.5. Safety review team (SRT)

The SRT is a GSK's Central Committee responsible for on-going safety monitoring of the entire project and will meet on a regular basis throughout the duration of the study. In order to keep blinded all people involved in the conduct, cleaning and final analysis of the study, the SRT will monitor safety in a blinded manner. The GSK Biologicals' SRT and iSRC chair will jointly review blinded safety data. If no potential holding rules (e.g. 1a, 1b or 1c, Table 26) or safety concerns are identified during this blinded review, then review of unblinded data by iSRC team may not be required and study can proceed with the next step. Should there be any concerns that would require the evaluation of unblinded safety data, the iSRC will perform unblinded review of safety data and proceed as specified in the iSRC charter.

Refer to the iSRC Charter for details about the safety assessment committees evaluation.

8.6.6. Internal Safety Review Committee (iSRC)

As this will be the first time that the *S. aureus* candidate vaccine will be administered in humans, the study will enroll and vaccinate subjects in several steps (see also Figure 7 and Figure 8). An iSRC authorised by the GSK's VSMB will review unblinded data and holding rules have been established to ensure the safety of the subjects in the study. Conditional review of unblinded data by iSRC (i.e. in case of any safety concern, see also Section 8.6.5) can be performed after any step of the study, as applicable. Predefined unblinded review by iSRC will be performed on Day 8 after vaccination Visit 1 of the fourth group of dose-escalation safety lead-in and on Day 8 after vaccination Visit 1 of the last subject of the approximately first 40 subjects of staggered enrolment of the PoP.

Details on safety assessment committees process is further described in the iSRC Charter.

9. DISCONTINUATION CRITERIA

9.1. Discontinuation from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data and samples collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make attempts (3 telephone calls [e.g. once every 3 days] and a certified letter to the last known address or local equivalent methods) to contact those subjects who do not return for scheduled visits or follow-up.

Primary reason for study withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Adverse events requiring expedited reporting (refer to Section 12.5.9.2 for details)
- Unsolicited non-serious adverse event
- Solicited adverse event
- Protocol deviation
- Withdrawal by subject, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up

- Sponsor study termination
- Other (specify)

*In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 12.5.11).

9.2. Discontinuation of study vaccine(s)

A 'withdrawal' from the study vaccine(s) refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccine(s) may continue further study procedures (e.g. safety, efficacy or immunogenicity) if planned in the study protocol, as deemed appropriate by the investigator.

Primary reason relative to premature discontinuation of the study vaccine(s) will be documented on the Vaccine Administration page/screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

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

9.3. Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up and last day of actual contact be recorded on termination page.

10. STATISTICAL CONSIDERATIONS

10.1. Sample size determination

10.1.1. Hypotheses related to primary and secondary objectives

For the primary safety objective no statistical hypotheses are applicable.

Two statistical hypotheses will be tested for the secondary efficacy objective.

1. Null Hypothesis : Hazard Ratio (HR) ≥1 after the second vaccination
   Alternative Hypothesis: HR <1
2. Null Hypothesis : Hazard Ratio (HR) ≥1 after the first vaccination
   Alternative Hypothesis: HR <1

If the first hypothesis is statistically significant, also the second hypothesis will be tested in a sequential procedure. In case the first hypothesis is not significant no conclusions will be taken with respect to the second hypothesis. Both hypotheses will be tested using the log rank test.

For the first hypothesis referring to the key efficacy endpoint two sequential analyses will be done following a Group Sequential Design using the O'Brien-Fleming spending function (with 48% and 100% of the total planned events). ***(Amended 6 October 2022)***

At the interim analysis the first hypothesis will be tested spending 1.61% alpha and 8.83% beta (this means a power equal to about 91%). At the final analysis the alpha will be 5.89% and the beta 11.17% (this means a power equal to about 89%). Overall after two sequential analyses the cumulative alpha will be 7.5% and the cumulative beta 20% (or power equal to 80%).

The assumptions to test the first hypothesis on the HR after the second vaccination are:

- to observe an HR (hazard ratio) equal or below to 0.39
- a true incidence rate for the SSTI equal to 0.07 (starting to count the events two weeks after the second dose)
- time to event follows an exponential distribution.

The second hypothesis of the secondary vaccine efficacy objective will be tested for all the events occurring after the first vaccination, with one-sided alpha equal to 5.89% and power 89% (both adjusted error values will be retrieved from the second group sequential test performed on the first hypothesis).

The following assumptions are made to test the hypothesis on the HR after the first dose of vaccine/placebo:

- to observe an HR below 0.43
- a true incidence rate equal to 0.12 (starting to count the events two weeks after the first dose)
- time to event follows an exponential distribution

The upper limit assumed for the HR equal to 0.43 allows to test the second hypothesis with alpha equal to 5,89% and power equal to 89%, assuming the incidence rate equal to 0.12, with the planned sample size for the first hypothesis (about 600 subjects).

10.1.2. Sample size calculation

The incidence rates of *S. aureus* SSTI (index cases and recurrences) at the selected study centre(s) are difficult to predict. For this reason, the study is designed as an event driven trial and includes CCI [redacted]. After the dose-escalation safety lead-in epoch and the PoP staggered enrolment step of PoP vaccination epoch are concluded and no safety issues are found, enrolment will continue with a randomisation of 1:1 ratio either to the *S. aureus* candidate vaccine or to the placebo group. It is estimated that approximately 500 to 600 subjects will be needed to achieve the CCI [redacted].

The key objective of clinical efficacy will be measured counting culture confirmed cases of recurrent *S. aureus* SSTIs occurring from 14 days after the second dose up to 12 months after the second dose. Before the second dose has elicited a proper response (i.e. from Day 61 to Day 75) subjects will be also monitored for SSTI.

The event driven design includes CCI [redacted] (culture confirmed *S. aureus* SSTI recurrences) overall after the second dose to test the null hypothesis of no efficacy assuming an HR equal to 0.39 from Day 75 (14 days after the second vaccination) up to 12 months after the second vaccination.

The study sample size is not fixed and the enrolment will proceed until reaching the planned number of events necessary to evaluate the first statistical hypothesis of no efficacy (HR≥1) with an overall power equal to 80% and an overall one-sided alpha equal to 7.5%.

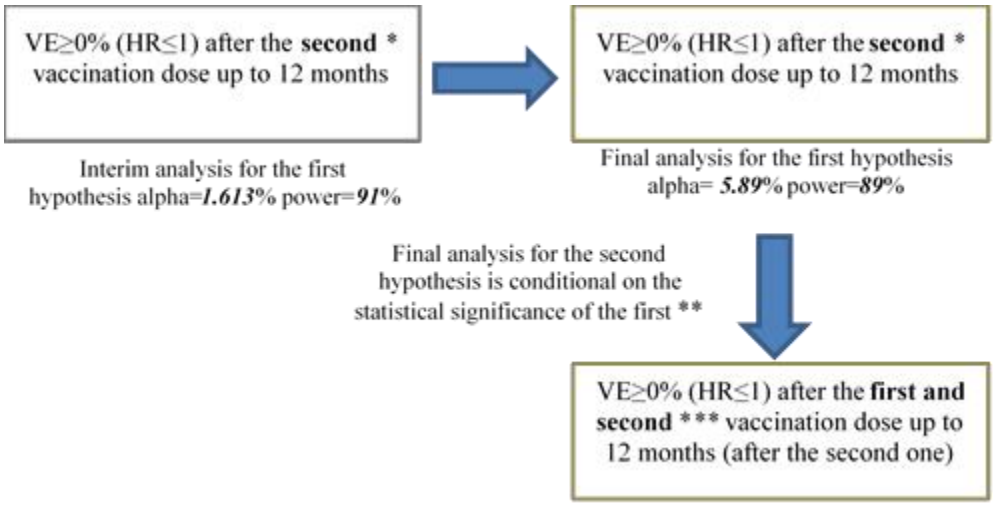
A group sequential design with the O'Brien Fleming spending function is applied to the first hypothesis after the second vaccination, CCI [redacted]

CCI

[redacted]

After the final analysis for the first hypothesis a sequential procedure will be used in order to control the overall type I error for the efficacy objective: starting from the first hypothesis on the efficacy after the second dose, the second hypothesis on the efficacy after the first dose will be tested only if the efficacy after two doses will be demonstrated.

Figure 12 Sequence for evaluating both efficacy objectives in order to control the overall type I error below 7.5% (one-sided) and the power equal to 80%



*All subjects who experience an SSTI recurrence at least two weeks after the second dose. If a subject experiences an event after the first and before the second dose the case will be not considered as first event after the second dose. If a subject experiences an event after the first and another after the second dose, only the case after the second dose will be considered as first event after the second dose.
**The adjusted alpha for this hypothesis can only be given at the time of analysis as the adjustment is dependent on the alpha spent at the interim analysis. A more detailed decision tree will be given in the statistical analysis plan.
***All subjects who experience an SSTI recurrence at least two weeks after the first dose.

10.2. Populations for analyses

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Screened	All subjects who were screened for eligibility
Enrolled	All subjects who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). The allocation in a group will be done in function of the randomized intervention; non-randomized subjects will be part of a "Non randomized" group. Note: screening failures (who never passed screening even if rescreened) and subjects screened but never enrolled into the study (met eligibility but ultimately not enrolled) are excluded from the Enrolled analysis set as they did not enter the study.
Exposed	All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.
Full Analysis Set (FAS)	All subjects who received at least 1 dose of the study treatment and have post-vaccination efficacy/ immunogenicity data
Modified Full Analysis Set (mFAS)	All subjects who received full study treatment course to which they are randomised and have post-vaccination efficacy/immunogenicity data
Per-Protocol (PP)	All subjects who received full study treatment course to which they are randomised and have post-vaccination data (mFAS) minus subjects with protocol deviations that lead to exclusion from PP
Unsolicited Safety	All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited Aes
Solicited Safety	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data in the period beginning 30 minutes after vaccination until 7 days after vaccination.
Solicited Safety 30m	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data during a period of 30 minutes after the vaccination.
Overall Safety Set	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data including 30 minutes data and during a period of 7 days from the vaccination and/or report unsolicited Aes/report not having unsolicited Aes

10.3. Statistical analyses

10.3.1. Subjects disposition

Number of screened, enrolled, vaccinated (at least 1 vaccination, full vaccination course) subjects, included in each group or in total for a given age category or for all age categories will be described. These might be additionally broken down by site.

10.3.2. Demography and baseline characteristics analyses

Demographic characteristics (age at first study vaccination in years, gender, race and ethnicity), SSTIs history (PoP only), will be summarised by overall and vaccine groups using descriptive statistics:

- Frequency tables will be generated for categorical variables such as centre.
- Mean, standard deviation, median, minimum and maximum will be provided for continuous data such as age, height, weight and body mass index (BMI).

Withdrawal status will be summarized by group using descriptive statistics:

- The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal
- The number of subjects enrolled into the study as well as the number of subjects excluded from the per-protocol set (PPS) and mFAS will be tabulated.

10.3.3. Efficacy analyses

The primary efficacy analysis will be based on the mFAS. A supplementary analysis may be based on the PPS.

10.3.3.1. Case accountability:

Rules for SSTI cases:

- All cases of SSTI will be reported, including multiple cases in the same subject.
- The start date of a case is the date of the visit during which the diagnosis is done by a treating physician or equivalent licensed medical professional or based on medical records review by a study physician.
- A new SSTI episode may be assessed by a study physician at site for any SSTI visit occurring after the clinical resolution of the previous SSTI and, if it does not represent a persistence of the previous episode as per medical judgement, it can be considered a new episode.

Endpoint	Statistical Analysis Methods
Key secondary	The analysis of efficacy will be based on the occurrence of the first case of SSTI anytime from 15 Days after the administration of the second dose of the study vaccine up to 12 months. All subjects from the mFAS will contribute to the comparison between the treatment and the placebo groups. Time to occurrence of key secondary endpoint during the defined efficacy follow-up period will be compared between groups by calculating the respective Hazard ratio (methods will be detailed in the SAP). Vaccine (VE) will be defined as 1 minus the hazard ratio times 100: VE = (1 – hazard ratio) x 100 Censoring will occur at the time of the last scheduled or medically attended visit without the occurrence of SSTI cases before the end of follow-up. Subjects who will complete the follow-up without events will be censored at 1 year. In order to check the statistical significance, 1-sided P-value for the log rank test will be calculated. 1-sided nominal type I error will be 1.61% at the interim analysis and 5.89% at the final analysis. The objective will be met if the 1-sided P-value calculated for the null hypothesis H0 = [occurrence SSTI VE =0%] is lower than defined 1-sided alpha level.
Co-secondary	The co- secondary endpoint will be analysed only if the statistical significance is demonstrated for the key secondary endpoint. For this analysis, the FAS will account for the first case of SSTI anytime from 15 Days after the administration of the first dose of the study vaccine up to 14 months. Time to occurrence of the co- secondary endpoint during the defined efficacy follow-up period will be compared between groups by calculating the respective Hazard ratio (methods will be detailed in the SAP).

Endpoint	Statistical Analysis Methods
	In order to check the statistical significance, 1-sided P-value for the log rank test will be calculated. 1-sided nominal type I error will be 5.89%. (the nominal alpha level is equal to the key secondary at the final analysis, because we use a sequential procedure). The objective will be met if the 1-sided P-value calculated for the null hypothesis H0=[occurrence SSTI VE =0%] is lower than defined 1-sided alpha level.

CCI [redacted]

10.3.4. Immunogenicity analyses

The main analysis set for immunogenicity will be the mFAS.

CCI [redacted]

10.3.5. Safety analyses

The primary analysis will be performed on the Solicited Safety and Unsolicited Safety sets.

Endpoint	Statistical Analysis Methods
Primary	**Within groups assessment** The overall incidence, with exact 95% confidence intervals (Cis) of any solicited AE (local or general), of at least 1 solicited local AE and of at least 1 solicited general AE during the 7-day (Day 1-7) period will be tabulated per study group and for each dose and overall. The same calculations will be performed for solicited Aes rated as grade 3 and fever >40°C/104°F. The overall incidence, with exact 95% confidence intervals (Cis) of any unsolicited AE, unsolicited Aes by MedDRA system organ class and by preferred term during the 30-day (Day 1-30) follow-up post-vaccination period will be tabulated per study group and after each dose and overall. The same calculations will be performed for unsolicited Aes rated as grade 3 and fever >40°C/104°F, for unsolicited Aes causally related to vaccination and for grade 3 unsolicited Aes causally related to vaccination. The number and percentages of subjects who experienced at least one SAE or any pIMD during the entire study period (Groups 1-3 Day 1-366, Groups 4 and 5 Day 1-426) will be reported. The percentage of subjects having haematology and biochemistry results below or above the normal laboratory ranges with the changes from the baseline values will be tabulated by time point for Group 1 to 4 and Group 5 Step 1. Duration will be presented. The verbatim reports of unsolicited symptoms will be reviewed by a GSK physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Event Terminology. Serious adverse events and withdrawal due to adverse event(s) will be described in detail.

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[redacted]

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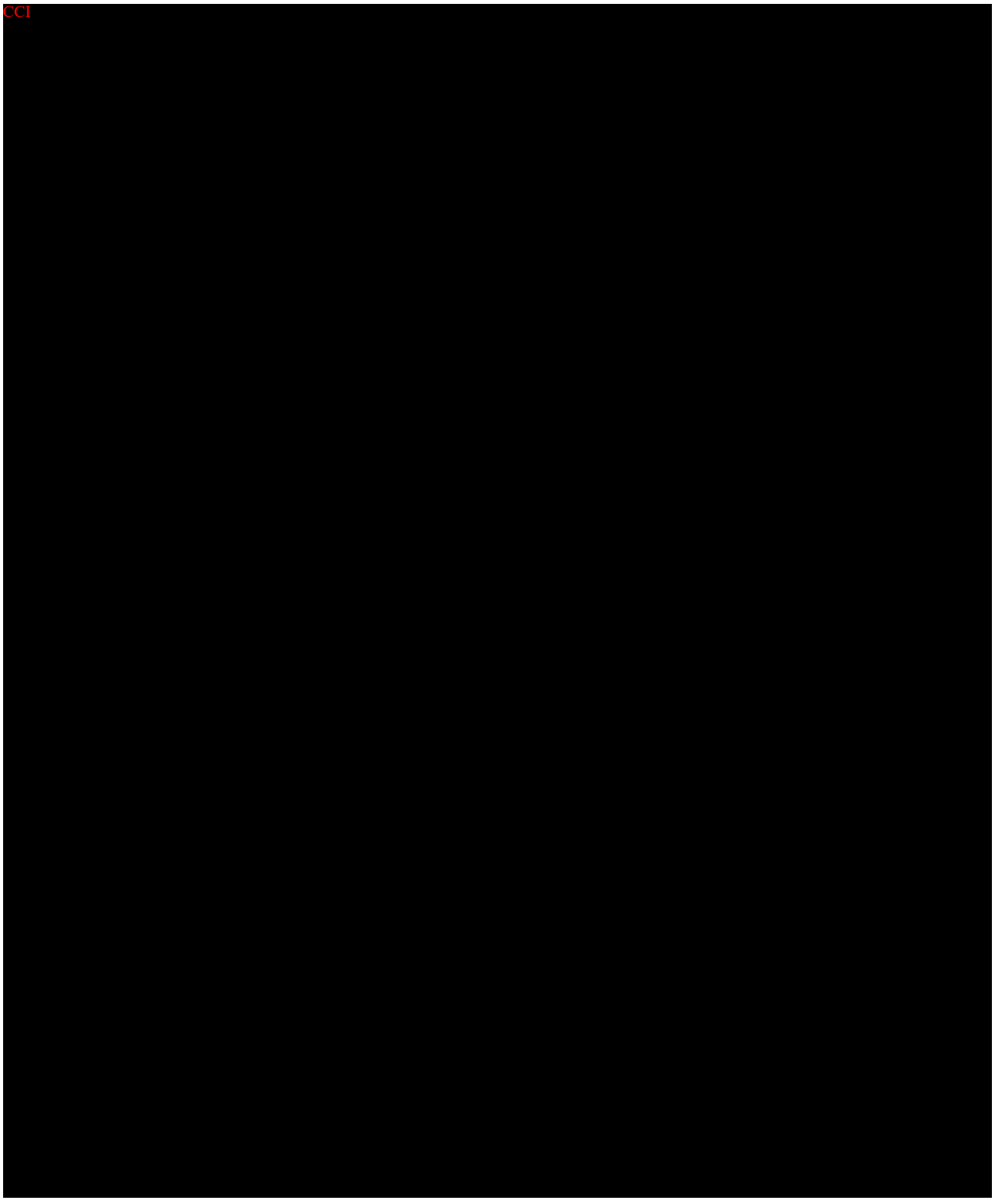

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12. APPENDICES

12.1. Appendix 1: Abbreviations, glossary of terms and trademarks

12.1.1. List of abbreviations

AE: Adverse Event

ANCOVA: Analysis of Covariance

CCI [redacted]

BSI: Blood Stream Infection

CDC: Centers for Disease Control

CI: Confidence Interval

CCI [redacted]

CLS: Clinical Laboratory Sciences

CCI [redacted]

CoP: Correlate of Protection

CCI [redacted]

DSSI: Deep Surgical Site Infection

eCRF: electronic Case Report Form

EMA: European Medicines Agency

EoS: End of Study

eTDF: Electronic Temperature excursion Decision Form

EU: European Union

FAS: Full Analysis Set

FDA: Food and Drug Administration, United States of America

FTIH: First Time in Human

GCP: Good Clinical Practice

CCI [redacted]

GSK: GlaxoSmithKline

CCI [redacted]

HR: Hazard Ratio

IB: Investigator Brochure

ICF: Informed Consent Form

ICH: International Council on Harmonisation

CCI [redacted]

IEC: Independent Ethics Committee

IMP: Investigational Medicinal Product

IND: Investigational New Drug

IRB: Institutional Review Board

IsdB: Iron-regulated surface determinant B

iSRC: Internal Safety Review Committee

LLOQ: Lower Limit of Quantitation

LOD: Limit of Detection

LSLV: Last Subject Last Visit

MACDP: Metropolitan Atlanta Congenital Defects Program

MedDRA: Medical Dictionary for Regulatory Activities

mFAS: Modified Full Analysis Set

CCI [redacted]

PCD:	Primary Completion Date
pIMD:	Potential Immune-Mediated Disease
PoP:	Proof of Principle
PP:	Per-protocol
PRO:	Patient Related Outcomes
RRA:	Recruitment/Randomisation Agreement
SAE:	Serious Adverse Event
SBIR:	Source data Base for Internet Randomisation
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics

CCI [redacted]

SPM:	Study Procedures Manual
SRT	Safety Review Team
SSI:	Surgical Site Infection
SSTI:	Skin and Soft Tissue Infection
US:	United States of America
VCSP:	Vaccines Clinical Safety and Pharmacovigilance
VE:	Vaccine Efficacy

12.1.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment (see Section 7.3 for details on observer-blinded studies).
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS) **(Synonym of End of Trial)**	For studies with collection of human biological samples, the EoS is defined as last subject last visit (Visit 10).
Epoch:	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomisation, treatment, follow-up), which applies across all arms of a study. NOTE: Epoch is intended as a standardised term to replace: period, cycle, phase, stage.

Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see Section 10.2 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions
Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
Primary completion: date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.

Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorised use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.

Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule…) at the time of enrolment.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.
Treatment number:	A number identifying a treatment to a subject, according to treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

12.2. Appendix 2: Clinical and safety laboratory tests

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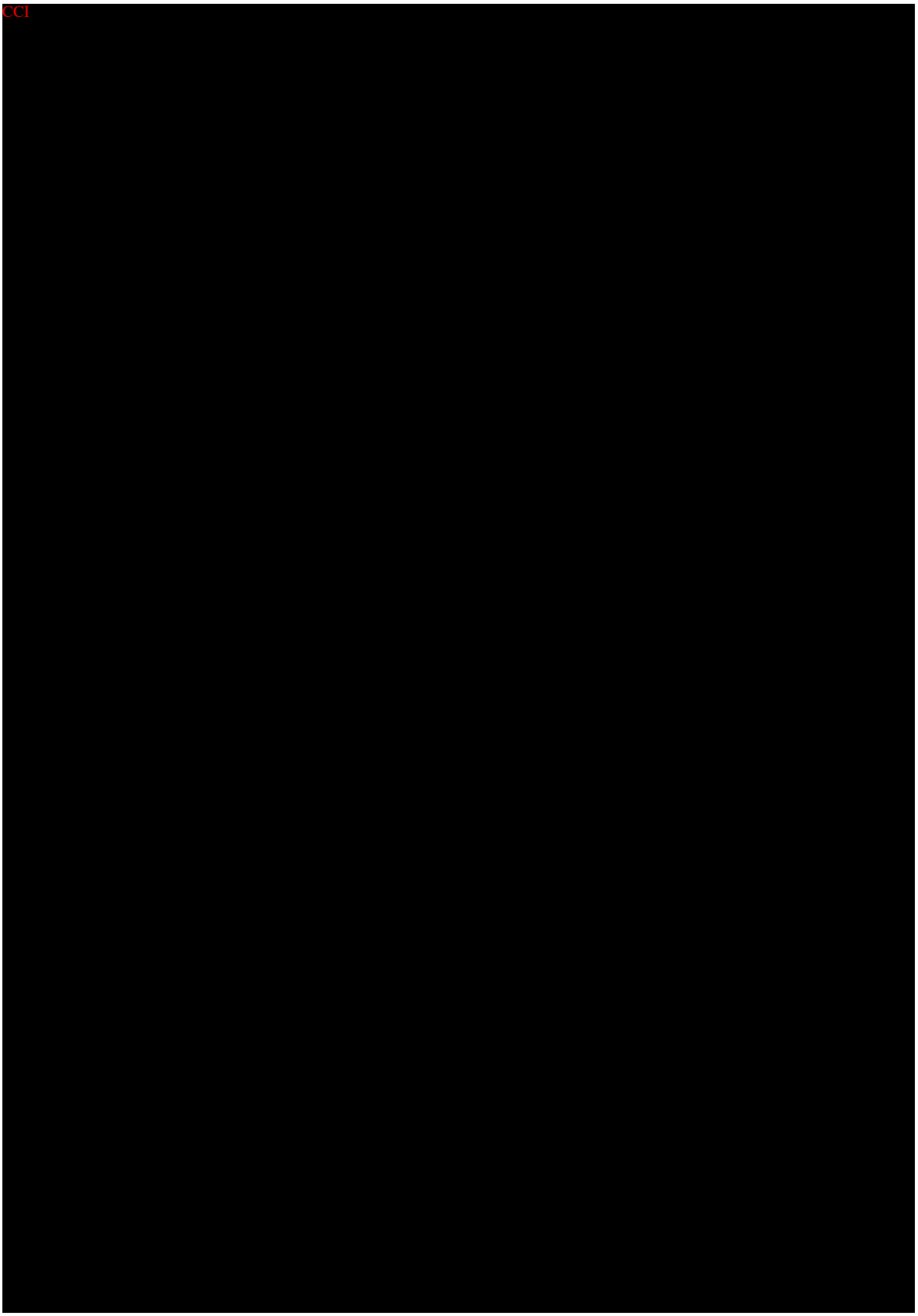

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12.2.2. Laboratory assays for safety evaluation

The tests detailed in Table 27 will be performed by the local laboratory. Results of tests will be needed before vaccination i.e. latest on the next day for dose-escalation safety lead-in and on the same day for PoP Step 1 (see also requirements for inclusion or exclusion of subjects detailed in Section 6 of the protocol).

Examples of clinically not significant abnormalities: (ULN = upper limit of normal; LLN = lower limit of normal) that can allow subjects to be enrolled:

- WBC > ULN, if WBC remain stable over time i.e. maximum 10% change with respect to baseline (prior to the first vaccination).
- Haemoglobin levels > the upper limit of the laboratory normal range (ULN).
- RBC > ULN.
- RBC < LLN and haemoglobin normal.
- ALT or AST < LLN
- If values out of normal ranges (Grade 1 considered clinically significant or above Grade 1) are observed (Refer to Appendix 7, Section 12.7), which are expected to be temporary (e.g., due to dehydration), the abnormal parameters can be re-assessed during a rescreening* visit but they must have returned to within local laboratory normal ranges for the subject to be eligible. If considered necessary by the investigator, related parameters outside of the panel can be (re-)tested in addition to the abnormal parameters (Haematology/Biochemistry). The subjects should be informed about the possibility of rescreening* in the informed consent form (ICF).

  * Rescreening of subjects in case of a transient clinical condition (e.g. previous screening failure due to non-S. aureus SSTI) at investigator discretion, is also possible. In such cases, the complete screening process should be reperformed.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 6 of the protocol.

The investigator is not allowed to do extra testing on samples outside of what has been agreed upon by the ethics committees.

Table 27 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Haematology	Platelet Count RBC Count Haemoglobin	WBC count with Differential: Neutrophils Lymphocytes Eosinophils
Clinical Chemistry	Creatinine	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)
		Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)
Other Screening Tests	Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) The results of each test carried out locally must be entered into the eCRF.	

RBC = Red Blood Cells; WBC = White Blood Cells
NOTES: Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Pre-vaccination on Visit 0 (dose-escalation safety lead-in) and Visit 1 (PoP Step 1) haematology and chemistry evaluation will not be blinded since abnormal laboratory results will be an exclusion criterion (see Section 6.2.1). Visit Days 8, 61 and 68 haematology and blood chemistry results will be blinded to study treatment. Unblinding is appropriate for safety issues, but unblinded data will only be reviewed by iSRC. Refer to the iSRC Charter for details about the safety assessment committees evaluation.

12.3. Appendix 3: Clinical laboratories

The laboratories (at the investigator's institution and/or at a laboratory designated by GSK Biologicals) that will perform the microbiology assessments are not yet identified.

A list of possible laboratories is given in Table 28 and Table 29.

In addition, other laboratories than those listed below might also be used to perform the exploratory assays.

Table 28 GSK laboratories

Laboratory*	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Biospecimen Reception-B7/44 Rue de l'Institut, 89 B-1330 Rixensart Belgium
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20 B-1300 Wavre Belgium
GSK Vaccines S.r.l Preclinical R&D, Italy	Via Fiorentina 1 53100 Siena Italy

*GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium or Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Siena, Italy or to an external laboratory.

Table 29 Outsourced laboratories

Laboratory	Address
Q² Solutions Clinical Trials (UK)	The Alba Campus Rosebank Livingston West Lothian, EH54 7EG Scotland, UK
Q² Solutions Clinical Trials (US)	27027 Tourney Road, Suite 2E Valencia, CA 91355 USA

12.4. Appendix 4: Study governance considerations

12.4.1. Regulatory and ethical considerations

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

12.4.2. Financial disclosure

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

12.4.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary.

Freely given and written or witnessed/thumb printed informed consent must be obtained from each subject prior to participation in the study.

The content of informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) or an ICF addendum during their participation in the study.

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

Subjects who are rescreened are required to sign a new ICF.

The ICF contains a specific section that addresses the use of remaining leftover samples for future use in accordance with SOP-GSKF-410. The investigator or authorised designee will inform each subject of the possibility of future use of left-over samples not related to the study/disease. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate tick box will be required to document a subject's agreement to allow any remaining leftover samples to be used for future use not related to the study/disease. Subjects who decline the use of left-over samples for objectives not related to the study/disease will tick the corresponding box.

12.4.4. Data protection

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject's names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

GSK will also ensure the protection of personal data of investigator and the site staff which will be collected within the framework and for the purpose of the study, in accordance with the Data Privacy Notice that will be sent to the site staff.

12.4.5. Publication policy

GSK aims to publish the results of this study in searchable, peer reviewed scientific literature. GSK will target to submit within 18 months from LSLV for interventional studies and from the completion of the analysis for non-interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

12.4.6. Dissemination of clinical study data

The key design elements of this protocol will be posted on the GSK Clinical Study Register and on publicly accessible registers including ClinicalTrials.gov. Where required, protocol summaries will also be posted on national or regional clinical trial registers or databases (e.g. EudraCT database) in compliance with the applicable regulations.

GSK also assures that results will be submitted to ClinicalTrials.gov within the required time frame, in compliance with the current regulations mentioned in the table below.

At the time of study results posting, the full study protocol and statistical analysis plan will also be posted on ClinicalTrials.gov.

In addition, for studies that are in scope of the EU Clinical Trial Directive, summaries of the results of GSK interventional studies (phase I-IV) in adult population will be posted within defined timelines on the publicly available EU Clinical Trial Register.

If it is not possible to submit a summary of the results within the required timelines in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

	Clinicaltrial.gov	EU
Protocol summary	Before enrolment of subjects	As per CTA submission/Before enrolment of subjects
Results summary	Within 12 months of PCD (Primary and safety endpoint results)/Within 12 months of LSLV* (for secondary endpoint results)	Within 6 months (for paediatric population studies)/Within 12 months (for adult population studies) of EoS*.

* As defined in the study protocol.

Under the framework of the SHARE initiative, anonymised patient-level data from GSK sponsored interventional studies that evaluate products will be made available within 6 months of this publication to independent researchers whose research proposals have been approved by an independent panel. Requests for access may be made through www.clinicalstudydatarequest.com.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12.4.7. Data quality assurance

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

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

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

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

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

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

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

Quality tolerance limits (QTLs) will be pre-defined in the study management plan and will be monitored during the study.

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

12.4.8. Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and source documents can be found in the glossary of terms.

12.4.9. Study and site start and closure

First act of recruitment

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

Study/Site termination

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will be upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development
- Total number of subjects included earlier than expected

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

12.5. Appendix 5: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

12.5.1. Definition of AE

12.5.1.1. AE Definition

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

12.5.1.2. Events Meeting the AE Definition

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccine(s) administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine(s) administration.

- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).
- Medically attended visits related to adverse events (e.g. Hospital stays, physician visits and emergency room visits).

AEs to be recorded as endpoints (solicited AEs) are described in Section 12.5.3. All other AEs will be recorded as UNSOLICITED AEs.

"Lack of efficacy" or "vaccination failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

12.5.1.3. Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF.

12.5.2. Definition of SAE

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred, or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

f. Grade 4 laboratory abnormalities (Refer to Appendix 7, Section 12.7).

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

12.5.3. Solicited adverse events

a. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

Table 30 Solicited local adverse events

Adults
Pain at injection site
Redness at injection site
Swelling at injection site

b. Solicited general adverse events

The following general AEs will be solicited:

Table 31 Solicited general adverse events

Adults
Fatigue
Fever
Nausea
Vomiting
Diarrhoea
Abdominal pain
Headache

Table 32 Additional solicited general adverse events (PoP only)

Adults
Myalgia
Shivering

Note: subjects will be instructed to measure and record the oral body temperature in the evening. Should additional temperature measurements be performed at other times of day, subjects will be instructed to record the highest temperature in the eDiary.

12.5.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subjects who has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalisation, or emergency room visit, or visit to/by a health care provider), or were of concern to the subjects. In case of such events, subjects will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by subjects will be collected during interview with the subjects and by review of available medical records at the next visit.

12.5.5. Adverse events of special interest (AESIs)

12.5.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 33. For details regarding the reporting procedure refer to Section 12.5.9.2.

However, the investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Table 33 List of potential immune-mediated diseases (pIMDs)

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders

• Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy).
• Optic neuritis.
• Multiple sclerosis.
• Transverse myelitis.
• Guillain-Barré syndrome, including Miller Fisher syndrome and other variants.
• Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis.
• Myasthenia gravis, including Lambert-Eaton myasthenic syndrome.
• Demyelinating peripheral neuropathies including:
• Chronic inflammatory demyelinating polyneuropathy,
• Multifocal motor neuropathy
• Polyneuropathies associated with monoclonal gammopathy.
• Narcolepsy.
	• Systemic lupus erythematosus and associated conditions
	• Systemic scleroderma (Systemic sclerosis), including:
	  • Diffuse Scleroderma
	  • CREST syndrome
	• Idiopathic inflammatory myopathies, including:
	  • Dermatomyositis
	  • Polymyositis
	  • Anti-synthetase syndrome.
	• Rheumatoid Arthritis and associated conditions including:
	  • Juvenile Idiopathic Arthritis
	  • Still's disease.
	  • Polymyalgia rheumatica.
	  • Spondyloarthropathies, including:
	  • Ankylosing Spondylitis,
	  • Reactive Arthritis (Reiter's Syndrome),
	  • Undifferentiated Spondyloarthritis,
	  • Psoriatic Arthritis,
	  • Enteropathic arthritis.
	  • Relapsing Polychondritis.
	  • Mixed Connective Tissue disorder.
	  • Gout.
		• Psoriasis.
		• Vitiligo.
		• Erythema nodosum.
		• Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis).
		• Lichen planus.
		• Sweet's syndrome.
		• Localised Scleroderma (Morphoea).

Vasculitis	Blood disorders	Others

• Large vessels vasculitis including:
  • Giant Cell Arteritis (Temporal Arteritis),
  • Takayasu's Arteritis.
• Medium sized and/or small vessels vasculitis including:
  • Polyarteritis nodosa,
  • Kawasaki's disease,
  • Microscopic Polyangiitis,
  • Wegener's Granulomatosis (granulomatosis with polyangiitis),
  • Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis),
  • Buerger's disease (thromboangiitis obliterans),
  • Necrotising vasculitis (cutaneous or systemic),
  • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified),
  • Henoch-Schonlein purpura (IgA vasculitis),
  • Behcet's syndrome,
  • Leukocytoclastic vasculitis.
	• Autoimmune haemolytic anemia.
	• Autoimmune thrombocytopenia.
	• Antiphospholipid syndrome.
	• Pernicious anemia.
	• Autoimmune aplastic anemia.
	• Autoimmune neutropenia.
	• Autoimmune pancytopenia.
		• Autoimmune glomerulonephritis including:
		  • IgA nephropathy,
		  • Glomerulonephritis rapidly progressive,
		  • Membranous glomerulonephritis,
		  • Membranoproliferative glomerulonephritis,
		  • Mesangioproliferative glomerulonephritis.
		  • Tubulointerstitial nephritis and uveitis syndrome.
		• Ocular autoimmune diseases including:
		  • Autoimmune uveitis
		  • Autoimmune retinitis.
		  • Autoimmune myocarditis.
		  • Sarcoidosis.
		  • Stevens-Johnson syndrome.
		  • Sjögren's syndrome.
		  • Alopecia areata.
		  • Idiopathic pulmonary fibrosis.
		  • Goodpasture syndrome.
		  • Raynaud's phenomenon.

Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis.	• Inflammatory Bowel disease, including: • Crohn's disease, • Ulcerative colitis, • Microscopic colitis, • Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type I. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.

When there is enough evidence to make any of the above diagnoses, the AE must be reported as pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMD until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

12.5.6. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. medical imaging) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 12.5.1 and 12.5.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

12.5.7. Events or outcomes not qualifying as adverse events or serious adverse events

12.5.7.1. Pregnancy

Female subjects who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine(s) but may continue other study procedures at the discretion of the investigator.

While pregnancy is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 12.5.9.1 and 12.5.9.4:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy

– stillbirth (intrauterine death of foetus after 22 weeks of gestation).

Note: the 22 weeks' cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognised that national regulations might be different.

- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccine(s) will be reported to GSK as described in Section 12.5.9. While the investigator is not obligated to actively seek this information from former subjects, he/she may learn of a pregnancy through spontaneous reporting.

12.5.8. Detecting and recording adverse events, serious adverse events and pregnancies

An eDiary hereafter referred to as Subject eDiary will be used in this study to capture solicited adverse events. The subject should be trained on how and when to complete each field of the Subject eDiary.

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

Subject eDiary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject eDiary.

- The same individual should complete the Subject eDiary throughout the course of the study.
- The subject should be trained on how to self-measure local solicited adverse events and body temperature.
- The measurement of solicited local adverse events is to be performed using the ruler provided by the site.
- Subjects will be instructed to measure and record the oral body temperature in the evening. Should additional temperature measurements be performed at other times of day, subjects will be instructed to record the highest temperature in the Subject eDiary.

Subject eDiary assignment and use:

- Each subject will be assigned a Subject eDiary and shown how to use the device – this will include how to access the eDiary, enter data to the eDiary screens, and how to charge and store the device.
- The subject will self-select a numeric access code secret to themselves. The same individual should make the assessments and complete the Subject eDiary throughout the course of the study.
- The subject will select an alarm time that suits their daily routines whilst ensuring compliance with protocol requirements.

Subject eDiary instructions must ensure that the subject understands the following:

- Timely completion of the Subject eDiary on a daily basis is a critical component to study participation.
- The Subject eDiary will allow certain time windows for completion of each day's observations.
- The Subject eDiary employs the use of audio-visual alarms to ensure timely completion of data entry.
- The trained and assigned user of the Subject eDiary must not share access codes with anyone.
- A helpdesk will be provisioned for users of Subject eDiary in case of technical issues, though it must be stressed that the Helpdesk is not a replacement for standard medical care and no medical issues can be discussed with the agents.
- The Subject eDiary itself must never be considered a substitute for direct medical care and any concerns must be communicated to site staff as soon as possible.
- For all groups the Subject eDiary will be used to collect solicited AEs until 7 days after each dose (i.e. day of vaccination and the 6 subsequent days). For groups 1a/b-3a/b of dose-escalation safety lead-in Subject eDiary will be returned on Day 8, for group 4a/b on Day 68 and for subjects in the PoP on Day 75 (groups 5a/b).
- The subject will be contacted by the site staff on Day 31 (all groups), Day 91 (dose-escalation safety lead-in Group 4 full dose adjuvanted and PoP both groups), Day 181 (Groups 1-3: half dose non-adjuvanted, full dose non-adjuvanted, half dose adjuvanted) and Day 241 (dose-escalation safety lead-in Group 4 full dose adjuvanted and PoP both groups) via a scripted safety follow-up phone call. Subjects in PoP Step 2 will also be contacted on Day 8 and Day 68 via a scripted safety follow-up phone call. At, or in advance of applicable phone call the site will review the eDiary web-portal for responses entered by the subject in order to solicit additional information during the phone call e.g. related to unsolicited adverse events, concomitant vaccinations/medication and medically attended events.
- Any new safety information reported during the safety follow-up phone call or site visits (including a solicited adverse event) cannot be entered into the Subject eDiary. Such information must be described in the source documents as a verbally-reported event. Any adverse event reported in this fashion must be described as an unsolicited

adverse event and therefore entered into the eCRF. This includes the assessment of COVID-19 cases per the WHO definition [WHO, 2020].

12.5.8.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All solicited AEs during 7 days following administration of each dose of study vaccine(s) (Day 1 to Day 7 and Day 61 to Day 67) must be recorded in the eDiary, irrespective of intensity or whether or not they are considered vaccination-related.

All other AEs during 30 days following administration of each dose of study vaccine(s) (Day 1 to Day 30 and Day 61 to Day 90) must be recorded in the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine(s) and will end 366 days following administration of the last dose of study vaccine(s) for each subject (i.e. the last study visit for each subject). See Section 12.5.9 for instructions on reporting of SAEs. However, any SAEs assessed as related to study participation (e.g. study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consent to participate in the study.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine(s).

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccine(s) and will end 366 days following administration of the last dose of study vaccine(s) (i.e. the last study visit for each subject). See Section 12.5.9 for instructions on reporting of pregnancies.

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine(s) and will end 366 days following administration of the last dose of study vaccine(s) (i.e. the last study visit for each subject). See Section 12.5.9.5 for instructions on reporting of pIMDs.

12.5.8.2. Evaluation of adverse events and serious adverse events

12.5.8.2.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine or since the previous visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. This includes the assessment of COVID-19 cases per the WHO definition [WHO, 2020]. The investigator is not allowed to send photocopies of the subject's medical records to GSK instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

12.5.8.2.2. Assessment of adverse events

Assessment of intensity

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

Table 34 Intensity scales for solicited adverse events in adults

Adults		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C/°F (with 1 decimal)
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Nausea	0	Normal
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Vomiting	0	Normal
	1	Mild: 1-2 times in 24 hours
	2	Moderate: 3-5 times in 24 hours
	3	Severe: 6 or more times in 24 hours or requires intravenous hydration
Diarrhoea	0	Normal
	1	Mild: 2 - 3 loose stools in 24 hours
	2	Moderate: 4 - 5 loose stools in 24 hours
	3	Severe: 6 or more loose stools in 24 hours or requires intravenous hydration
Abdominal pain	0	Normal
	1	Mild: No interference with daily activity
	2	Moderate: Interferes with daily activity
	3	Severe: Prevents daily activity
Myalgia	0	Normal
	1	Mild: No interference with daily activity
	2	Moderate: Interferes with daily activity
	3	Severe: Prevents daily activity
Shivering	0	Normal
	1	Mild: No interference with daily activity
	2	Moderate: Interferes with daily activity
	3	Severe: Prevents daily activity

*Fever is defined as temperature ≥ 38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity for adult subjects.
If any of the solicited symptoms meet the SAE criteria they will reported as a SAE.

The maximum intensity of local injection site redness/swelling/fever will be scored at GSK as follows:

0	:	< 25 mm diameter
1	:	≥ 25 mm to ≤ 50 mm diameter
2	:	> 50 mm to ≤ 100 mm diameter
3	:	> 100 mm diameter

Temperature will be scored at GSK Biologicals as follows:

0	:	< 100.4°F (38.0°C)
1	:	≥ 100.4°F (38.0°C) < 102.1°F (39.0°C)
2	:	≥ 102.1°F (39.0°C) ≤ 104°F (40.0°C)
3	:	> 104°F (40.0°C)

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

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

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

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in Section 12.5.2.

Grading of laboratory parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (Refer to Appendix 7, Section 12.7). Those laboratory parameters not included in the FDA Toxicity Grading Scale will not be graded.

Assessment of causality

The investigator is obligated to assess the relationship between study vaccine(s) and the occurrence of each AE/SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (i.e. investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s) cannot be determined, the investigator should indicate the AE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine(s) will be considered and investigated. The investigator will also consult the IB and to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

All solicited local (injection site) and solicited general adverse events will be considered causally related to vaccination.

Causality of all other AEs should be assessed by the investigator using the following question:

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

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

If an event meets the criteria to be determined as ‘serious’ (see Section 12.5.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol-required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccines, if applicable.
- Erroneous administration.
- Other cause (specify).

Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

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

12.5.9. Reporting of serious adverse events, pregnancies, and other events

12.5.9.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK

SAEs that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 23, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 23, once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 23, once the investigator determines that the event meets the protocol definition of a pIMD.

12.5.9.2. SAEs requiring expedited reporting to GSK

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the ‘reviewed’ box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

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

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

12.5.9.4. Completion and transmission of pregnancy reports to GSK

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 24 HOURS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

12.5.9.5. Reporting of pIMDs to GSK

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows specify that the event is a pIMD and whether it is serious or non-serious. The report will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMDs standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the pIMD causality by ticking the ‘reviewed’ box in the electronic Expedited Adverse Events Report within 72 hours of submission of the pIMD.

Refer to Section 12.5.9.3 for back-up system in case the electronic reporting system does not work.

12.5.10. Updating of SAE, pregnancy, and AESI information after removal of write access to the subject's eCRF

When additional SAE, pregnancy, or pIMD information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 23.

12.5.11. Follow-up of adverse events, serious adverse events, and pregnancies

12.5.11.1. Follow-up of adverse events and serious adverse events

12.5.11.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK (within 24 hours for SAEs; refer to Table 23).

All SAEs and pIMDs (serious or non-serious) documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last visit of the subject.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

12.5.11.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, pIMDs (serious or non-serious), or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- with other non-serious AEs, until event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or if the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies

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

12.5.11.2. Follow-up of pregnancies

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

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

12.6. Appendix 6: Contraceptive guidance and collection of pregnancy information

12.6.1. Definitions

12.6.1.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

12.6.1.1.1. Women in the following categories are not considered WOCBP

- Premenarchal:

  Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of subject's medical records, medical examination, or medical history interview.

- Postmenopausal female:

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

- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

12.6.2. Contraception guidance

- Female subjects of childbearing potential are eligible to participate if they agree to use an adequate contraception consistently and correctly according to the methods listed in GSK list of highly effective contraceptive methods provided in Table 35.

Table 35 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] **Failure rate of <1% per year when used consistently and correctly.**
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • oral • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomised partner *(A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject, *(The information on the male sterility can come from the site personnel's review of the subject's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

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

12.6.3. Collection of pregnancy information

12.6.3.1. Female Subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.5.9. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

  Any female subject who becomes pregnant while participating will be discontinued from study treatment and followed-up until the final outcome.

12.7. Appendix 7: FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007)

Tables for Laboratory Abnormalities

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

Table 36 FDA toxicity grading scales for hematology/ biochemistry parameters evaluated in the current study

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life-Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
*** "ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10 800 – 15 000	15 001 – 20 000	20 001 – 25 000	> 25 000
WBC Decrease - cell/mm^3	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000
Lymphocytes Decrease - cell/mm^3	750 – 1 000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1 500	1 501 - 5 000	> 5 000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000

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

12.8. Appendix 8: Protocol Amendment History

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

DOCUMENT HISTORY	
Document	Date of Issue
Amendment 6	6 October 2022
Amendment 5	22 June 2022
Amendment 4	30 November 2021
Amendment 3	15 June 2021
Amendment 2	2 April 2021
Amendment 1	26 May 2020
Protocol Version 1	4 September 2019

12.8.1. Protocol Amendment 6

Overall Rationale for the Amendment: The aim of this protocol amendment is to **ensure consistency across the different protocol sections related to the interim efficacy analysis, with reference to the possibility to continue the enrolment up to the planned number of events needed for the key efficacy endpoint evaluation (i.e.** CCI **and in case futility or efficacy criteria are met at the interim analysis based** CCI **. In addition, removal of previous GSK logo, correction of typographical errors, and minor edits for clarification have been made (refer to Section 12.8.1 for information).**

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Synopsis; Section 5.2.2	CCI [redacted]	
Section 10.1.1 Hypotheses related to primary and secondary	Update to text linked to hypotheses related to primary and secondary	To ensure consistency across the different protocol sections related to

Section # and Name	Description of Change	Brief Rationale
objectives	objectives	the interim efficacy analysis
Section 10.1.2 Sample size calculation	Update to text linked to sample size calculation and clarification for the basis of assumptions	To ensure consistency across the different protocol sections related to the interim efficacy analysis
CCI [redacted]		

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

In the Title page:

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'Institut 89,
1330 Rixensart, Belgium

Co-ordinating author(s)	PPD [redacted] (Scientific Writer ***for GSK***)
Contributing authors	• PPD [redacted] (~~CRDL~~***CSL***) • PPD [redacted] (SDL) • PPD [redacted] (~~ODM~~***DMQL***)

In the Sponsor Signatory page:

Sponsor signatory	Michele Pellegrini Clinical ~~& Epidemiology~~ Project Lead

In the Synopsis:

CCI [redacted]

In Section 5.2.2 PoP in subjects with recent S. aureus SSTI Group 5a/b (Phase II):

The study will follow a group sequential design with two analyses. CCI [redacted].

CCI

[redacted]

In Section 10.2. Sample size calculation:

CCI

[redacted]

12.8.2. Protocol Amendment 5

Overall Rationale for the Amendment: The aim of this protocol amendment is to add that during study conduct a presentation of the placebo in a prefilled syringe (PFS) may be used. In addition, correction of typographical error, minor edits for clarification, and the alignment of some sections to the current Company protocol template have also been made (refer to Section 12.8.1 for information).

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Section 7 Treatment	An additional presentation of placebo (saline line) has been added	Considering that current placebo presentation (Hollister Saline in vial) is expected to be discontinued in future, placebo (saline solution) in prefilled syringe presentation has been added as it might replace in future current vial presentation
Section 10.2. Population for analyses	Changed the definition of the enrolled set	To remove screening failures from the enrolled set
Section 10.2. Population for analyses	Added screened set within the population for analyses	A specific analytical set comprising of all subjects that were screened for eligibility

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

In the Title page:

Co-ordinating author(s)

PPD ***(Scientific Writer)*** ~~PPD (Scientific Writer for GSK)~~

Contributing authors

- PPD (CRDL)
- PPD (SDL)
- PPD (ODM)
- PPD (Study Statistician) ~~PPD (Study Statistician)~~
- PPD (Lead Statistician)
- PPD (CLS CRT-L)
- PPD (Safety Physician)
- PPD (Safety Scientist)
- PPD (GRA)
- PPD ~~(LML)~~
- PPD ~~(Lead VDL)~~

The following change in units:

From ml to m***L*** has been applied throughout the Protocol. This change has been indicated as black bold italics.

In Section 2 Schedule of Activities (SOA), Table 4:

[g] The blood sampling for safety lab evaluation only (~6 mL to be drawn from PoP Step 1 subject only) should occur on Day 1 ***and Day 61*** but, as an alternative, can be performed up to 1 day before vaccine administration.
[h]***Unscheduled visits can occur at any time after first study vaccination and should happen as soon as possible after signs/symptoms onset***
[i]***Occurrence of solicited AEs within 30 minutes post vaccination observation must be recorded in the eCRF***

In Section 2 Schedule of Activities (SOA), Table 6:

* Vaccination should occur after clinical resolution of culture confirmed SSTI caused by *S. aureus* ***and must occur within 30 days from the date of skin drainage for microbiology assessment (done either outside or in the study)***

In Section 6.2.1.1 Subjects to be enrolled in the dose-escalation safety lead-in epochs

*The investigator should use his/her clinical judgement to decide which abnormalities are clinically significant as follows: all Haematology/ Biochemistry parameters should be within local laboratory normal ranges for the subject to be eligible, unless the laboratory abnormalities are of Grade 1 ***(Refer to Appendix 7, Section 12.7)*** and considered not clinically significant by the investigator. See Appendix 2, Section ***12.2.2*** ~~12.2~~ for examples.

In Section 6.2.1.2 Subjects to be enrolled in the proof of principle epochs

*The investigator should use his/her clinical judgement to decide which abnormalities are clinically significant as follows: all Haematology/ Biochemistry parameters should be within local laboratory normal ranges for the subject to be eligible, unless the laboratory abnormalities are of Grade 1 ***(Refer to Appendix 7, Section 12.7)*** and considered not clinically significant by the investigator. See Appendix 2, Section ***12.2.2*** ~~12.2~~ for examples.

In Section 7.1 Treatments Administered, (Table 12)

Study Treatment Name:	**Sa-5Ag half dose non-adjuvanted**		**Sa-5Ag full dose non-adjuvanted**		**Sa-5Ag half dose adjuvanted**		**Sa-5Ag full dose adjuvanted ***		**Placebo**
Study intervention name	CCI [redacted]								
Study intervention formulation:									
Presentation	Powder for solution for injection/ vial	Solution for injection/ vial	Powder for solution for injection/ vial	Solution for injection/ vial	Powder for solution for injection/ vial	Suspension for suspension for injection/ vial	Powder for solution for injection/ vial	Suspension for suspension for injection/ vial	Solution for injection/ vial ***or prefilled syringe*** *****
Type	Study	Co-administration	Study	Co-administration	Study	Co-administration	Study	Co-administration	Control
Product category	Biological product	Biological product	Biological product	Biological product	Biological product	Biological product	Biological product	Biological product	~~Biological product~~ ***Combination product***
Route of Administration	IM		IM		IM		IM		IM
Administration site:									
Location	Deltoid		Deltoid		Deltoid		Deltoid		Deltoid
Directionality	Upper		Upper		Upper		Upper		Upper

Study Treatment Name:	**Sa-5Ag half dose non-adjuvanted**	**Sa-5Ag full dose non-adjuvanted**	**Sa-5Ag half dose adjuvanted**	**Sa-5Ag full dose adjuvanted ***	**Placebo**
Laterality * **	Non-dominant	Non-dominant	Non-dominant	Non-dominant	Non-dominant
Number of doses to be administered:	1	1	1	2****	1 or 2 ****
Volume to be administered ***	0.5 m***L***	0.5 m***L***	0.5 m***L***	0.5 m***L***	***at least 0.5*** m***L*** ~~0.5 m***L***~~
Packaging and Labelling	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	CCI [redacted]				

CCI [redacted] SPM = Study Procedures Manual

Note: The half dosage and the full dosage derive from the same product obtained by resuspending the lyophilised product with different volumes (NaCl CCI).

* *S. aureus* candidate vaccine

CCI [redacted]

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

**** The total number of doses is 1 or 2 depending on the study group, i.e. 2 doses only for subjects in group 4 dose-escalation safety lead-in treatment epoch and PoP treatment epoch

***** Refer to the SPM for the volume after reconstitution

****** ***The volume in the syringe may be between 0.6 mL and 0.8 mL. The full volume is to be injected.***

In Section 7.1 Treatments Administered

The subjects will be observed closely for at least 60 minutes following the administration of vaccine/placebo, with appropriate medical treatment readily available in case of anaphylaxis and syncope. ***Occurrence of solicited AEs within 30 minutes post vaccination observation must be recorded in the eCRF (Table 4).***

CCI

[redacted]

In Section 8.6.1. Staggered vaccination

Occurrence of solicited AEs within 30 minutes post vaccination observation must be recorded in the CRF (Table 4).

In Section 8.6.3. Study holding rules

Of note, no formal holding rules will be applied for other safety data such as non-life-threatening SAEs, missed visits due to vaccine-related AEs, Grade 1 and Grade 2 ***(Refer to Section 12.5.8.2.2)*** solicited and unsolicited AEs in the 7-day follow-up period and unsolicited AEs collected from Day 8 to Day 30 after vaccination. However, these data, if available, will also be reviewed by the safety assessment committee (SRT/iSRC as applicable) in order to allow for an overall assessment of the benefit/risk ratio of vaccination.

In Section 10.2. Populations for analyses

Screened	***All subjects who were screened for eligibility***
Enrolled	***All subjects who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). The allocation in a group will be done in function of the randomized intervention; non-randomized subjects will be part of a "Non randomized" group. Note: screening failures (who never passed screening even if rescreened) and subjects screened but never enrolled into the study (met eligibility but ultimately not enrolled) are excluded from the Enrolled analysis set as they did not enter the study.*** ~~All subjects who sign informed consent~~
~~Randomized~~	~~All subjects who sign informed consent and are randomized to the treatment group~~

CCI

In Section 12.3. Clinical laboratories Table 28

Laboratory*	**Address**
GSK Biological's Clinical Laboratory Sciences, Rixensart	Biospecimen Reception-B7/44 Rue de l'Institut, 89 B-1330 Rixensart Belgium
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20 B-1300 Wavre Belgium
GSK Vaccines S.r.l Preclinical R&D, Italy	Via Fiorentina 1 53100 Siena Italy

GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium or Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Siena, Italy or to an external laboratory.

In Section 12.3. Clinical laboratories Table 29

Laboratory	**Address**
Q^2 Solutions Clinical Trials (UK)	The Alba Campus Rosebank Livingston West Lothian, EH54 7EG Scotland, UK
Q^2 Solutions Clinical Trials (US)	27027 Tourney Road, Suite 2E Valencia, CA 91355 USA
~~Nexelis Impfstoffforschung (Marburg, Germany)~~	~~Emil-von-Behring-Str. 76~~ ~~35041 Marburg~~ ~~Germany~~

In Section 12.5.2. Definition of SAE

Grade 4 laboratory abnormalities ***(Refer to Appendix 7, Section 12.7)***.

In Section 12.5.8.2.2. Assessment of adverse events

Grading of laboratory parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (Refer to Appendix 7, Section 12.7). Those laboratory parameters not included in the FDA Toxicity Grading Scale will not be graded.

12.8.3. Protocol Amendment 4

Overall Rationale for the Amendment: The aim of this protocol amendment is to facilitate the enrolment of subjects with *S. aureus* SSTIs for the PoP phase (Phase II) of the study, by extending the allowed upper age limit from 50 to 64 years, allowing enrolment of subjects with well-controlled type 2 diabetes mellitus and/or arterial hypertension, and extending the interval between *S. aureus* SSTI microbiological diagnosis and signature of the informed consent from 14 days to 30 days. In addition, correction of typographical error, minor edits for clarification, and the alignment of some sections to the current Company protocol template have also been made (refer to Section 12.8.1 for information).

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Title page and signature pages (short title and title) Synopsis, Figure 1 and Figure 3 Section 5.2 Overall design, Figure 4 Section 5.2.2 PoP in subjects with recent S. aureus SSTI Group 5a/b (Phase II),Figure 6, Table 11 Section 6.1 Inclusion criteria for enrolment	The age range has been extended from 18 to 50 years of age to 18 to 64 years of age	To facilitate the enrolment of subjects with *S. aureus* SSTIs for the PoP phase (Phase II) of the study.
Synopsis (including Figure 3) Section 2 Schedule of Activities, Table 4 and footnote Section 2 Schedule of Activities, Table 7 and footnote Section 5.2.2 PoP in subjects with recent S. aureus SSTI Group 5a/b (Phase II): Figure 6 and footnote,	The time interval between *S. Aureus* SSTI microbiological diagnosis and the signing of the informed consent form has been extended from 14 to 30 days in the PoP screening phase	To facilitate the enrolment of subjects with *S. aureus* SSTIs for the PoP phase (Phase II) of the study.

Section # and Name	Description of Change	Brief Rationale
duration of the study, and sampling schedule Section 6.1 Inclusion criteria for enrolment, Additional inclusion criteria only for subjects to be enrolled in the PoP screening epoch Section 8.4.2.1 Sampling for efficacy assessments and Table 14 Section 8.5.2 Time period and frequency for collecting AE and serious adverse event (SAE) information, Table 22 Reporting periods for collecting safety information (PoP)		
Section 6.2.1.2 Subjects to be enrolled in the proof of principle (PoP) epochs, Exclusion criteria to be considered at study entry	Wording was added to clarify that subjects with well-controlled type 2 diabetes mellitus (defined as HbA1c <7%) and well-controlled hypertension (defined as blood pressure < 140/90 mmHg) may be considered for enrolment in the study	To facilitate the enrolment of subjects with *S. aureus* SSTIs for the PoP phase (Phase II) of the study.
Section 8.5.4 Reporting of serious adverse events, pregnancies, and other events, Table 23 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Section 12.5.9.4 Completion and transmission of pregnancy reports to GSK Section12.6.3.1 Female subjects who become pregnant	Change the timeframe for submitting pregnancy reports to GSK from 2 weeks to 24 hours and correct the footnote	To update the timeframe for submitting pregnancy reports to GSK to align with current Company requirements

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

In the Title page:

EudraCT number	***2021-006215-29***
Short title	Safety, immunogenicity and efficacy of GSK *S. aureus* candidate vaccine (GSK3878858A) when administered to healthy adults (dose-escalation) and

	to adults 18 to ***64~~50~~*** years of age with a recent *S. aureus* skin and soft tissue infection (SSTI).
Title	A Phase I/II, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK S. aureus candidate vaccine when administered to healthy adults (dose-escalation) and to adults 18 to ***64~~50~~*** years of age with a recent S. aureus skin and soft tissue infection (SSTI).
Co-ordinating author(s)	PPD ~~and~~ PPD ~~(Scientific Writers)~~ PPD ***(Scientific Writer for GSK)***
Contributing authors	• PPD ~~and~~ PPD (CLS CRT-L) • PPD ~~(LDL)~~ • PPD ~~(DPL)~~ PPD ***(Lead VDL)***

In Protocol Amendment 4 Sponsor signatory approval:

EudraCT number	***2021-006215-29***
Title	A Phase I/II, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK S. aureus candidate vaccine when administered to healthy adults (dose-escalation) and to adults 18 to ***64~~50~~*** years of age with a recent S. aureus skin and soft tissue infection (SSTI).

In Protocol Amendment 4 Investigator agreement:

- ***That I will comply with the terms of the site agreement.***

EudraCT number	***2021-006215-29***
Title	A Phase I/II, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK S. aureus candidate vaccine when administered to healthy adults (dose-escalation) and to adults 18 to ***64~~50~~*** years of age with a recent S. aureus skin and soft tissue infection (SSTI).

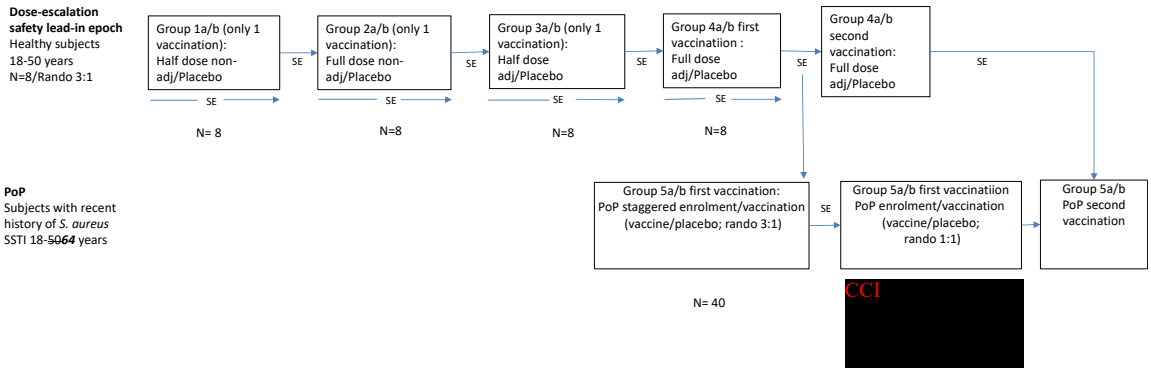
In Synopsis:

CCI

CCI

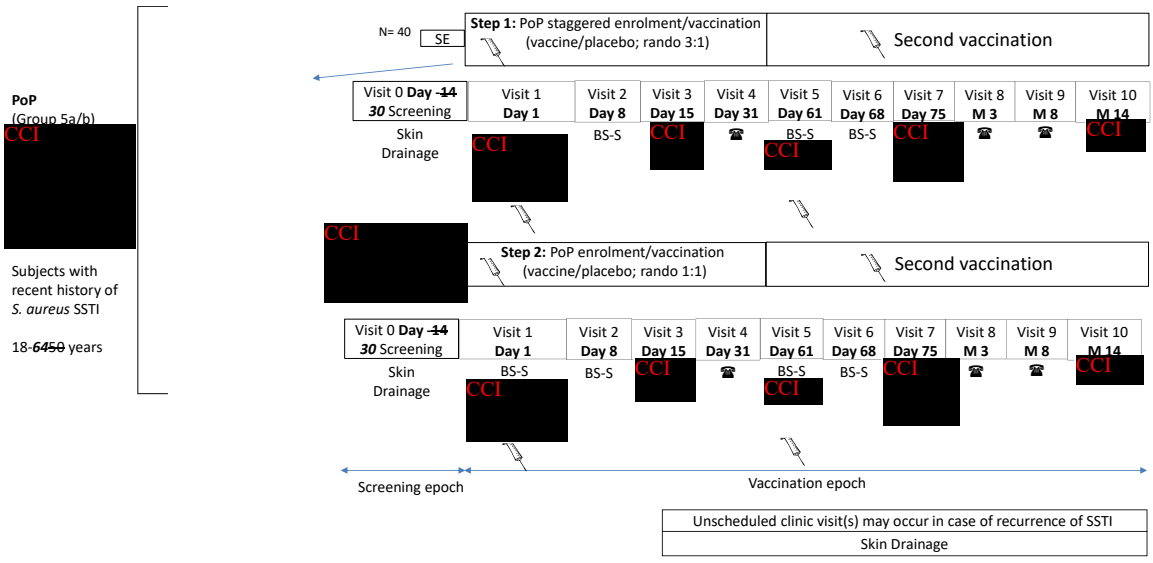
[redacted]

Overall design, Figure 1 Overall design



PoP in subjects with recent *S. aureus* SSTI:

Figure 3 Study design overview PoP in subjects with a recent *S. aureus* SSTI Group 5a/b:



Note: CDISC is not calculating with Day 0, i.e. interval between Day –***30*** and Day 1 is ***30*** days.

In the PoP screening epoch, study subjects can be selected according to the following ways:

1. Subjects with signs and symptoms of an ongoing skin infection and purulent lesion, i.e. SSTI, suspected to be caused by *S. aureus* will be enrolled after signing an informed consent form (ICF). ***Subjects with surgical site infections are not eligible for entry in this study.*** Subjects with surgical site infections are not included in the target population. After demonstration of *S. aureus* positive culture, performed as a study procedure, and confirmation by investigator that *S. aureus* is the most likely cause of SSTI, subjects will continue in the study. Diagnosis (e.g. abscess or cellulitis) and body location will be collected in the eCRF. In addition, data related to *S. aureus* CCI [redacted] and recorded in the eCRF. Specific treatment will be given in compliance with the standard medical practice for the management of *S. aureus* SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures. After conclusion of the specific treatment for the skin lesion and after clinical resolution of the SSTI (e.g. no signs of ongoing infection such as swelling, erythema, pain or drainage), the first dose of *S. aureus* candidate vaccine or placebo will be administered.
2. Subjects with an ongoing *S. aureus* SSTI (i.e. *S. aureus* is the most likely cause), as confirmed by positive culture performed outside the study procedures and not earlier than ~~14~~***30*** days prior to ICF signature. ***Subjects with surgical site infections are not eligible for entry in this study.*** Diagnosis (e.g. abscess or cellulitis) and body location will be collected in the eCRF. In addition, *S. aureus* CCI [redacted] and recorded in the eCRF. These subjects will be enrolled whether they have or have not already started specific treatment of the infection. In case they have not started the treatment, this will be then given in compliance with the standard medical practice for the management of *S. aureus* SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures. After conclusion of the specific treatment for the skin lesion and after clinical resolution of the SSTI (e.g. no signs of ongoing infection such as swelling, erythema, pain or drainage), the first dose of *S. aureus* candidate vaccine or placebo will be administered.

In Section 2 Schedule of Activities (SOA), Table 2:

CCI [redacted]

Safety assessments
Medical history
History of administration of adjuvanted vaccine
Urine pregnancy test
Check contraindications and warnings and precautions to vaccination
Pre-vaccination body temperature
Blood sampling for safety laboratory evaluation (~6 m***L***)

In Section 2 Schedule of Activities (SOA), Table 3:

CCI

[redacted]

In Section 2 Schedule of Activities (SOA), Table 4 and footnote:

Table 4 Schedule of activities (Group 5a/b, PoP screening epoch, PoP vaccination epochs)

Epoch	PoP screening	PoP vaccination										
Type of contact	V0	V1	V2 Clinic visit or Phone call[e]	V3	V4 Phone call	V5	V6 Clinic visit or Phone call[e]	V7	V8 Phone call	V9 Phone call	V10	Unscheduled visit
Time points	Day –*30*[a]	Day 1	Day 8	Day 15	Day 31	Day 61	Day 68	Day 75	Day 91 (M 3)	Day 241 (M 8)	Day 426 (M 14)	
Sampling time points		Pre-Vac1				Pre-Vac2						
Informed consent by subjects	●											
Check inclusion/exclusion criteria	●	●										
Physical examination	O	●				●						
Verification of clinical resolution of SSTI		●										
Collect demographic data	●											
Vaccine(s)/Product(s)												
Study group and treatment number allocation		O										
Treatment number allocation for subsequent doses						O						
Recording of administered treatment number		●				●						
Vaccine administration		●				●						
CCI [redacted]												
Clinical Specimens for microbiology assessments												
Sampling of drainage for cultures performed in the study	●											●[c]
Check of culture test report for SA-SSTI confirmation	●											●
CCI [redacted]												

Epoch	**PoP screening**	**PoP vaccination**										
Type of contact	**V0**	**V1**	**V2 Clinic visit or Phone call[e]**	**V3**	**V4 Phone call**	**V5**	**V6 Clinic visit or Phone call [e]**	**V7**	**V8 Phone call**	**V9 Phone call**	**V10**	**Unscheduled visit**
Time points	**Day –*30*[a]**	**Day 1**	**Day 8**	**Day 15**	**Day 31**	**Day 61**	**Day 68**	**Day 75**	**Day 91 (M 3)**	**Day 241 (M 8)**	**Day 426 (M 14)**	
Sampling time points		**Pre-Vac1**				**Pre-Vac2**						
Safety assessments												
Medical history	●	●										
History of administration of adjuvanted vaccine	●	●										
Urine pregnancy test	●	●				●						
Check contraindications and warnings and precautions to vaccination	O	O				O						
Pre-vaccination body temperature		●				●						
Blood sampling for safety laboratory evaluation (~6 m*L*) (PoP Step 1 subjects only)[g]		●	●			●	●					
Phone contact (PoP Step 2 subjects only)			●				●					
Record any concomitant medication/vaccination		●	●	●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●	●	●	●
Distribution of eDiaries and training		O				O[f]						
Review of eDiary data		O	O				O					
Return of eDiaries to the sites								O				
Phone contact (all subjects)					●				●	●		
Recording of solicited adverse events		O				O						
Recording of unsolicited adverse events		●	●	●	●	●	●	●	●			
Occurrence of solicited AEs at the investigator's site within 30 minutes post-vaccination observation		●				●						
Reporting of pIMDs		●	●	●	●	●	●	●	●	●	●	●
Reporting of SAEs, pregnancies and pregnancy outcomes	●	●	●	●	●	●	●	●	●	●	●	●
Study Conclusion											●	

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

[a] CDISC is not calculating with Day 0, i.e. interval between Day –***30*** and Day 1 is ***30*** days.

[b] [redacted].

[c] SSTI must be amenable to microbiological culturing per standard clinical practice.

CCI [redacted]

[e] Visit 2 and 6: Clinical visit for PoP Step 1 subjects (i.e. first 40 subjects enrolled in the PoP) where 6 ml of whole blood for safety laboratory evaluation will be collected; Phone call for PoP Step 2 subjects (i.e. all those following subjects after the first 40 enrolled in the PoP Step 1).

[f] Remind subjects that the device is now ready to collect after Dose 2 data.

[g] ***The blood sampling for safety lab evaluation only (~6 mL to be drawn from PoP Step 1 subject only) should occur on Day 1 but, as an alternative, can be performed up to 1 day before vaccine administration.***

a/b = vaccine/placebo

CCI [redacted]

pIMDs = potential Immune-Mediated Diseases
SAE = Serious Adverse Event
Vac = Vaccination
M = Month
V = Visit

In Section 2 Schedule of Activities (SOA), Table 7 and footnote:

Table 7 Intervals between study visits (PoP epochs)

Group 5a/b	Interval	Length of interval	Allowed interval
~~Subjects with *S. aureus* positive culture, performed as a study procedure~~	~~V0 (Day –14) →V1 (Day 1)~~	~~14 days~~	~~14 - 29 days*~~
~~Subjects with *S. aureus* positive culture performed outside **or in** the study procedures~~ ***All subjects***	V0 (Day -***30***~~14~~ up to Day 1) →V1 (Day 1)	up to ***30*** ~~14~~ days	0 - ~~29~~***30*** days*
	V1 (Day 1)→V2 (Day 8)	7 days	7 - 9 days
	V1 (Day 1)→V3 (Day 15)	14 days	14 - 21 days
	V1 (Day 1)→V4 (Day 31)	30 days	30 - 37 days
	V1 (Day 1)→V5 (Day 61)	60 days	60 - 67 days
	V5 (Day 61)→V6 (Day 68)	7 days	7 - 9 days
	V5 (Day 61)→V7 (Day 75)	14 days	14 - 21 days
	V5 (Day 61)→V8 (Month 3, day 91)	30 days	30 - 40 days
	V5 (Day 61)→V9 (Month 8, day 241)	180 days	180 - 190 days
	V5 (Day 61)→V10 (Month 14, day 426)	365 days	365 - 380 days

Note: CDISC is not calculating with Day 0, i.e. interval between Day –***30***~~14~~ and Day 1 is ***30***~~14~~ days.

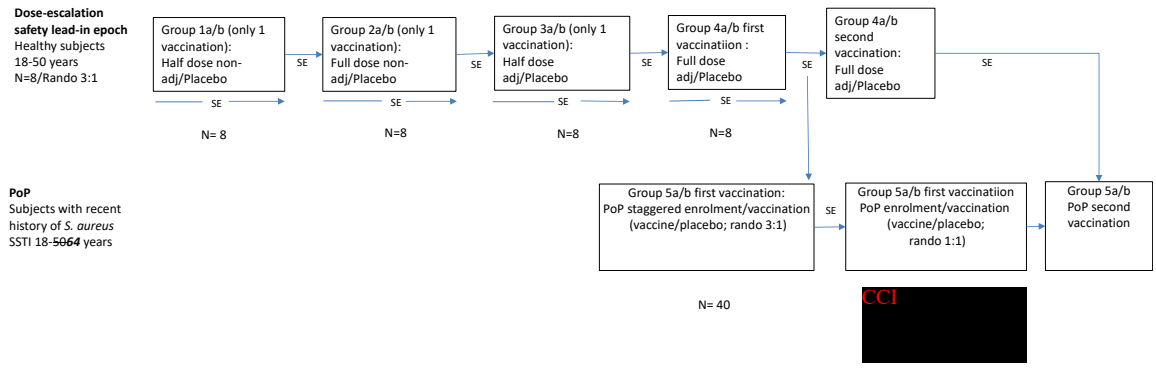
In Section 3.2.2 GSK Biologicals *Staphylococcus aureus* candidate vaccine:

CCI [redacted]

CCI [redacted]

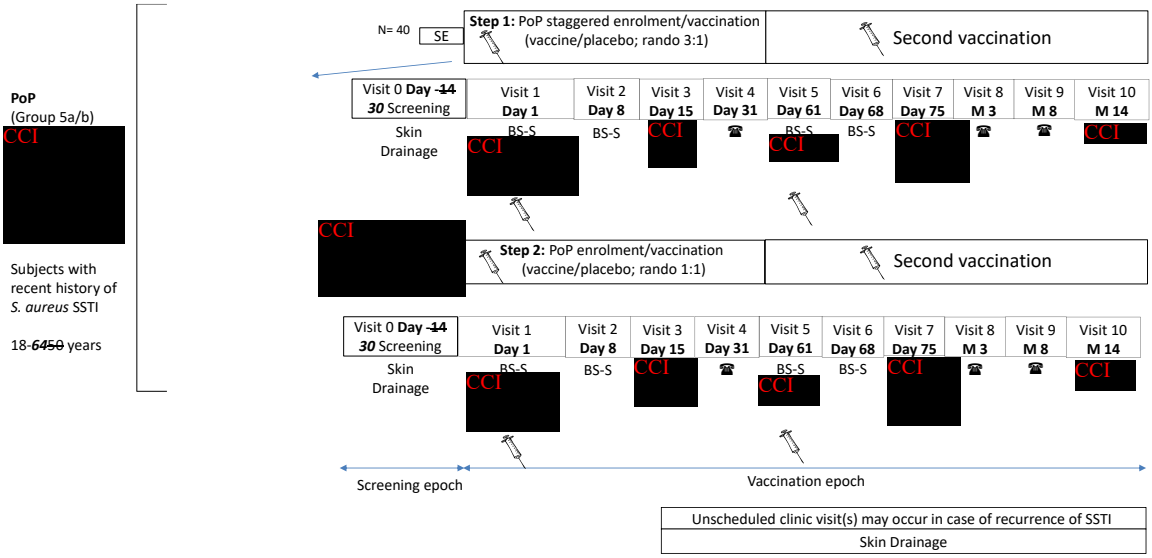
In Section 5.2 Overall design, Figure 4:

Figure 4 Overall design



In Section 5.2.2 PoP in subjects with recent S. aureus SSTI Group 5a/b (Phase II):

Figure 6 Study design overview PoP in subjects with a recent *S. aureus* SSTI and footnote:



Note: CDISC is not calculating with Day 0, i.e. interval between Day –*30*~~14~~ and Day 1 is *30*~~14~~ days.

Duration of the study:

- PoP screening epoch: starting at Visit 0 ~~(Day -14)~~ and ending just before Visit 1~~(Day 1)~~.
- PoP vaccination epoch: starting with vaccination at Visit 1 ~~(Day 1)~~ and ending just before Visit 10 ~~(Month 14 [Day 426])~~.

In the PoP screening epoch, study subjects can be selected according to the following ways:

1. Subjects with signs and symptoms of an ongoing skin infection and purulent lesion, i.e. SSTI, suspected to be caused by *S. aureus* will be enrolled after signing an informed consent form (ICF). ***Subjects with surgical site infections are not eligible for entry in this study.*** After demonstration of *S. aureus* positive culture, performed as a study procedure, and confirmation by investigator that *S. aureus* is the most likely cause of SSTI, subjects will continue in the study. Diagnosis (e.g. abscess or cellulitis) and body location will be collected in the eCRF. In addition, data related to *S. aureus* CCI [redacted] and recorded in the eCRF. Specific treatment will be given in compliance with the standard medical practice for the management of *S. aureus* SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures. After conclusion of the specific treatment for the skin lesion and after clinical resolution of the SSTI (e.g. no signs of ongoing infection such as swelling, erythema, pain or drainage), the first dose of *S. aureus* candidate vaccine or placebo will be administered.
2. Subjects with an ongoing *S. aureus* SSTI (i.e. *S. aureus* is the most likely cause), as confirmed by positive culture, performed outside the study procedures and not earlier than ~~14~~***30*** days prior to ICF signature. ***Subjects with surgical site infections are not eligible for entry in this study.*** Diagnosis (e.g. abscess or cellulitis) and body location will be collected in the eCRF. In addition, *S. aureus* CCI [redacted] and recorded in the eCRF. These subjects will be enrolled whether they have or have not already started specific treatment of the infection. In case they have not started the treatment, this will be then given in compliance with the standard medical practice for the management of *S. aureus* SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures. After conclusion of the specific treatment for the skin lesion and after clinical resolution of the SSTI (e.g. no signs of ongoing infection such as swelling, erythema, pain or drainage), the first dose of *S. aureus* candidate vaccine or placebo will be administered.

Study groups, Table 11:

Table 11: Study groups, treatment and epochs foreseen in the study (PoP epochs)

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Epochs (Blinding)	
				PoP screening (N/A)	PoP vaccination (observer-blind)
Group 5a Vaccine	250*	18 – ***64*** ~~50~~ years	Sa-5Ag full dose adjuvanted	•	•
Group 5b Placebo	250*	18 - ***64*** ~~50~~ years	Placebo	•	•

N/A = Not Applicable
*Design of the study is event driven and it can be only estimated that approximately 250 to 300 subjects per study group may be needed. Enrolment may continue until CCI [redacted] are reached.

Sampling schedule:

- Drainage samples will be taken from those subjects performing culture test as study procedures at screening (i.e. ~~Day -14 [~~Visit 0~~]~~) and from all subjects with recurrences at the time of recurrence.

In Section 6.1 Inclusion criteria for enrolment:

- A male or female:
  - ***Dose escalation and safety lead-in phase: A***ged between 18 and 50 years of age, inclusive, at the time of first vaccination.
  - ***PoP phase: Aged between 18 and 64 years of age, inclusive, at the time of first vaccination.***
- Female subjects of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause. ***Refer to Section 12.6.1 for definitions of women of child-bearing potential, menarche and menopause.***

In Section 6.1 Inclusion criteria for enrolment, Additional inclusion criteria only for subjects to be enrolled in the PoP screening epoch:

- Healthy subjects as established by medical history and clinical examination before entering into the study with an ongoing *S. aureus* SSTI (i.e. *S. aureus* is the most likely cause), as confirmed by a *S. aureus* positive culture performed outside the study procedures and not earlier than ***30***~~14~~ days prior to ICF signature.

In Section 6.2.1.2 Subjects to be enrolled in the proof of principle epochs, Exclusion criteria to be considered at study entry:

- Acute or chronic, clinically significant pulmonary, cardiovascular*****, hepatic or renal functional abnormality, neoplasm, diabetes type 1 and ***uncontrolled diabetes type*** 2*****, as determined by physical examination or laboratory screening tests.

  **** Note: Well-controlled type 2 diabetes mellitus (HbA1c <7%) and well-controlled arterial hypertension (blood pressure <140/90 mmHg) can be considered for inclusion in the study.***

In Section 6.2.2 Prior/concomitant therapy:

- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first vaccine/placebo dose. For corticosteroids, this will mean prednisone ≥***20***~~5~~ mg/day, or equivalent. Inhaled and topical steroids are allowed.

In Section 7.1 Treatments administered, Table 12:

Table 12 Treatments administered

Study Treatment Name:	**Sa-5Ag half dose non-adjuvanted**		**Sa-5Ag full dose non-adjuvanted**		**Sa-5Ag half dose adjuvanted**		**Sa-5Ag full dose adjuvanted ***		**Placebo**
Study intervention ~~**Vaccine(s)/ Product(s)**~~ **name**	CCI [redacted]								
Study intervention ~~**Vaccine(s) / Product(s)**~~ **formulation:**									
Presentation	~~Lyophilized form in vial~~ ***Powder for solution for injection/*** vial	***Solution for injection/*** ~~Liquid in~~ vial	~~Lyophilized form in vial~~ ***Powder for solution for injection/*** vial	***Solution for injection/*** ~~Liquid in~~ vial	~~Lyophilized form in vial~~ ***Powder for solution for injection/*** vial	~~Liquid in~~ ***Suspension for suspension for injection/*** vial	~~Lyophilized form in vial~~ ***Powder for solution for injection/*** vial	~~Liquid in~~ ***Suspension for suspension for injection/*** vial	***Solution for injection/*** ~~Liquid in~~ vial
Type	***Study***	***Co-administration***	***Study***	***Co-administration***	***Study***	***Co-administration***	***Study***	***Co-administration***	***Control***
Product category	***Biological product***	***Biological product***	***Biological product***	***Biological product***	***Biological product***	***Biological product***	***Biological product***	***Biological product***	***Biological product***
Route of Administration	IM		IM		IM		IM		IM

Study Treatment Name:	**Sa-5Ag half dose non-adjuvanted**	**Sa-5Ag full dose non-adjuvanted**	**Sa-5Ag half dose adjuvanted**	**Sa-5Ag full dose adjuvanted ***	**Placebo**
Administration site:					
Location	Deltoid	Deltoid	Deltoid	Deltoid	Deltoid
Directionality	Upper	Upper	Upper	Upper	Upper
Laterality * **	Non-dominant	Non-dominant	Non-dominant	Non-dominant	Non-dominant
Number of doses to be administered:	1	1	1	2****	1 or 2 ****
Volume to be administered ***	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Packaging and Labelling	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	CCI [redacted]				

In Section 7.3.1 Emergency unblinding, Table 13:

GSK Helpdesk 24 hours/7 days availability
The Helpdesk is available by phone, fax and email Phone: +32 2 656 68 04 Fax: +32 2 401 25 75 email: rix.ugrdehelpdesk@gsk.com For US Toll-free number: ***1 844 446 3133***~~877 870 0019~~

In Section 7.5.2 Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥***20***~~5~~ mg/day, or equivalent. Inhaled and topical steroids are allowed.

In Section 8.3 Case definition of recurrent *S.aureus* SSTI:

- If results from microbiological diagnostics in the investigator's opinion suggest that *S. aureus* is the primary cause of the SSTI, then the case will be considered ***as*** a culture confirmed recurrence.
- If results from microbiological diagnostics are inconclusive, or if no microbiological testing was performed, then the case will be considered ***as*** a suspected recurrence.

CCI [redacted]

In Section 8.4.2.1 Sampling for efficacy assessments:

Skin drainage samples will be collected from those subjects in the PoP performing culture test as a study procedure at screening (i.e. Day ~~–14~~***30*** [Visit 0]) and from all subjects at the time of their recurrence of SSTI (i.e. unscheduled visits).

Drainage samples will not be stored.

Table 14 Biological samples for efficacy assessment (PoP)

Sample type	Quantity	Unit	Timepoint	Subjects
Drainage samples	Depends on availability		Day ~~–14~~***30*** (V0) Unscheduled*	Subjects with SSTI who perform culture test as a study procedure at screening Subjects with suspected SA-SSTI

V = Visit

* Additionally, subjects with recurrent SSTI at the time of recurrence

In Section 8.4.2.2 Blood sampling for immunogenicity response assessments:

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 125 ~~ml~~ ***mL*** for subjects participating in the dose-escalation safety lead-in and will not exceed 274 ~~ml~~ ***mL*** for subjects participating in the PoP.

CCI

[redacted]

In Section 8.5.2 Time period and frequency for collecting AE and serious adverse event (SAE) information, Table 22

Table 22 Reporting periods for collecting safety information (PoP)

Event	Study group	Pre-Vac	Vac1			Vac2			Study Conclusion
	Vaccine Placebo	D–***30****	D1	D7	D30	D61	D67	D90	D426 M14

In Section 8.5.4 Reporting of serious adverse events, pregnancies, and other events, Table 23 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK

Table 23 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	***24 hours*** ~~2 weeks~~*	electronic pregnancy report	***24 hours*** ~~2 weeks~~*	electronic pregnancy report
pIMDs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours*	Electronic Expedited Adverse Events Report

***** Timeframe allowed after receipt or awareness of the information.
******Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.
‡ The investigator will be required to confirm review of the SAE/pIMD causality ~~by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report~~ within 72 hours of submission of the SAE/pIMD.

In Section 10.3.3.1 Case accountability:

Endpoint	Statistical Analysis Methods
Key secondary	The analysis of efficacy will be based on the occurrence of the first case of SSTI anytime from 15 Days after the administration of the second dose of the study vaccine up to 12 months. All subjects from the mFAS will contribute to the comparison between the treatment and the placebo groups. Time to occurrence of key secondary endpoint during the defined efficacy follow-up period will be compared between groups by calculating the respective Hazard ratio (methods will be detailed in the SAP). Vaccine (VE) will be defined as 1 minus the hazard ratio times 100: VE = (1 – hazard ratio) x 100 Censoring will occur at the time of the last scheduled or medically attended visit without the occurrence of SSTI cases before the end of follow-up. Subjects who will complete the follow-up without events will be censored at 1 year. In order to check the statistical significance, 1-sided P-value for the log rank test will be calculated. 1-sided nominal type I error will be 1.61% at the interim analysis and 5.89% at the final analysis. The objective will be met if the 1-sided P-value calculated for the null hypothesis H0 = [occurrence SSTI VE **=≥**0%] is lower than defined 1-sided alpha level.
Co-secondary	The co- secondary endpoint will be analysed only if the statistical significance is demonstrated for the key secondary endpoint. For this analysis, the ~~m~~FAS will account for the first case of SSTI anytime from 15 Days after the administration of the first dose of the study vaccine up to 14 months. Time to occurrence of the co- secondary endpoint during the defined efficacy follow-up period will be compared between groups by calculating the respective Hazard ratio (methods will be detailed in the SAP). In order to check the statistical significance, 1-sided P-value for the log rank test will be calculated. 1-sided nominal type I error will be 5.89%. (the nominal alpha level is equal to the key secondary at the final analysis, because we use a sequential procedure). The objective will be met if the 1-sided P-value calculated for the null hypothesis H0=[occurrence SSTI VE **=≥**0%] is lower than defined 1-sided alpha level.

In Section 10.3.4 Immunogenicity analyses

Endpoint	Statistical Analysis Methods
CCI [redacted]	

CCI [redacted]

In Section 12.1.1 List of abbreviations:

CCI [redacted]

LOD: ***Limit of Detection***

LLOQ: ***Lower Limit of Quantitation***

In Section 12.2.2 Laboratory assays for safety evaluation:

- If values out of normal ranges (Grade 1 considered clinically significant or above Grade 1) are observed, which are expected to be temporary (e.g., due to dehydration), the abnormal parameters can be re-assessed during a rescreening* visit but they must have returned to within local laboratory normal ranges for the subject to be eligible. If considered necessary by the investigator, related parameters outside of the panel can be (re-)tested in addition to the abnormal parameters (Haematology/Biochemistry). The subjects should be informed about the possibility of rescreening* in the informed consent form (ICF).

  **** Rescreening of subjects with previous screening failure due to non-S. aureus SSTI is also possible. In such cases, the complete screening process should be reperformed.***

In Section 12.4.4 Data protection:

GSK will also ensure the protection of personal data of investigator and the site staff which will be collected within the frame***work*** and for the purpose of the study***, in accordance with the Data Privacy Notice that will be sent to the site staff.***

In Section 12.4.9 Study and site start and closure:

Heading: Section 12.4.9 Study and site ***start and*** closure

First act of recruitment

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

Study/Site termination

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will be upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development
- ***Total number of subjects included earlier than expected***

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

~~The investigator will:~~

- ~~Review data collected to ensure accuracy and completeness.~~
- ~~Complete the Study Conclusion screen in the eCRF.~~

In Section 12.5.8 Detecting and recording adverse events, serious adverse events and pregnancies:

Subject eDiary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject eDiary. ~~This individual may not be the subject, but if a person other than the subject enters information into the Subject eDiary, this must be documented in the subject's source record. Any individual that makes entries into the Subject eDiary must receive training on completion of the Subject eDiary at the time of the visit when Subject eDiary is dispensed. This training must be documented in the subject's source record.~~

Subject eDiary assignment and use:

- Each subject will be assigned a Subject eDiary and shown how to use the device – this will include how to access the eDiary, ~~performing test data entry on sample questions~~ ***enter data into the eDiary screens***, and how to charge and store the device.

In Section 12.5.9.4 Completion and transmission of pregnancy reports to GSK:

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN ~~2 WEEKS~~ ***24 HOURS***.

In Section 12.6.2 Contraception guidance, Table 35 Highly Effective Contraceptive Methods and footnote:

Highly Effective Contraceptive Methods That Are User Dependent [a] ***Failure rate of <1% per year when used consistently and correctly.***
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • oral • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomised partner *(A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject, *(The information on the male sterility can come from the site personnel's review of the subject's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:
a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.
~~b Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilised during the treatment period and for at least 30 days after the last dose of study treatment~~

In Section 12.6.3.1 Female subjects who become pregnant:

- Information will be recorded on the appropriate form and submitted to GSK within ***24 hours*** ~~2 weeks~~ of learning of a subject's pregnancy.

12.8.4. Protocol Amendment 3

Overall Rationale for the Amendment: The sponsor is updating the clinical research phase of the study from Phase I toPhase I/II to account for the design of the study which, in its Proof of Principle epoch, aims to also generate evidence on the efficacy of the vaccine to prevent recurrences of Skin and Soft Tissue Infections due to *Staphylococcus aureus* in the target population.

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Title page and signature pages Synopsis Section 3.1, Study rationale Section 5.1, Scientific rationale for study design Section 5.2, Overall design	The phase has been modified from Phase I to Phase I/II.	Change to account for the design of the study which, in its Proof of Principle epoch,.aims to also generate evidence on the efficacy of the vaccine to prevent recurrences of Skin and Soft Tissue Infections due to *Staphylococcus aureus* in the target population
Section 8.5.4.1, Contact information for reporting of serious adverse events (SAEs), pIMDs, pregnancies and study holding rules	The contact phone numbers and e-mail address for non-US sites were added.	Change needed to allow other countries, outside the US, to potentially support screening and enrolment of participants of the POP part of the study .

Detailed description of Protocol Amendment 3:

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

In the Title page:

Title	A Phase I***/II***, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK *S. aureus* candidate vaccine when administered to healthy adults (dose-escalation) and

	to adults 18 to 50 years of age with a recent *S. aureus* skin and soft tissue infection (SSTI).
Co-ordinating author(s)	PPD and PPD (Scientific Writers) ~~and~~PPD ~~(Scientific writer for GSK)~~

In Protocol Amendment 3 Sponsor signatory approval and Protocol Amendment 3 Investigator agreement:

Title	A Phase I***/II***, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK *S. aureus* candidate vaccine when administered to healthy adults (dose-escalation) and to adults 18 to 50 years of age with a recent *S. aureus* skin and soft tissue infection (SSTI).

In Synopsis:

Rationale: The purpose of this ***seamless Phase I/II,*** first time in human - proof of principle (FTIH-PoP) study is to assess safety and reactogenicity, to perform a preliminary evaluation of clinical efficacy and to explore immunogenicity of GSK Biologicals' *S. aureus* vaccine compared to placebo (saline), both administered in a 2-dose schedule on Day 1 and Day 61.

Overall design: This is a Phase I***/II***, placebo-controlled, observer-blind, randomised, multi-centric study.

In Section 3.1, Study rationale:

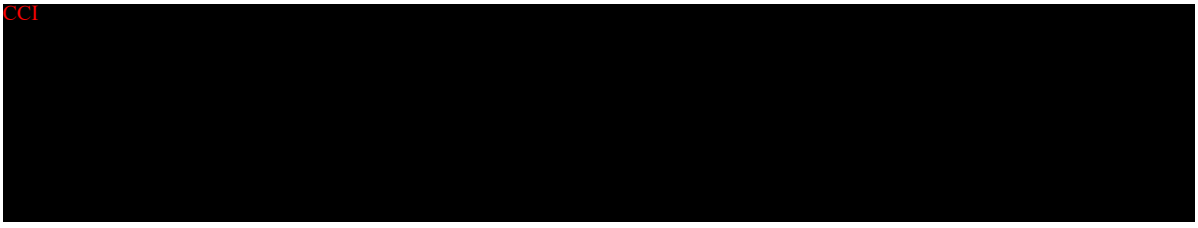
The purpose of this ***seamless*** Phase I***/II*** first time in human - proof of principle (FTIH-PoP) study is to evaluate safety and reactogenicity, to perform a preliminary evaluation of clinical efficacy and to explore immunogenicity of GSK Biologicals' *S. aureus* vaccine compared to placebo (saline), both administered in a 2-dose schedule on Day 1 and Day 61.

In Section 5.1, Scientific rationale for study design:

The rationale for the vaccine composition and dosage is provided in Section 3.2.2.

This is a seamless Phase I/II self-contained study comprising of 2 phases: ~~The~~ ***the*** study design comprises a combined FTIH evaluation and PoP demonstration aiming to provide an agile pathway from the concept to the clinical PoP.

CCI



CCI [redacted] CCI [redacted]). For details of study design refer to Section 5.2; details about the internal safety evaluation by iSRC will be described in the iSRC Charter.

The primary objective of this FTIH study is the assessment of safety and reactogenicity of the investigational *S. aureus* vaccine.

Endpoints and statistical considerations of the secondary objective "vaccine efficacy (VE) in the prevention of recurrent culture confirmed *S. aureus* SSTIs compared to placebo" are based on the results of a study (207908 [EPI-STAPH-006 BOD DB]) which retrospectively reviewed the databases of three hospitals in the US that had available data on SSTI. The retrospective review focused on adult outpatients attending the outpatient and emergency departments and that were diagnosed with SSTI with the purpose of investigating the frequency of *S. aureus* SSTIs.

The PoP phase ***(Phase II)*** is designed as an event driven study and subjects will be enrolled until CCI [redacted]. Since there is currently no licensed vaccine against *S. aureus* infections the comparator group will receive placebo (saline).

In the protocol ahead, Phase I is called as the dose-escalation safety lead-in or safety lead-in phase and Phase II is called as PoP phase.

In Section 5.2, Overall design:

5.2.1 **Dose-Escalation safety lead-in healthy subjects *(Phase I)***

5.2.2. **PoP in subjects with recent *S. aureus* SSTI Group 5a/b *(Phase II)***

- **Experimental design:** Phase ~~I~~ ***II***, observer-blind, randomised, controlled, group sequential, multi-centric study with 2 parallel groups in the PoP vaccination epoch.

In Section 8.4.2.2, Blood sampling for immunogenicity response assessments:

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 125 ml for subjects participating in the dose-escalation safety lead-in and will not exceed ~~310~~ ***274*** ml for subjects participating in the PoP.

In Section 8.5.4.1, Contact information for reporting of serious adverse events (SAEs), pIMDs, pregnancies and study holding rules:

Table 25 Contact information for reporting of serious adverse events (SAEs), pIMDs, pregnancies and study holding rules

Study contact for questions regarding SAEs, pIMDs, pregnancies and study holding rules
Refer to the local study contact information document
Study Contact for Reporting of study holding rules
As soon as the investigator is aware that a holding rule is met, he/she must immediately inform the Local Medical Lead (LML).
Back-up Study Contact for Reporting SAEs, pIMDs, pregnancies and study holding rules
24 hours/7 days availability:
GSK Clinical Safety & Pharmacovigilance
Outside US sites:
Fax: +32 2 656 51 16 or +32 2 656 80 09
Email address: Rix.CT-safety-vac@gsk.com
US sites only:
Fax: 1-610-787-7053

In Section 11, References:

~~WHO. Global Surveillance for human infection with coronavirus disease (COVID-19). Interim guidance. https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov). Accessed May 15, 2020~~

WHO. Public health surveillance for COVID-19. Interim guidance: December 2020; . https://www.who.int/publications/i/item/who-2019-nCoV-surveillanceguidance-2020.8 Accessed June 15, 2021.

12.8.5. Protocol Amendment 2

Overall Rationale for the Amendment: The main reasons for this protocol amendment have been to simplify the study procedures for the proof of principle (PoP) phase, including those related to the screening of subjects and to outline specific measures related to an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) that may be applicable during the subjects' participation in the study. Additionally, some minor corrections have been made as well**.**

List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Synopsis and Section 5.2 Overall design Section 2: Schedule of activities Section 6.1: Inclusion criteria	To allow also subjects with documented recent SA-SSTI, as diagnosed outside the study procedures by external laboratories, the possibility to have access to the screening procedures for study eligibility in the PoP phase.	To maximize the possibility to enrol the target population of the PoP phase in the context of Covid-19 pandemic.
Synopsis and Section 5.2 Overall design Section 2: Schedule of activities	To restrict the collection of blood samples for safety evaluation to the first 40 subjects enrolled in the proof of principle (PoP) phase (i.e. staggered enrollment, Step 1). To change Visits 2 and 6 for PoP Step 2 participants from clinic visits to safety phone calls, as no other invasive procedures were foreseen, apart the safety blood draws.	To simplify study procedures in the context of Covid-19 pandemic, and considering that holding rules related to laboratory abnormalities were not applicable for subjects belonging to PoP Step 2, blood sample for safety will be collected for PoP Step 1 subjects only and will not be collected PoP Step 2.
Section 6.2.2: Prior/Concomitant therapy	Specific measures related to vaccination against emergency mass vaccination that may be applicable during the subjects' participation in the study	To add instructions on how to manage possible emergency mass vaccinations done outside the study
Synopsis and Section 4: Objectives and endpoints	CCI [redacted]	
Section 2: Schedule of activities		

Detailed description of Protocol Amendment 2:

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

In the Title page:

Primary Study vaccine	• GlaxoSmithKline (GSK) Biologicals *Staphylococcus aureus* candidate vaccine (*S. aureus* candidate vaccine [Sa-5Ag adjuvanted])
Co-ordinating author(s)	• PPD ***and*** PPD (Scientific Writer***s***) ***and*** PPD ***(Scientific Writer for GSK)***
Contributing authors	• PPD ~~(CRDL)~~ • PPD ***(Study Statistician)*** • PPD ***(GRA)*** • PPD ~~(GRA)~~

In Protocol Amendment 2 Sponsor Signatory Approval:

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

In the whole document:

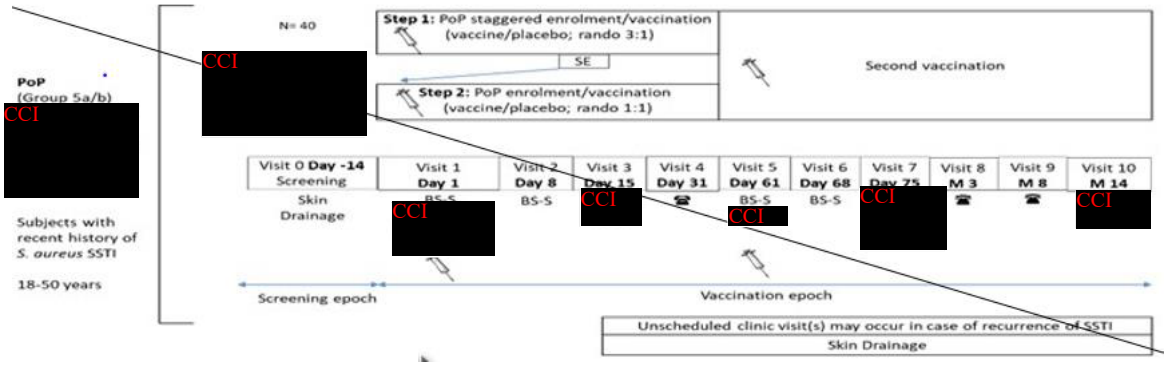
Covid-19 has been written as ***COVID-19***

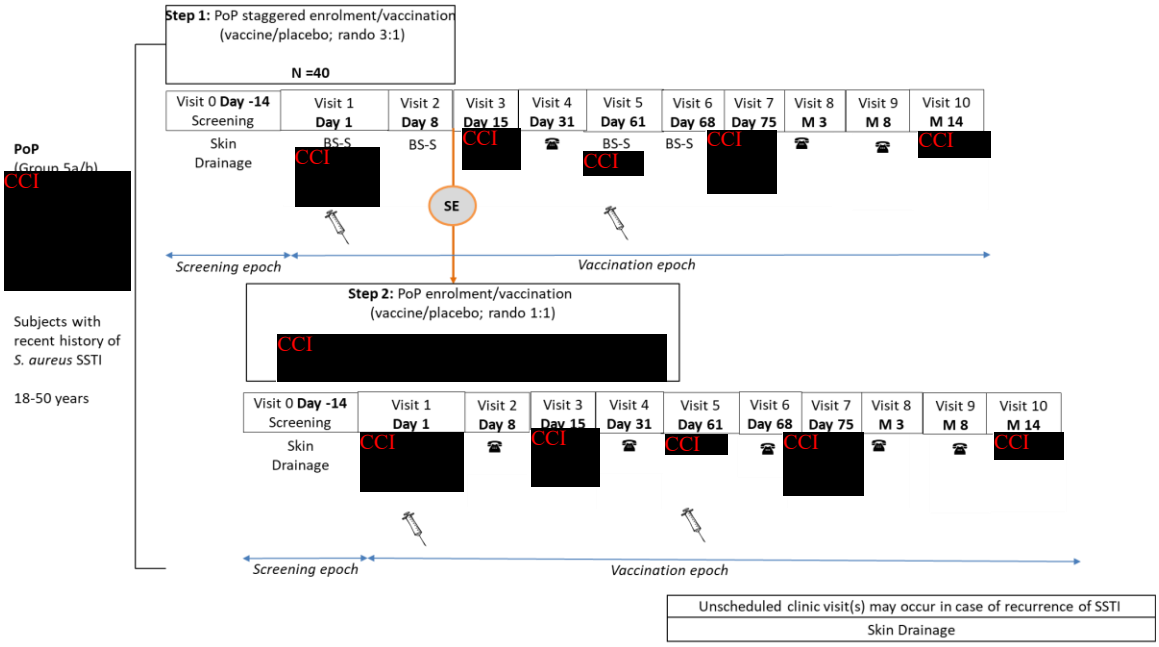
In Synopsis and Section 4: Objectives and Endpoints:

Objectives	Endpoints
Primary	
Descriptive: • To assess safety and reactogenicity of investigational *S. aureus* vaccine	• Occurrence and intensity of solicited local and general AEs during 7 days after each dose (i.e. day of vaccination and the 6 subsequent days) in all subjects by vaccination group. • Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days after each dose (i.e. day of injection and the 29 subsequent days) in all subjects by vaccination group. • Occurrence, intensity and relationship to vaccination of all SAEs in all subjects by vaccination group:

Objectives	Endpoints
	– Groups 1 to 3 from Day 1 (day of vaccination) until Day 366. – Groups 4 and 5 from Day 1 (day of vaccination) until Day 426. • Occurrence, intensity and relationship to vaccination of all potential immune-mediated disease (pIMDs) during in all subjects by vaccination group. – Groups 1 to 3 from Day 1 (day of vaccination) until Day 366. – Groups 4 and 5 from Day 1 (day of vaccination) until Day 426. • Occurrence of haematological and biochemical laboratory abnormalities, and changes from the baseline values after vaccination~~, in all subjects by vaccination group on Days 8, and 68 (i.e. 7 days after dose 1 and dose 2), respectively~~***:*** – ***In all subjects of Groups 1 to 3 on Day 8.*** – ***In all subjects of Group 4 on Days 8 and 68 (i.e. 7 days after dose 1 and dose 2), respectively.*** – ***Subjects in Group 5 Step 1 (i.e. first 40 subjects enrolled in the PoP) on Days 8 and 68 (i.e. 7 days after dose 1 and dose 2), respectively.***
CCI [redacted]	

In Synopsis and Section 5.2 Overall design – Figure 3 Study design overview PoP in subjects with a recent *S. aureus* SSTI Group 5a/b





CCI

In the PoP screening epoch, study subjects ***can*** ~~will~~ be selected ***according to the following ways:***

3. ~~based on~~ ***Subjects with*** signs and symptoms of an ongoing skin infection and purulent lesion, i.e. SSTI, ***suspected to be caused by S. aureus***~~. Subjects~~ will ~~then~~ be enrolled after signing an informed consent form (ICF). After demonstration of *S. aureus* positive ***culture***, ***performed as a study procedure,*** and confirmation by investigator that *S. aureus* is the most likely cause of SSTI, subjects will continue in the study. ***Diagnosis (e.g. abscess or cellulitis) and body location will be collected in the eCRF. In addition, data related to S. aureus*** CCI

CCI [redacted] ***and recorded in the eCRF.*** Specific treatment will be given in compliance with the standard medical practice for the management of *S. aureus* SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, ***outside the study procedures***. After conclusion of the specific treatment for the skin lesion and after clinical resolution of the SSTI ***(e.g. no signs of ongoing infection such as swelling, erythema, pain or drainage)***, the first dose of *S. aureus* candidate vaccine or placebo will be administered.

4. ***Subjects with an ongoing S. aureus SSTI (i.e. S. aureus is the most likely cause), as confirmed by positive culture performed outside the study procedures and not earlier than 14 days prior to ICF signature. Diagnosis (e.g. abscess or cellulitis) and body location will be collected in the eCRF. In addition, S. aureus*** CCI [redacted] ***and recorded in the eCRF. These subjects will be enrolled whether they have or have not already started specific treatment of the infection. In case they have not started the treatment, this will be then given in compliance with the standard medical practice for the management of S. aureus SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures. After conclusion of the specific treatment for the skin lesion and after clinical resolution of the SSTI (e.g. no signs of ongoing infection such as swelling, erythema, pain or drainage), the first dose of S. aureus candidate vaccine or placebo will be administered.***

In Section 2 Schedule of activities (SoA):

Table 5 Schedule of activities (Group 5a/b, PoP screening epoch, PoP vaccination epochs)

Epoch	PoP screening	PoP vaccination										
Type of contact	V0	V1	V2 *Clinic visit or Phone call* [e]	V3	V4 Phone call	V5	V6 *Clinic visit or Phone call* [e]	V7	V8 Phone call	V9 Phone call	V10	Unscheduled visit
Time points	Day –14[a]	Day 1	Day 8	Day 15	Day 31	Day 61	Day 68	Day 75	Day 91 (M 3)	Day 241 (M 8)	Day 426 (M 14)	
Sampling time points		Pre-Vac1				Pre-Vac2						
Informed consent by subjects	●											
Check inclusion/exclusion criteria	●	●										
Physical examination	O	●				●						
Verification of clinical resolution of SSTI		●										
Collect demographic data	●											
Vaccine(s)/Product(s)												

Epoch	**PoP screening**	**PoP vaccination**										
Type of contact	**V0**	**V1**	**V2** ***Clinic visit or Phone call*** [e]	**V3**	**V4 Phone call**	**V5**	**V6** ***Clinic visit or Phone call*** [e]	**V7**	**V8 Phone call**	**V9 Phone call**	**V10**	**Unscheduled visit**
Time points	**Day –14**[a]	**Day 1**	**Day 8**	**Day 15**	**Day 31**	**Day 61**	**Day 68**	**Day 75**	**Day 91 (M 3)**	**Day 241 (M 8)**	**Day 426 (M 14)**	
Sampling time points		**Pre-Vac1**				**Pre-Vac2**						
Study group and treatment number allocation		O										
Treatment number allocation for subsequent doses						O						
Recording of administered treatment number		●				●						
Vaccine administration		●				●						
CCI [redacted]												
Clinical Specimens for microbiology assessments												
Sampling of drainage for culture***s performed in the study***	●											●[c]
Check of culture test report for SA-SSTI confirmation	●											●
CCI [redacted]												
Safety assessments												
Medical history	●	●										
History of administration of adjuvanted vaccine	●	●										
Urine pregnancy test	●	●				●						
Check contraindications and warnings and precautions to vaccination	O	O				O						
Pre-vaccination body temperature		●				●						

Epoch	PoP screening	PoP vaccination										
Type of contact	**V0**	**V1**	**V2 *Clinic visit or Phone call*** [e]	**V3**	**V4 Phone call**	**V5**	**V6 *Clinic visit or Phone call*** [e]	**V7**	**V8 Phone call**	**V9 Phone call**	**V10**	**Unscheduled visit**
Time points / **Sampling time points**	**Day –14**[a]	**Day 1** / **Pre-Vac1**	**Day 8**	**Day 15**	**Day 31**	**Day 61** / **Pre-Vac2**	**Day 68**	**Day 75**	**Day 91 (M 3)**	**Day 241 (M 8)**	**Day 426 (M 14)**	
Blood sampling for safety laboratory evaluation (~6 ml) ***(PoP Step 1 subjects only)***		●	●			●	●					
Phone contact (PoP Step 2 subjects only)			●				●					
Record any concomitant medication/vaccination		●	●	●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●	●	●	●
Distribution of eDiaries and training		O				O[f]						
Review of eDiary data		O	O	~~O~~	~~O~~	~~O~~	O	~~O~~				
Return of eDiaries to the sites								O				
Phone contact ***(all subjects)***					●				●	●		
Recording of solicited adverse events		O				O						
Recording of unsolicited adverse events		●	●	●	●	●	●	●	●			
Occurrence of solicited AEs at the investigator's site within 30 minutes post-vaccination observation		●				●						
Reporting of pIMDs		●	●	●	●	●	●	●	●	●	●	●
Reporting of SAEs, pregnancies and pregnancy outcomes	●	●	●	●	●	●	●	●	●	●	●	●
Study Conclusion											●	

~~Note: The double-line borders indicate analyses which will be performed on all data obtained up to those time points.~~

* [a] CDISC is not calculating with Day 0, i.e. interval between Day –14 and Day 1 is 14 days.

CCI [redacted]

*** [c] ~~If possible.~~***SSTI must be amenable to microbiological culturing per standard clinical practice.***

CCI [redacted]

***** [e] ***Visit 2 and 6: Clinical visit for PoP Step 1 subjects (i.e. first 40 subjects enrolled in the PoP) where 6 ml of whole blood for safety laboratory evaluation will be collected; Phone call for PoP Step 2 subjects (i.e. all those following subjects after the first 40 enrolled in the PoP Step 1.***

****** [f] Remind subjects that the device is now ready to collect after Dose 2 data.

CCI [redacted]

CCI [redacted]

Table 7 Intervals between study visits (PoP epochs)

Group 5a/b	Interval	Length of interval	Allowed interval
Subjects with S. aureus positive culture, performed as a study procedure	V0 (Day –14)→V1 (Day 1)	14 days	14 - 29 days*
Subjects with S. aureus positive culture performed outside the study procedures	***V0 (Day -14 up to Day 1)→V1 (Day 1)***	***up to 14 days***	***0 - 29 days****
All subjects	V1 (Day 1)→V2 (Day 8)	7 days	7 - 9 days
	V1 (Day 1)→V3 (Day 15)	14 days	14 - 21 days
	V1 (Day 1)→V4 (Day 31)	30 days	30 - 37 days
	V1 (Day 1)→V5 (Day 61)	60 days	60 - 67 days
	V5 (Day 61)→V6 (Day 68)	7 days	7 - 9 days
	V5 (Day 61)→V7 (Day 75)	14 days	14 - 21 days
	V5 (Day 61)→V8 (Month 3, day 91)	30 days	30 - 40 days
	V5 (Day 61)→V9 (Month 8, day 241)	180 days	180 - 190 days
	V5 (Day 61)→V10 (Month 14, day 426)	365 days	365 - 380 days

a/b = vaccine/placebo; PoP = Proof of Principle; V = Visit
Note: CDISC is not calculating with Day 0, i.e. interval between Day –14 and Day 1 is 14 days.
**** Vaccination should occur after clinical resolution of culture confirmed SSTI caused by S. aureus***

In Section 5.2: Overall design

- **Sampling schedule:**
  - Blood samples for laboratory safety evaluation ~~and~~ ***will be drawn from the first 40 subjects enrolled (i.e. subjects belonging to PoP Step 1).***

CCI [redacted]

  - Drainage samples will be taken from ~~all~~ ***those*** subjects ***performing culture test as study procedures*** at ***screening (i.e.*** Day –14 [Visit 0]***)*** and from ***all*** subjects with recurrences at the time of recurrence.

In Section 6.1: Inclusion criteria for enrolment:

Additional inclusion criteria only for subjects to be enrolled in the PoP screening epoch:

- Healthy subjects as established by medical history and clinical examination before entering into the study with an ongoing SSTI suspected to be caused by *S. aureus,* as diagnosed by investigator (before randomisation subjects have to be treated until clinical resolution of culture confirmed SSTI caused by *S. aureus*). SSTI must be amenable to microbiological culturing per standard clinical practice (i.e. recovery of drainage sample from abscess or suppurative cellulitis).

  OR

- ***Healthy subjects as established by medical history and clinical examination before entering into the study with an ongoing S. aureus SSTI (i.e. S. aureus is the most likely cause), as confirmed by a S. aureus positive culture performed outside the study procedures and not earlier than 14 days prior to ICF signature. Before randomisation subjects have to be treated until clinical resolution of the culture confirmed SSTI caused by S. aureus. These subjects will be enrolled whether they have or have not already started specific treatment of the infection. In case they have not started the treatment, this will be then given in compliance with the standard medical practice for the management of S. aureus SSTIs and the choice and judgment of the most appropriate treatment will be applied by the investigator, outside the study procedures.***

In Section 6.2 Exclusion criteria; Section 6.2.2 Prior/Concomitant therapy

- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 15 days before the first dose and ending 15 days after the last dose of vaccine(s) administration***** with the exception of any non-adjuvanted influenza vaccine which may be administered ≥7 days before or after each study vaccination.

  ****In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine, provided it is licensed and used according to its Product Information***.

In Section 6.4: Screen and baseline failures

PoP:

Screening activities will continue at sites until the target number of events is reached.

The following information will be collected ***in the eCRF*** for screening failures (dose-escalation safety lead-in and PoP):

- Informed consent.
- Demographic data.

- Inclusion/exclusion criteria.
- Screening conclusion.
- Concomitant medication/vaccination ***(if applicable)***.
- SAEs related to study participation, to concomitant use of GSK products or any fatal SAEs ***(if applicable)***.
- Microbiology results (PoP only) ***(if applicable).***

In Section 7.5.2: Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

- A vaccine not foreseen by the study protocol administered during the period starting 15 days before the first dose and ending 15 days after the last dose of vaccine(s)/placebo administration*, with the exception of any non-adjuvanted influenza vaccine which may be administered ≥7 days before or after each study vaccination.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine, provided it is licensed and used according to its ~~Summary of Product Characteristics (SmPC) or Prescribing~~ ***Product*** Information ~~and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained~~.

In Section 8.4.2.1: Sampling for efficacy assessments

Skin drainage samples will be collected from ~~all screened subjects with SSTI in the PoP at the screening visit and during the study in subjects with SSTI recurrences at unscheduled visits~~ ***those subjects in the PoP performing culture test as a study procedure at screening (i.e. Day –14 [Visit 0]) and from all subjects at the time of their recurrence of SSTI (i.e. unscheduled visits).***

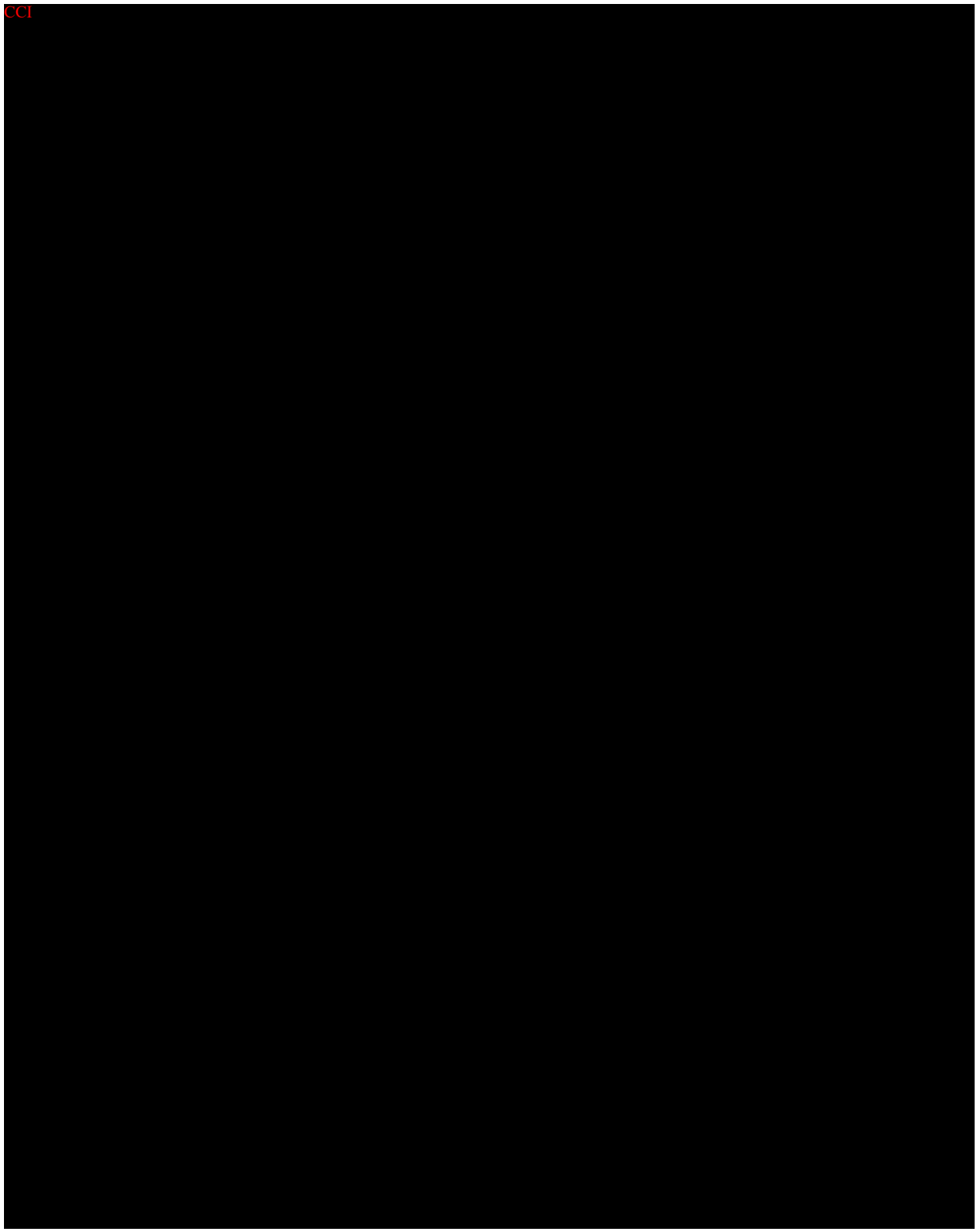
Drainage samples will not be stored.

Table 15 Biological samples for efficacy assessment (PoP)

Sample type	Quantity	Unit	Timepoint	Subjects
Drainage samples	Depends on availability		Day –14 (V0) Unscheduled*	***Subjects with SSTI who perform culture test as a study procedure at screening*** Subjects with suspected ***SA-***SSTI

V = Visit
* Additionally, subjects with recurrent SSTI at the time of recurrence

CCI



In Section 8.4.3.1: Microbiology assessment for efficacy

Table 18 Microbiology

System	Component	Method	Laboratory
Skin drainage	*S. aureus* ***identification*** CCI [redacted]	Standard bacteriological methods	Investigator's institution and/ or at a laboratory designated by GSK Biologicals

In Section 8.4.3.2: Assays for immunogenicity assessments

CCI [redacted]

In Section 8.5.7: Clinical safety laboratory assessments:

In the dose-escalation safety lead-in and in the PoP ***Step 1 (i.e. first 40 subjects enrolled in the PoP)***: a volume of approximately 6 ml of whole blood should be drawn from all subjects for each analysis for haematology and chemistry assessments at each pre-defined timepoint (Table 26). Part of the whole blood will be processed into serum and will be managed according to local laboratory practices.

Table 26 Biological samples for haematology and chemistry assessments

Sample type	Quantity	Unit	Study group	Timepoint	Subjects
Blood for haematology and chemistry	~6	ml	1a/b Half dose non-adjuvanted 2a/b Full dose non-adjuvanted 3a/b Half dose adjuvanted	Day –1 (V0-Grp1-3) Day 8 (V2-Grp1-3)	All subjects
			4a/b Full dose adjuvanted	Day –1 (V0-Grp4) Day 8 (V2-Grp4) Day 61 (V4-Grp4) Day 68 (V5-Grp4)	All subjects
	~6	ml	5a/b vaccine/placebo	Day 1 (V1) Day 8 (V2) Day 61 (V5) Day 68 (V6)	~~All subjects~~ ***PoP Step 1 (i.e. first 40 subjects enrolled in the PoP)***

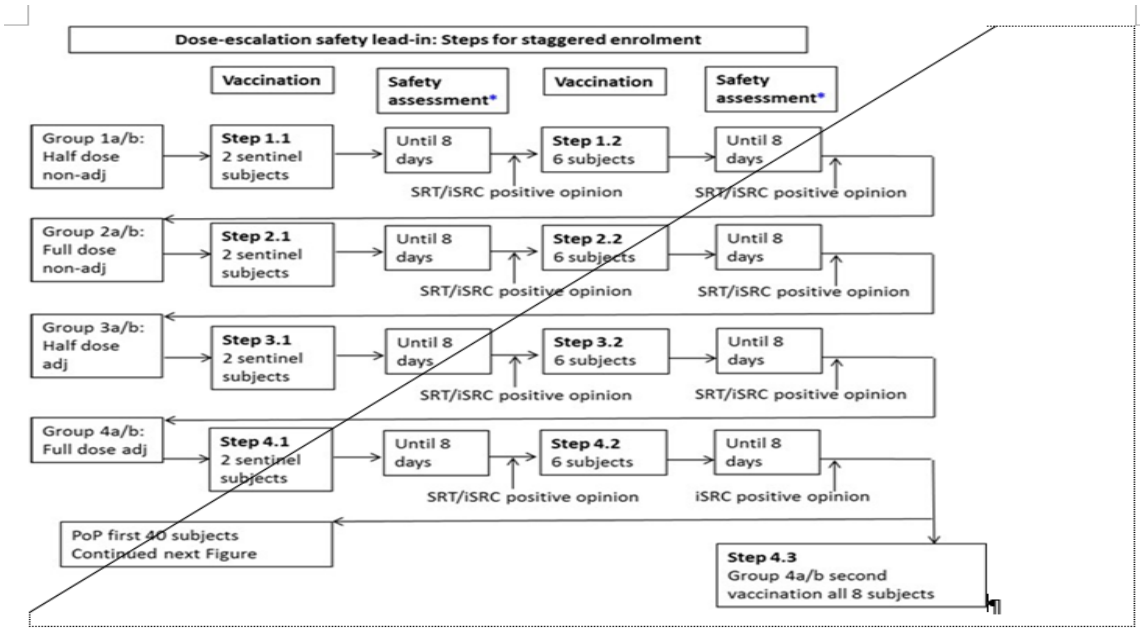
V = Visit; Grp = Group; a/b = vaccine/placebo

Refer to Section 12.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The tests detailed in Appendix 2, Section 12.2 will be performed by the local laboratory at the investigator's site. Results of tests will be needed before vaccination i.e. on the same of the blood draw day for PoP ***Step 1*** or latest on the next day for dose-escalation safety lead-in (see also Section 6.2 exclusion criteria).

In Section 8.6.1: Staggered vaccination (under Section 8.6: Holding rules and safety monitoring):

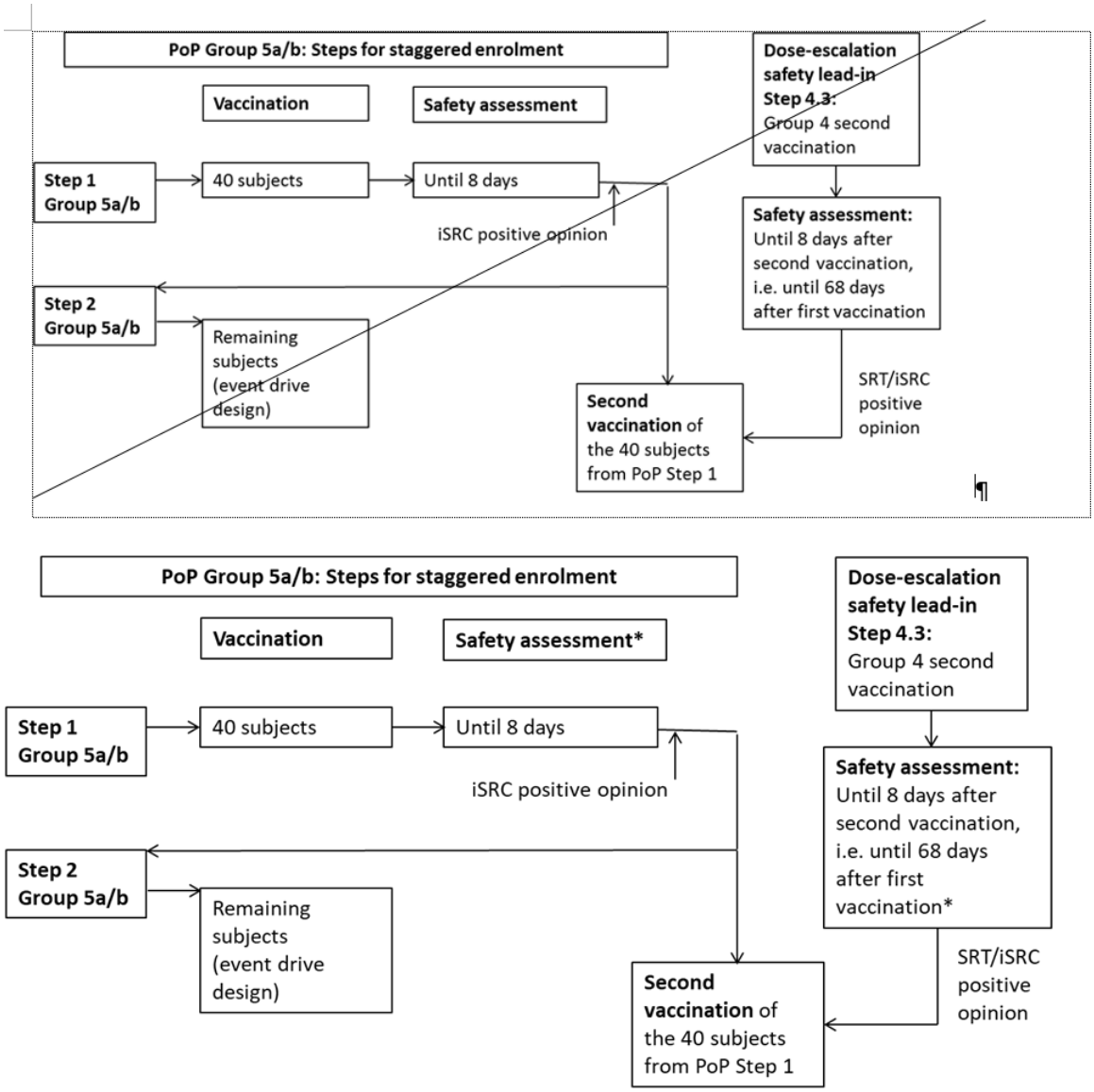
Figure 6 Overview of staggered enrolment and safety evaluation (dose-escalation safety lead-in)



Dose-escalation safety lead-in: Steps for staggered enrolment
Vaccination
Safety assessment*
Vaccination
Safety assessment*
Group 1a/b: Half dose non-adj
Step 1.1 2 sentinel subjects
Until 8 days
Step 1.2 6 subjects
Until 8 days
SRT/iSRC positive opinion
SRT/iSRC positive opinion
Group 2a/b: Full dose non-adj
Step 2.1 2 sentinel subjects
Until 8 days
Step 2.2 6 subjects
Until 8 days
SRT/iSRC positive opinion
SRT/iSRC positive opinion
Group 3a/b: Half dose adj
Step 3.1 2 sentinel subjects
Until 8 days
Step 3.2 6 subjects
Until 8 days
SRT/iSRC positive opinion
SRT/iSRC positive opinion
Group 4a/b: Full dose adj
Step 4.1 2 sentinel subjects
Until 8 days
Step 4.2 6 subjects
Until 8 days
SRT/iSRC positive opinion
iSRC positive opinion
PoP first 40 subjects
Continued next Figure
Step 4.3
Group 4a/b second vaccination all 8 subjects

**** Safety reviews will take into account all safety data accumulated up to the specified timepoint***

Figure 7 Overview of staggered enrolment and safety evaluation (PoP)



**** All safety reviews (i.e. SRTs/iSRCs) will take into account all safety data accumulated up to the specified timepoint***

In Section 8.6.2: Outcome of safety evaluation:

If no safety signal is observed, the favourable outcome of the safety evaluations will be documented and provided in writing (scanned and e-mailed), authorising the investigator to start vaccination of subjects with the subsequent dose as well as enrolment and vaccination of the remaining subjects in the next step of the study, as ~~applicbale~~ ***applicable.***

In Section 8.6.3: Study holding rules

Table 27 Study holding rules

Holding rule	Event	FTIH Dose-escalation Safety Lead-In steps 1-4	Staggered enrolment step of PoP vaccination epoch (PoP step 1)	Full enrolment step of PoP vaccination epoch (PoP step 2)
		Number of subjects needed to trigger the hold	Number and % of subjects needed to trigger the hold	Number of subjects needed to trigger the hold
1a	Death or any life-threatening SAE	≥ 1	≥ 1	≥ 1
1b	Any withdrawal from the study (by investigator or subject request) following a Grade 3 AE that cannot reasonably be attributed to a cause other than vaccination	≥ 1	≥ 1	N/A
1c	Any local or general solicited AE leading to hospitalization, or fever >40°C (104°F) or necrosis at the injection site, within the 7-day (Days 1-7) post-vaccination period	≥ 1	≥ 1	N/A
2a	Any Grade 3 solicited local AE (lasting 48h or more) in an investigational group, within the 7-day (Day 1-7) post-vaccination period	≥ 1	≥ 6/30 or 20%	N/A
2b	Any Grade 3 solicited general AE (lasting 48h or more) in an investigational group, within the 7-day (Day 1-7) post-vaccination period	≥ 1	≥ 6/30 or 20%	N/A
2c	Any Grade 3 unsolicited AE in an investigational group, that cannot reasonably be attributed to a cause other than vaccination, within the 7-day (Day 1-7) post-vaccination period or any Grade 3 abnormality in pre-specified haematological or biochemical laboratory parameters in an investigational group within the 7-day (Day 1-7) post-vaccination period *	≥ 1	≥ 6/30 or 20%	N/A

AE = Adverse Event; SAE = Serious Adverse Event; FTIH = First Time in Human; PoP = Proof of Principle; N/A = Not Applicable

* Grading of laboratory parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (refer to Appendix 7, Section 12.7). Those laboratory parameters not included in the FDA Toxicity Grading Scale will not be graded.

Holding rules 1a ***(in all steps),*** 1b and 1c ***(during the dose-escalation safety lead-In epoch and the PoP Step 1)*** will be monitored by the investigators on a continuous basis for as long as vaccination is ongoing in the study. Meeting any of these holding rules will trigger a hold of vaccination irrespective of the number of subjects vaccinated.

Holding rules 2a, 2b and 2c are reviewed during unblinded review in the planned or ad-hoc iSRC. These rules will be applied only during the dose-escalation safety lead-In epoch and the staggered enrolment step of PoP vaccination epoch. Also in this case, different cut-offs are considered based on the sample size of the study group.

CCI

[redacted]

In Section 10.3.3.1 Case accountability (under Section 10.3.3: Efficacy analyses):

Endpoint	Statistical Analysis Methods
CCI [redacted]	

In Section 10.3.5: Safety analyses:

Endpoint	Statistical Analysis Methods
Primary	**Within groups assessment** The overall incidence, with exact 95% confidence intervals (CIs) of any solicited AE (local or general), of at least 1 solicited local AE and of at least 1 solicited general AE during the 7-day (Day 1-7) period will be tabulated per study group and for each dose and overall. The same calculations will be performed for solicited AEs rated as grade 3 and fever >40°C/104°F. The overall incidence, with exact 95% confidence intervals (CIs) of any unsolicited AE, unsolicited AEs by MedDRA system organ class and by preferred term during the 30-day (Day 1-30) follow-up post-vaccination period will be tabulated per study group and after each dose and overall. The same calculations will be performed for unsolicited AEs rated as grade 3 and fever >40°C/104°F, for unsolicited AEs causally related to vaccination and for grade 3 unsolicited AEs causally related to vaccination. The number and percentages of subjects who experienced at least one SAE or any pIMD during the entire study period (Groups 1-3 Day 1-366, Groups 4 and 5 Day 1-426) will be reported. The percentage of subjects having haematology and biochemistry results below or above the normal laboratory ranges with the changes from the baseline values will be tabulated by time point ***for Group 1 to 4 and Group 5 Step 1***. Duration will be presented. The verbatim reports of unsolicited symptoms will be reviewed by a GSK physician and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Event Terminology. Serious adverse events and withdrawal due to adverse event(s) will be described in detail.

In Section 11: References

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (Doc. Ref. EMEA/CHMP/313666/2005) 'adopted at Community level in May 2006);
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf

~~http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf.~~ Accessed ~~January 17, 2019~~ ***31 March 2021***

In Section 12.1.1: List of abbreviations

CCI [redacted]

~~**PP:**~~ ~~Per-protocol~~

PP: Per-protocol

In Section 12.2.2 Laboratory assays for safety evaluation

The tests detailed in Table 28 will be performed by the local laboratory. Results of tests will be needed before vaccination i.e. latest on the next day for dose-escalation safety lead-in and on the same day for PoP ***Step 1*** (see also requirements for inclusion or exclusion of subjects detailed in Section 6 of the protocol).

Pre-vaccination on Visit 0 (dose-escalation safety lead-in) and Visit 1 (PoP ***Step 1***) haematology and chemistry evaluation will not be blinded since abnormal laboratory results will be an exclusion criterion (see Section 6.2.1).

In Section 12.3 Appendix 3: Clinical laboratories:

Table 29 GSK laboratories

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Biospecimen Reception-B7/44 Rue de l'Institut, 89 B-1330 Rixensart Belgium
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20 B-1300 Wavre Belgium
~~GSK Vaccines GmbH Clinical Laboratory Sciences, Marburg, Germany~~	~~Emil-von-Behring-Str. 76 35041 Marburg Germany~~
GSK Vaccines S.r.l Preclinical R&D, Italy	Via Fiorentina 1 53100 Siena Italy

Table 30 Outsourced laboratories

Laboratory	Address
Q^2 Solutions Clinical Trials (UK)	The Alba Campus Rosebank Livingston West Lothian, EH54 7EG Scotland, UK
Q^2 Solutions Clinical Trials (US)	27027 Tourney Road, Suite 2E Valencia, CA 91355 USA
Nexelis Impfstoffforschung (Marburg, Germany)	***Emil-von-Behring-Str. 76 35041 Marburg Germany***

In Section 12.4.2 Financial disclosure

~~Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interest prior initiation of the centre and at the end of the study. Investigators are responsible for providing an update of Financial Disclosure if their financial interest changes at any point during their participation in a study and for 1 year after completion of the study.~~

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

In Section 12.4.7: Data quality assurance

Quality tolerance limits (QTLs) will be pre-defined in the study management plan and will be monitored during the study.

In Section 12.5.8: Detecting and recording adverse events, serious adverse events and pregnancies

The subject will be contacted by the site staff on Day 31 (all groups), Day 91 (dose-escalation safety lead-in Group 4 full dose adjuvanted and PoP both groups), Day 181 (Groups 1-3: half dose non-adjuvanted, full dose non-adjuvanted, half dose adjuvanted) and Day 241 (dose-escalation safety lead-in Group 4 full dose adjuvanted and PoP both groups) via a scripted safety follow-up phone call. ***Subjects in PoP Step 2 will also be contacted on Day 8 and Day 68 via a scripted safety follow-up phone call.*** At, or in advance of applicable phone call the site will review the eDiary web-portal for responses entered by the subject in order to solicit additional information during the phone call e.g. related to unsolicited adverse events, concomitant vaccinations/medication and medically attended events.

In Section 12.6.2 Contraception guidance

Table 36 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] ***Failure rate of <1% per year when used consistently and correctly.***
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • ***oral*** • injectable

12.8.6. Protocol Amendment 1

Overall Rationale for the Amendment 1 is to make some minor corrections, remove the CCI [redacted], and to comply with selected recommendations from Center for Biologics Evaluation and Research (CBER). This protocol amendment 1 outlines also measures that may be applicable during special circumstances (e.g., C~~ovid~~***OVID***-19 pandemic), to protect participant's welfare and safety, and promote data integrity.

List of main changes in the protocol and their rationale:

Section # and Name	Description of Change	Brief Rationale
Cover page Sponsor signature page Investigator signature page	To swap the identifiers "short title" and "title". To add the IND number.	Identifiers have been corrected,as applicable and the IND number has been added.
2. Schedule of activities (SOA)	CCI [redacted]	Simplification of study procedures.
5.1. Scientific rationale for study design		To address CBER's comment
5.2. Overall design		
5.3. Number of subjects		
7.2.2.1.1. Study group and treatment number allocation		
8. Study assessment and procedures	To add information related to study procedures conduction during special circumstances (e.g. C~~ovid~~***OVID***-19 pandemic).	Adds alternative ways to conduct study procedures
8.4.2.2. Blood sampling for immunogenicity response assessments	CCI [redacted]	Simplification of study procedures
10.1.1. Hypotheses related to primary and secondary objectives	To change the number of total planned events for the final efficacy analysis and the percentage of events for the interim To change alpha and beta of the first and second hypotheses for interim and final analysis. To change the hazard ratio (HR).	To address CBER's comment
10.1.2. Sample size calculation	CCI [redacted]	To address CBER's comment

Section # and Name	Description of Change	Brief Rationale
10.2. Populations for analyses	To add the overall safety set. To split the solicited safety set in: i) solicited safety set until 30 minutes after vaccination, ii) solicited safety set including only subjects with data from 30 minutes until 7 days after vaccination.	To generate data requires for public disclosure and improve the display of the solicited AEs data.
10.3.3.1. Case accountability	To change alpha and beta for interim and final analysis according changes in Section 10.1.1.	To address CBER's comment
CCI [redacted]		
12.5.3. Solicited adverse events	Added a Table 33 to add the general adverse events myalgia and shivering to be solicited for the PoP population.	To address CBER's comment
12.5.8.2.2. Assessment of adverse events	Updated Table 35 to add the solicited general adverse events myalgia and shivering.	To address CBER's comment.
12.5.8.2.2. Assessment of adverse events	Fever grading scale revised as follows: grade 1: ≥ 38.0°C and < 39.0°C, grade 2: ≥ 39.00°C and ≤ 40.0°C, grade 3: > 40.0°C.	To correct a typo

Detailed description of Protocol Amendment 1:

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

Coverpage

Investigational New Drug (IND) number	~~To be done~~ ***IND 19408***
Date of protocol	Final Version 1: 04 September 2019
Date of protocol amendment/administrative change	***Amendment 1 Final: 26 May 2020***
***Short t*~~T~~itle**	Safety, immunogenicity and efficacy of GSK *S. aureus* candidate vaccine (GSK3878858A) when administered to healthy adults (dose-escalation) and to adults 18 to 50 years of age with a recent *S. aureus* skin and soft tissue infection (SSTI).

~~**Short t***~~**Title**	A Phase I, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK *S. aureus* candidate vaccine when administered to healthy adults (dose-escalation) and to adults 18 to 50 years of age with a recent *S. aureus* skin and soft tissue infection (SSTI).
Contributing authors	• PPD (CRDL) • PPD ***(CRDL)*** • PPD (SDL) • PPD (ODM) • PPD ~~(Lead Statistical Analyst)~~ • PPD (Lead Statistician) • PPD ~~(CTSM, Vaccine supply)~~ • PPD (CLS CRT-L) • PPD (Safety Physician) • PPD (Safety Scientist) • PPD (GRA) • PPD (LDL) • PPD (LML) • PPD (DPL)

Protocol *Amendment 1* Sponsor Signatory Approval

IND number	~~To be done~~ ***IND 19408***
~~**Date of protocol**~~	~~Final Version 1: 04 September 2019~~
Date of protocol amendment/administrative change	***Amendment 1 Final: 26 May 2020***
~~**Short t***~~**Title**	A Phase I, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK *S. aureus* candidate vaccine when administered to healthy adults (dose-escalation) and to adults 18 to 50 years of age with a recent *S. aureus* skin and soft tissue infection (SSTI).

Protocol *Amendment 1* Investigator Agreement

IND number	~~To be done~~ ***IND 19408***
~~**Date of protocol**~~	~~Final Version 1: 04 September 2019~~
Date of protocol amendment/administrative change	***Amendment 1 Final: 26 May 2020***
~~**Short t***~~**Title**	A Phase I, observer-blind, randomised, placebo-controlled study to assess safety, immunogenicity and efficacy of GSK *S. aureus* candidate vaccine when administered to healthy adults (dose-escalation) and to adults 18 to 50 years of age with a recent *S. aureus* skin and soft tissue infection (SSTI).

Section 1. SYNOPSIS

Objectives and Endpoints:

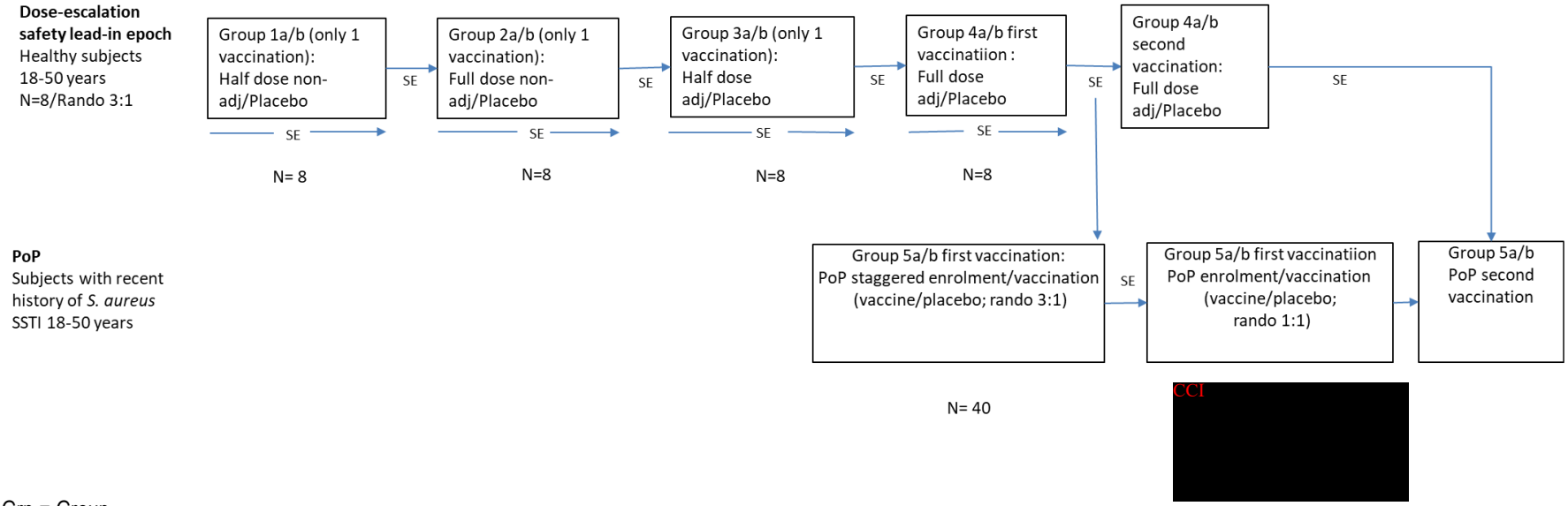
Objectives	Endpoints
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	[redacted]

Ab = Antibody; AE = Adverse Event; CD = Cluster of Differentiation EAP = Exploratory Analysis Plan; CCI [redacted] CCI [redacted] pIMDs = potential Immune-Mediated Disease; SAE = Serious Adverse Events; CCI [redacted]; SSTI = Skin and Soft Tissue Infection; VE = Vaccine Efficacy;

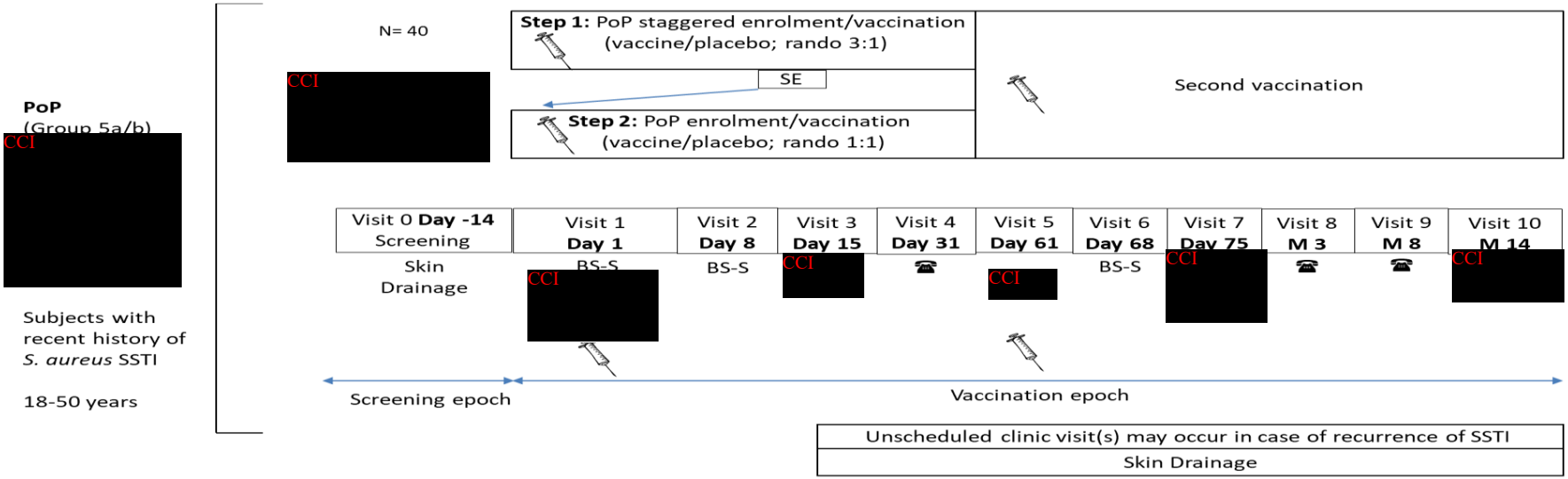
Section 1. SYNOPSIS

Synopsis Figure 1 Overall design



Grp = Group
a/b = vaccine/placebo.
Rando = Randomisation
adj = adjuvanted
SE = Safety evaluation by SRT/ iSRC chair (blinded review) or iSRC (unblinded review), for details refer to Section 8.6
PoP = Proof of Principle

Synopsis Figure 3 Study design overview PoP in subjects with a recent *S. aureus* SSTI Group 5a/b



Note: CDISC is not calculating with Day 0, i.e. interval between Day –14 and Day 1 is 14 days.
a/b = vaccine/placebo
SE = Safety evaluation by iSRC (unblinded review), for details refer to Section 8.6
Rando = Randomisation
PoP = Proof of Principle
SSTI = Skin and Soft Tissue Infection
Vac = Vaccine

Plac = Placebo
M = Month
V = Vaccination
BS-S = Blood Sample for Safety evaluation

CCI

The enrolment in the PoP phase will also follow a staggered approach. Enrolment will be stopped as soon as 40 subjects have been vaccinated with the first dose of the GSK *S. aureus* candidate vaccine or placebo. Only subjects who already signed the ICF and entered the screening phase, at the time of enrolment hold, will be allowed to continue the study; therefore, approximately 40 subjects (30 subjects receiving GSK *S. aureus* candidate vaccine and 10 receiving placebo) will be evaluated for safety. After the iSRC evaluation of unblinded safety data collected up to the Day 8 after first dose (including laboratory assessments) for the last vaccinated subject of this staggered subset has shown lack of safety issues, the full enrolment of the remaining subjects in the PoP epochs will continue with a randomisation of a 1:1 ratio either to the GSK *S. aureus* candidate vaccine or to the placebo group. CCI [redacted]

Section 2 SCHEDULE OF ACTIVITIES

Table 3 Schedule of activities (dose-escalation safety lead-in epochs, Groups 1-3a/b)

Epoch		Dose-escalation safety lead-in screening	Dose-escalation safety lead-in vaccination				
Type of contact	Group 1a/b Half dose non-adjuvanted Group 2a/b Full dose non-adjuvanted Group 3a/b Half dose adjuvanted	**V0-Grp1-3 Screening**	**V1-Grp1-3**	**V2-Grp1-3**	**V3-Grp1-3 phone call**	**V4-Grp1-3 phone call**	**V5-Grp1-3**
Time points		**Day –1***	**Day 1**	**Day 8**	**Day 31**	**Day 181 (M 6)**	**Day 366 (M 12)**
Sampling time points			**Pre-Vac1**				
Informed consent by subjects		●					
Check inclusion/exclusion criteria		●					
Physical examination		O	●				
Collect demographic data		●					
Vaccine(s)/Product(s)							
Study group and treatment number allocation			O				
Recording of administered treatment number			●				
Vaccine administration			●				
CCI [redacted]							
Safety assessments							
Medical history		●					
History of administration of adjuvanted vaccine		●					
Urine pregnancy test		●					
Check contraindications and warnings and precautions to vaccination		O	O				
Pre-vaccination body temperature			●				
Blood sampling for safety laboratory evaluation (~6 ml)		●		●			
Record any concomitant medication/vaccination		●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●	●
Distribution of eDiaries and training			O				
Review of eDiary data			O	O			
Return of eDiaries to the sites				O			
Phone contact					●	●	
Recording of solicited adverse events			O				
Recording of unsolicited adverse events			●	●	●		

Epoch		Dose-escalation safety lead-in screening	Dose-escalation safety lead-in vaccination				
Type of contact	Group 1a/b Half dose non-adjuvanted Group 2a/b Full dose non-adjuvanted Group 3a/b Half dose adjuvanted	**V0-Grp1-3 Screening**	**V1-Grp1-3**	**V2-Grp1-3**	**V3-Grp1-3 phone call**	**V4-Grp1-3 phone call**	**V5-Grp1-3**
Time points		**Day –1***	**Day 1**	**Day 8**	**Day 31**	**Day 181 (M 6)**	**Day 366 (M 12)**
Sampling time points			**Pre-Vac1**				
Occurrence of solicited AEs at the investigator's site within 30 minutes post-vaccination observation			●				
Reporting of pIMDs			●	●	●	●	●
Reporting of SAEs, pregnancies and pregnancy outcomes		●	●	●	●	●	●
Study Conclusion							●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
*CDISC is not calculating with Day 0, i.e. interval between Day –1 and Day 1 is 1 day.

CCI [redacted]

a/b = vaccine/placebo

CCI [redacted]

~~pIMDs = potential Immune-Mediated Diseases~~
SAE = Serious Adverse Event
Vac = Vaccination
M = Month
V = Visit

Table 5 Schedule of activities (Group 5a/b, PoP screening epoch, PoP vaccination epochs)

Epoch	PoP screening	PoP vaccination										
Type of contact	V0	V1	V2	V3	V4 Phone call	V5	V6	V7	V8 Phone call	V9 Phone call	V10	Unscheduled visit
Time points	Day –14*	Day 1	Day 8	Day 15	Day 31	Day 61	Day 68	Day 75	Day 91 (M 3)	Day 241 (M 8)	Day 426 (M 14)	
Sampling time points		Pre-Vac1				Pre-Vac2						
Informed consent by subjects	●											
Check inclusion/exclusion criteria	●	●										
Physical examination	O	●				●						
Verification of clinical resolution of SSTI		●										
Collect demographic data	●											
Vaccine(s)/Product(s)												
Study group and treatment number allocation		O										
Treatment number allocation for subsequent doses						O						
Recording of administered treatment number		●				●						
Vaccine administration		●				●						
CCI [redacted]												
Clinical Specimens for microbiology assessments												
Sampling of drainage for culture	●											●***
Safety assessments												
Medical history	●	●										
History of administration of adjuvanted vaccine	●	●										
Urine pregnancy test	●	●				●						
Check contraindications and warnings and precautions to vaccination	O	O				O						
Pre-vaccination body temperature		●				●						
Blood sampling for safety laboratory evaluation (~6 ml)		●	●			●	●					

Epoch	**PoP screening**	**PoP vaccination**										
Type of contact	**V0**	**V1**	**V2**	**V3**	**V4 Phone call**	**V5**	**V6**	**V7**	**V8 Phone call**	**V9 Phone call**	**V10**	**Unscheduled visit**
Time points	**Day –14***	**Day 1**	**Day 8**	**Day 15**	**Day 31**	**Day 61**	**Day 68**	**Day 75**	**Day 91 (M 3)**	**Day 241 (M 8)**	**Day 426 (M 14)**	
Sampling time points		**Pre-Vac1**				**Pre-Vac2**						
Record any concomitant medication/vaccination		●	●	●	●	●	●	●	●	●	●	●
Record any intercurrent medical conditions		●	●	●	●	●	●	●	●	●	●	●
Distribution of eDiaries and training		O				O*****						
Review of eDiary data		O	O	O	O	O	O	O				
Return of eDiaries to the sites								O				
Phone contact					●				●	●		
Recording of solicited adverse events		O				O						
Recording of unsolicited adverse events		●	●	●	●	●	●	●	●			
Occurrence of solicited AEs at the investigator's site within 30 minutes post-vaccination observation		●				●						
Reporting of pIMDs		●	●	●	●	●	●	●	●	●	●	●
Reporting of SAEs, pregnancies and pregnancy outcomes	●	●	●	●	●	●	●	●	●	●	●	●
Study Conclusion											●	

Note: The double-line borders indicate analyses which will be performed on all data obtained up to those time points.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
*CDISC is not calculating with Day 0, i.e. interval between Day –14 and Day 1 is 14 days.
CCI [redacted]
***If possible.
CCI [redacted]
*****Remind subjects that the device is now ready to collect after Dose 2 data.
a/b = vaccine/placebo
CCI [redacted]
pIMDs = potential Immune-Mediated Diseases
SAE = Serious Adverse Event
Vac = Vaccination
M = Month
V = Visit

Section 4. OBJECTIVE(S) AND ENDPOINT(S)

Table 10 Study objectives and endpoints

Objectives	Endpoints
CCI [redacted]	

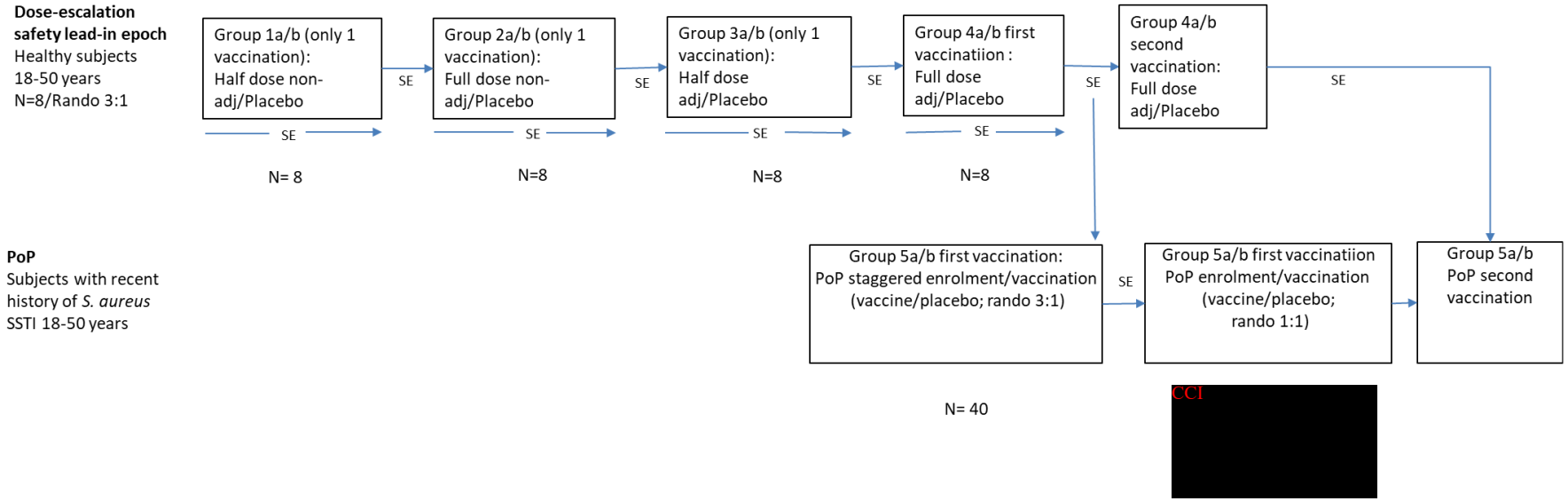
Ab = Antibody; AE = Adverse Event; CD = Cluster of Differentiation EAP = Exploratory Analysis Plan; CCI [redacted] pIMDs = potential Immune-Mediated Disease; SAE = Serious Adverse Avent CCI [redacted] SSTI = Skin and Soft Tissue Infection; VE = Vaccine Efficacy;

Section 5.1. Scientific rationale for study design

The PoP phase is designed as an event driven study and subjects will be enrolled CCI [redacted] Since there is currently no licensed vaccine against *S. aureus* infections the comparator group will receive placebo (saline).

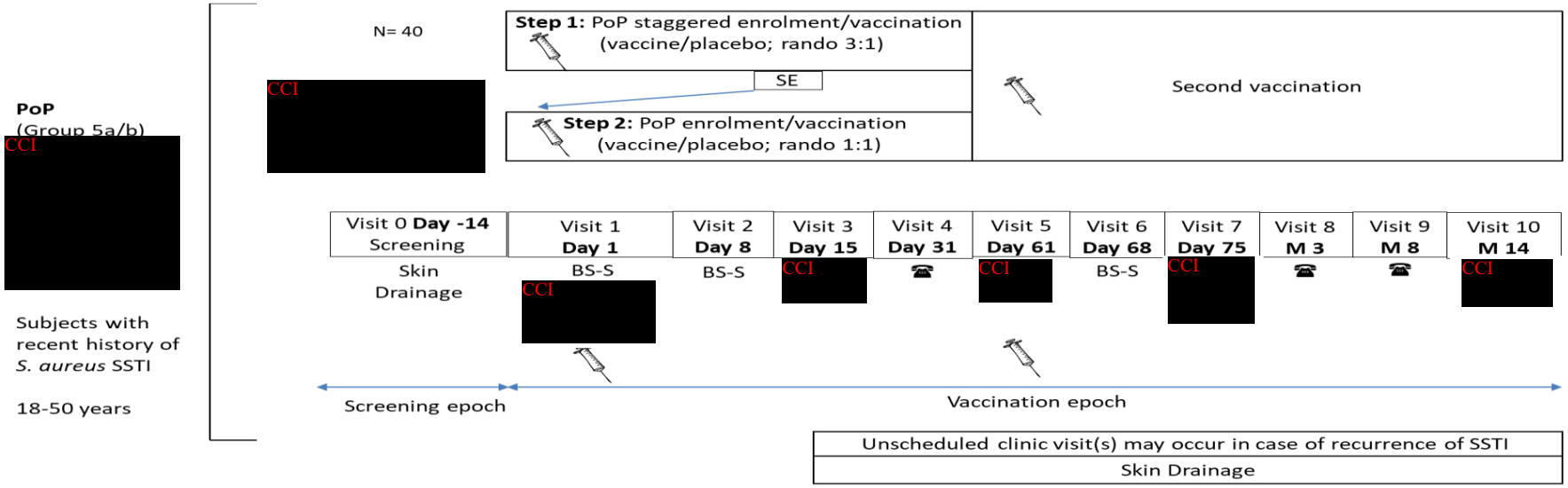
Section 5.2 Overall design

Figure 1 Overall design



adj = adjuvanted
Grp = Group
a/b = vaccine/placebo
Rando = Randomisation
SE = Safety evaluation by SRT/ iSRC chair (blinded review) or iSRC (unblinded review), for details refer to Section 8.6
PoP = Proof of Principle

Figure 3 Study design overview PoP in subjects with a recent *S. aureus* SSTI



Note: CDISC is not calculating with Day 0, i.e. interval between Day –14 and Day 1 is 14 days.
a/b = vaccine/placebo
SE = Safety evaluation by iSRC (unblinded), for details refer to Section 8.6
PoP = Proof of Principle
SSTI = Skin and Soft Tissue Infection
Rando = Randomization
Vac = Vaccine
Plac = Placebo
M = Month
V = Vaccination
BS-S = Blood Sample for Safety evaluation
CCI

The enrolment and vaccination in the PoP phase will also follow a staggered approach. Details are given below in bullet "Safety monitoring" and Section 8.6.1. The study will follow a group sequential design with two analyses. An event driven interim analysis will be performed when 50% CCI [redacted] (event driven design). It is estimated that then a total of approximately 500 to 600 subjects will be vaccinated in the CCI [redacted]

Table 12 Study groups, treatment and epochs foreseen in the study (PoP epochs)

Study Groups	Number of subjects	Age (Min-Max)	Treatment name	Epochs (Blinding)	
				PoP screening (N/A)	PoP vaccination (observer-blind)
Group 5a Vaccine	250*	18 - 50 years	Sa-5Ag full dose adjuvanted	•	•
Group 5b Placebo	250*	18 - 50 years	Placebo	•	•

N/A = Not Applicable
*Design of the study is event driven and it can be only estimated that approximately 250 to 300 subjects per study group may be needed. CCI [redacted].

- **Data collection:** standardised eCRF. Solicited AEs will be collected using a subject eDiary.~~)~~

Section 5.3. Number of subjects

PoP epochs:

The design of the PoP phase of the study is event driven. Vaccination of subjects with a randomisation of a 1:1 ratio either to the GSK *S. aureus* candidate vaccine or to the placebo group is planned CCI [redacted] It is estimated that a total of approximately 500 to 600 subjects will be vaccinated in the PoP.

Section 7.2.2.1.1. Study group and treatment number allocation

PoP:

CCI [redacted] The enrolment in the PoP phase will also follow a staggered approach:

- The remaining subjects in the PoP epochs will be enrolled approximately 8 days after the last of the approximately 40 subjects was vaccinated (for safety evaluation and consequence on study progress refer to Section 8.6.1). The subjects will be randomised with a 1:1 ratio either to receive the GSK *S. aureus* candidate vaccine or

placebo until CCI [redacted] (event driven design). It is estimated that a total of approximately 500 to 600 subjects will be vaccinated in the PoP CCI [redacted] (see Section 10.1.2).

Section 7.3.1. Emergency unblinding

Table 14 Contact information for emergency unblinding

GSK Helpdesk 24 hours/7 days availability
The Helpdesk is available by phone, fax and email Phone: +32 2 656 68 04 For ~~Canada,~~ US ~~and Puerto Rico~~ Toll-free number: 877 870 0019 Fax: +32 2 401 25 75 email: rix.ugrdehelpdesk@gsk.com

Section 8. STUDY ASSESSMENTS AND PROCEDURES

Under special circumstances, modification of specific study procedures may be implemented:

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- ***Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.***
- ***If the eDiary device was provided to the participant, it may be returned to the site by conventional mail after the end of the relevant data collection.***
- ***Blood samples for safety assessment may be collected at a different location[2] other than the study site or at participant's home. Blood samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.***

[2] ***It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.***

Section 8.4. Efficacy/immunogenicity assessments

Refer also to the ***Amendment 1*** Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Section 8.4.2.2. Blood sampling for immunogenicity response assessments

Refer to the SPM for detailed information on sample collection and storage.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 125 ml for subjects participating in the dose-escalation safety lead-in and will not exceed ~~370~~***310*** ml for subjects participating in the PoP.

CCI

[redacted]

Section 8.5. Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. ***This includes the assessment of Covid-19 cases per the WHO definition [WHO, 2020].***

Table 22 Reporting periods for collecting safety information (dose-escalation safety lead-in)

Event	Study group	Pre-Vac	Vac1			Vac2			Study Conclusion
	Half dose non-adjuvanted Full dose non-adjuvanted Half dose adjuvanted	**D–1***	**D1**	**D7**	**D30**	**NA**	**NA**	**NA**	**D366 M12**
	Full dose adjuvanted	**D–1***	**D1**	**D7**	**D30**	**D61**	**D67**	**D90**	**D426 M14**
Solicited local and general AEs									
Unsolicited AEs**									
AEs/SAEs leading to withdrawal from the study									
SAEs**									
SAEs related to the study vaccine(s)									
SAEs related to study participation or concurrent GSK medication/vaccine									
Pregnancies									
pIMDs									

* i.e. consent obtained.

***** Unsolicited AEs/SAEs due to Covid-19 will be recorded according to the WHO case definition [WHO, 2020].***

AEs = Adverse Events; SAEs = Serious Adverse Events; pIMDs = potential Immune-Mediated Diseases; Pre-Vac = Pre-Vaccination; Vac = Vaccination; D = Day; M = Month

Table 23 Reporting periods for collecting safety information (PoP)

Event	Study group	Pre-Vac	Vac1			Vac2			Study Conclusion
	Vaccine Placebo	D–14*	D1	D7	D30	D61	D67	D90	D426 M14
Solicited local and general AEs									
Unsolicited AEs**									
AEs/SAEs leading to withdrawal from the study									
SAEs**									
SAEs related to the study vaccine(s)									
SAEs related to study participation or concurrent GSK medication/vaccine									
Pregnancies									
pIMDs									

* i.e. consent obtained.

** ***Unsolicited AEs/SAEs due to Covid-19 will be recorded according to the WHO case definition [WHO, 2020].***

AEs = Adverse Events; SAEs = Serious Adverse Events; pIMDs= potential Immune-Mediated Diseases; Pre-Vac = Pre-Vaccination; Vac = Vaccination; D = Day; ***M = Month***

CCI

[redacted]

CCI

~~**Figure 9 Sequence for evaluating both efficacy objectives in order to control the overall type I error below 7.5% (one-sided)) and the power equal to 80%**~~

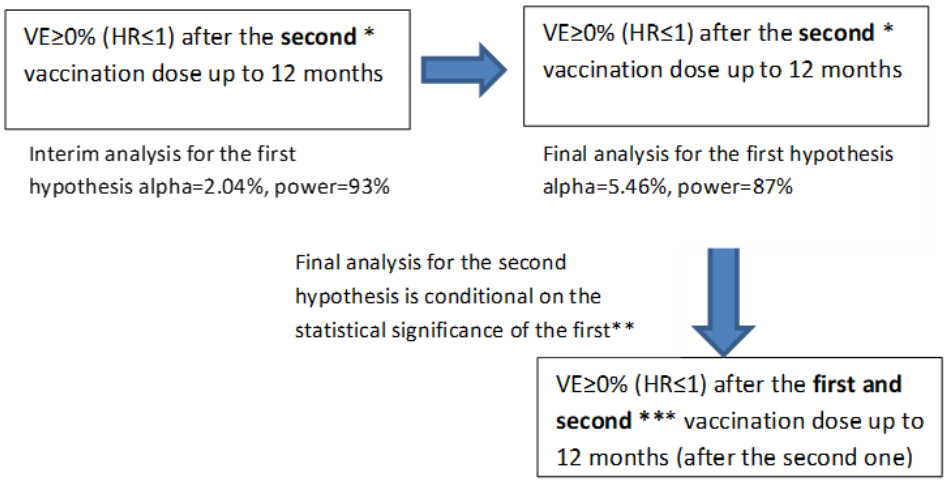
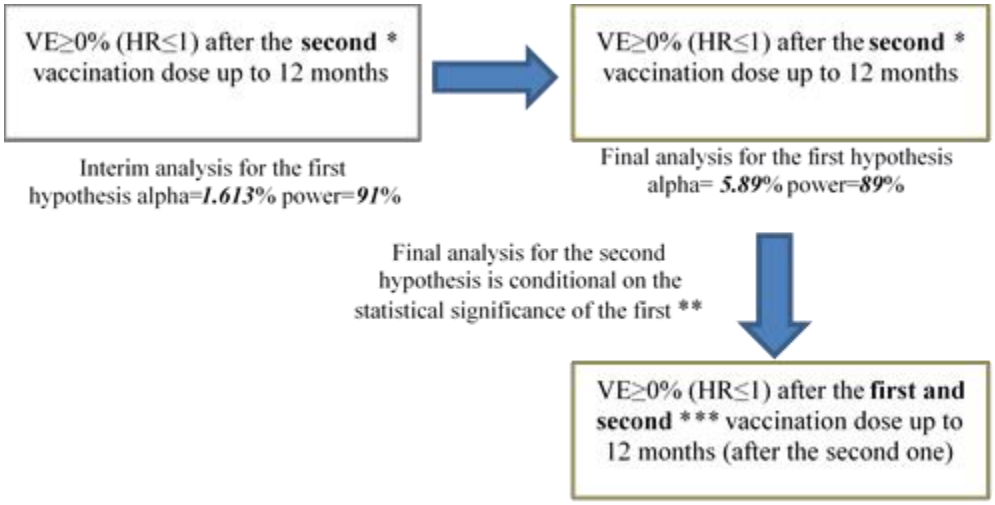


Figure 9 Sequence for evaluating both efficacy objectives in order to control the overall type I error below 7.5% (one-sided)) and the power equal to 80%



Section 10.2. Populations for analyses

Analysis Set	Description
Enrolled	All subjects who sign informed consent
Randomized	All subjects who sign informed consent and are randomized to the treatment group
Exposed	All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.
Full Analysis Set (FAS)	All subjects who received at least 1 dose of the study treatment and have post-vaccination efficacy/ immunogenicity data
Modified Full Analysis Set (mFAS)	All subjects who received full study treatment course to which they are randomised and have post-vaccination efficacy/immunogenicity data
Per-Protocol (PP)	All subjects who received full study treatment course to which they are randomised and have post-vaccination data (mFAS) minus subjects with protocol deviations that lead to exclusion from PP
Unsolicited Safety	All subjects who received at least 1 dose of the study treatment (Exposed Set) that report unsolicited AEs/report not having unsolicited AEs
Solicited Safety	All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data ***in the period beginning 30 minutes after vaccination until 7 days after vaccination.***
Solicited Safety 30m	***All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data during a period of 30 minutes after the vaccination.***
Overall Safety Set	***All subjects who received at least 1 dose of the study treatment (Exposed Set) who have solicited safety data including 30 minutes data and during a period of 7 days from the vaccination and/or report unsolicited AEs/report not having unsolicited AEs***

Section 10.3.3.1. Case accountability:

Endpoint	Statistical Analysis Methods
Key secondary	The analysis of efficacy will be based on the occurrence of the first case of SSTI anytime from 15 Days after the administration of the second dose of the study vaccine up to 12 months. All subjects from the mFAS will contribute to the comparison between the treatment and the placebo groups. Time to occurrence of key secondary endpoint during the defined efficacy follow-up period will be compared between groups by calculating the respective Hazard ratio (methods will be detailed in the SAP). Vaccine (VE) will be defined as 1 minus the hazard ratio times 100: VE = (1 – hazard ratio) x 100 Censoring will occur at the time of the last scheduled or medically attended visit without the occurrence of SSTI cases before the end of follow-up. Subjects who will complete the follow-up without events will be censored at 1 year. In order to check the statistical significance, 1-sided P-value for the log rank test will be calculated. 1-sided nominal type I error will be ***1.61***~~2.04~~% at the interim analysis and 5.***89***~~46~~% at the final analysis. The objective will be met if the 1-sided P-value calculated for the null hypothesis H0 = [occurrence SSTI VE ≥0%] is lower than defined 1-sided alpha level.
Co-secondary	The co- secondary endpoint will be analysed only if the statistical significance is demonstrated for the key secondary endpoint. For this analysis, the mFAS will account for the first case of SSTI any***ti***me from 15 Days after the administration of the first dose of the study vaccine up to 14 months. Time to occurrence of the co- secondary endpoint during the defined efficacy follow-up period will be compared between groups by calculating the respective Hazard ratio (methods will be detailed in the SAP).

Endpoint	Statistical Analysis Methods
	In order to check the statistical significance, 1-sided P-value for the log rank test will be calculated. 1-sided nominal type I error will be 5.***89***~~46~~%. (the nominal alpha level is equal to the key secondary at the final analysis, because we use a sequential procedure). The objective will be met if the 1-sided P-value calculated for the null hypothesis H0=[occurrence SSTI VE ≥0%] is lower than defined 1-sided alpha level.

CCI

[redacted]

CCI

[redacted]

Section 11. REFERENCES

WHO. Global Surveillance for human infection with coronavirus disease (COVID-19). Interim guidance. Last update in March 2020; https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov). Accessed May 15, 2020.

Section 12.5.3. Solicited adverse events

b. Solicited general adverse events

Table 33 Additional solicited general adverse events (PoP only)

Adults
Myalgia
Shivering

Section 12.5.8. Detecting and recording adverse events, serious adverse events and pregnancies

Subject eDiary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject eDiary. This individual may not be the subject, but if a person other than the subject enters information into the Subject eDiary, this ~~person's identity~~ must be documented in the ***subject's source record***~~Subject eDiary~~. Any individual that makes entries into the Subject eDiary must receive training on completion of the Subject eDiary at the time of the visit when Subject eDiary is dispensed. This training must be documented in the subject's source record.

Subject eDiary instructions must ensure that the subject understands the following:

- Any new safety information reported during the safety follow-up phone call or site visits (including a solicited adverse event) cannot be entered into the Subject eDiary. Such information must be described in the source documents as a verbally-reported event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore entered into the eCRF. ***This includes the assessment of Covid-19 cases per the WHO definition [WHO, 2020].***

Section 12.5.8.2.1. Active questioning to detect adverse events and serious adverse events

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. ***This includes the assessment of Covid-19 cases per the WHO definition [WHO, 2020].*** The investigator is not allowed to send photocopies of the subject's medical records to GSK instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK.

Section 12.5.8.2.2. Assessment of adverse events

Table 35 Intensity scales for solicited adverse events in adults

Adults		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C/°F (with 1 decimal)
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Nausea	0	Normal
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Vomiting	0	Normal
	1	Mild: 1-2 times in 24 hours
	2	Moderate: 3-5 times in 24 hours
	3	Severe: 6 or more times in 24 hours or requires intravenous hydration
Diarrhoea	0	Normal
	1	Mild: 2 - 3 loose stools in 24 hours
	2	Moderate: 4 - 5 loose stools in 24 hours
	3	Severe: 6 or more loose stools in 24 hours or requires intravenous hydration
Abdominal pain	0	Normal
	1	Mild: No interference with daily activity

Adults		
Adverse Event	**Intensity grade**	**Parameter**
	2	Moderate: Interferes with daily activity
	3	Severe: Prevents daily activity
Myalgia	***0***	***Normal***
	1	***Mild: No interference with daily activity***
	2	***Moderate: Interferes with daily activity***
	3	***Severe: Prevents daily activity***
Shivering	***0***	***Normal***
	1	***Mild: No interference with daily activity***
	2	***Moderate: Interferes with daily activity***
	3	***Severe: Prevents daily activity***

*Fever is defined as temperature ≥ 38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity for adult subjects.
If any of the solicited symptoms meet the SAE criteria they will reported as a SAE.

Temperature will be scored at GSK Biologicals as follows:

0 : < 100.4°F (38.0°C)
1 : ≥ 100.4°F (38.0°C) ≦ < 102.1°F (39.0°C)
2 : ≥ 102.1°F (39.0°C) ≤ 104°F (40.0°C)
3 : > 104°F (40.0°C)

Possible contributing factors include:

- Lack of efficacy of the vaccine~~(s)/product(s) (delete as applicable)~~, if applicable.

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 11-Oct-2022 07:21:14 GMT+0000