Protocol Amendment 5

Study ID: 217895

Official Title of the Study: A Phase 1 randomized, dose escalation study to evaluate the safety, reactogenicity and immunogenicity of an mRNA-based monovalent influenza vaccine candidate in healthy younger and older adults.

NCT Number: NCT05446740

Date of Document: 23 June 2023

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA (GSK)

Primary study intervention(s)	BIO FLU SV MRNA (GSK4382276A)
Other study intervention(s)	GlaxoSmithKline Flu D-QIV (*α-RIX-Tetra* [Belgium])
eTrack study number and abbreviated title	217895 (FLU SV MRNA-003)
EudraCT number	2022-000489-17
Date of protocol	Final: 15 April 2022
Date of protocol amendment	Amendment 1 Final: 19 May 2022 Amendment 2 Final: 08 July 2022 Amendment 3 Final: 12 January 2023 Amendment 4 Final: 14 February 2023 Amendment 5 Final: 20 June 2023
Title	A Phase 1 randomized, dose escalation study to evaluate the safety, reactogenicity and immunogenicity of an mRNA-based monovalent influenza vaccine candidate in healthy younger and older adults.
Brief title	A study on the safety, reactogenicity and immune response of a vaccine against influenza in healthy younger and older adults.
Sponsor signatory	Pascal Peeters, MD Senior Director Clinical Project Lead

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.3

Protocol Amendment 5 Investigator Agreement

I agree:

- **To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.**
- **To assume responsibility for the proper conduct of the study at this site.**
- **That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.**
- **That I will comply with the terms of the site agreement.**
- **To comply with local bio-safety legislation.**
- **To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.**
- **To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.**
- **To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.**
- **To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.**
- **To co-operate with representative(s) of GSK in the monitoring process of the study and in resolution of queries about the data.**
- **To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).**
- **To have control of all essential documents and records generated under my responsibility before, during, and after the study.**
- **That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the investigational intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.**

Hence, I:

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

eTrack study number and abbreviated title	217895 (FLU SV MRNA-003)
EudraCT number	2022-000489-17
Date of protocol amendment	Amendment 5 Final: 20 June 2023
Title	A Phase 1 randomized, dose escalation study to evaluate the safety, reactogenicity and immunogenicity of an mRNA-based monovalent influenza vaccine candidate in healthy younger and older adults.
Investigator name	
Signature	
Date	

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document.

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

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

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

5. GSK Helpdesk for emergency unblinding

Refer to Section 6.3.5.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 5 (20 June 2023):

This amendment is considered substantial based on the criteria defined in Article 10 (a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall rationale for the current Amendment:

Available data from the CCI and CCI dose cohorts in this study show CCI . The aim of the current protocol amendment is to assess the immunogenicity of CCI and CCI dose levels in order to expand the therapeutic window of this monovalent H1 vaccine candidate in younger adults. Data from this amendment will be used to further characterize the mRNA platform, and may inform the dose selection for future mRNA-based vaccine candidates and/or vaccine combinations.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
4.1. Overall design 4.3. Justification for dose 4.3.2. Justification for additional doses in YAs, evaluated in Amendment 5	Addition of 2 dose levels to the study CCI and CCI	To assess the immunogenicity of the monovalent H1 vaccine candidate at these dose levels
1.1. Synopsis 2.1. Study rationale	Clarification that only younger adults will be enrolled in the CCI and CCI dose cohort	To be able to compare the safety/immunogenicity results against the dose levels previously tested in this study (all previous dose levels were tested in this population)
1.1 Synopsis 1.3. Schedule of Activities (SoA) 2.1. Study rationale 2.3. Benefit/Risk assessment 4.1. Overall design 8.2.3.1.1. Staggered enrollment of OAs	Removal of sentinel participants for the CCI and CCI dose cohort	As (i) CCI , and (ii) CCI have showed CCI (incidence of Grade 3 solicited adverse events ranging from CCI depending on dose group)

Section # and title	Description of change	Brief rationale
1.1. Synopsis 2.1. Study rationale 4.1. Overall design	No dose escalation and parallel enrollment for the CCI and CCI dose cohort	CC and CCI dose levels are CCI than the CCI and CCI dose levels that have been tested previously in this study with a CCI CCI (incidence of Grade 3 solicited adverse events ranging from CCI depending on dose group)
1.1. Synopsis 2.1. Study rationale 4.1. Overall design 4.2.1. Choice of active comparator	No active control for the CC and CCI dose cohort	The sample size of the currently available control group (N=30) is already similar to the sample size of each additional dose group to be tested (N=24). It is considered sufficiently large, given that the main objective is an assessment of immunogencity.
1.3. Schedule of Activities (SoA) 9.4.1. Sequence of planned analyses	Addition of a planned interim analysis upon availability of all primary endpoints up to Day 29 for the CC and CCI dose cohort	To allow an interim analysis of primary endpoints for this cohort
8.1.3. Immunological read-outs	Revision of the number of participants included for each immunological readout	To reflect the 9 dose levels planned to date and the additional number of participants planned in the CC and CCI dose cohort
6.1. Study intervention(s) administered	Addition of the CCI and CCI Flu mRNA vaccines in the study intervention table	To reflect all the dose levels used in this study
4.1. Overall design 4.2.2. Rationale for study blinding 6.3.5. Blinding and unblinding	Clarification that the blinding level for CC and CCI dose cohort will be single-blind	Two different Flu mRNA doses will be used, therefore the persons reconstituting the interventions will be aware of the dose of the allocated Flu mRNA vaccine. This requires unblinding the randomization system for this cohort and accordingly all users of the randomization system will be unblinded and only the participant will remain blinded

Section # and title	Description of change	Brief rationale
6.3.2. Randomization to study intervention	Clarification that full block sizes including active control will be shipped for the CCI and CCI dose cohort, and that the active control arm will be blocked at randomization.	Control arm will be blocked as no active control is used for the CCI and CCI dose cohort. Since active control and Flu mRNA vaccines are already present in the same blocks to support a previous amendment of this study, full block sizes – including active control – will be shipped to avoid risks of potential handling errors at the contract manufacturing organization.

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1. PROTOCOL SUMMARY

1.1. Synopsis *(Amended: 20 June 2023)*

Rationale:

Annual influenza vaccination is currently the most effective mean of controlling influenza and preventing its complications and mortality [WHO, 2018].

In the United States of America (USA), the Center for Disease Control and Prevention (CDC) recommends annual immunization for everyone 6 months and older. Vaccination is particularly important for older adults, children younger than 2 years old, pregnant women, and individuals of all ages with certain chronic medical conditions [Grohskopf, 2020].

Influenza viruses constantly change their surface glycoproteins that are the targets of most immune responses, allowing them to escape pre-existing immunity, a process called antigenic drift. Therefore, seasonal influenza vaccines must be reformulated and re-administered on an annual basis [WHO, 2021]. Currently licensed seasonal influenza vaccines are efficacious when they are well-matched with the circulating virus strains. Hence, seasonal influenza vaccine effectiveness ranges from only 10% in years when vaccine strains are mismatched, to maximum 60% when they are highly matched [CDC, 2020].

Moreover, licensed seasonal influenza vaccines are less effective in older adults, since immunity wanes rapidly after immunization. In addition, the egg-based manufacturing process that requires strain adaptation is thought to negatively impact the immunogenicity [CDC, 2020].

New vaccines have been developed to circumvent those hurdles. High-dose vaccines [DiazGranados, 2014; Dunkle, 2017a; Dunkle, 2017b], adjuvanted vaccines [Novavax, 2021] and non-egg-based vaccines [Divino, 2020; Freyn, 2020] have all demonstrated improved immunogenicity and/or efficacy over classical egg-based standard-dose vaccines.

However, considering the need to improve supply continuity and to develop a more flexible, adaptable vaccine that can provide optimal strain-adapted protection in all age groups in a timely manner, GSK in collaboration with CureVac are developing a new seasonal flu vaccine based on a messenger RNA (mRNA) platform. The use of an mRNA platform circumvents the immunological limitations caused by viral mutations occurring during the egg-adaptation process [CDC, 2020a]. The use of an egg-independent manufacturing process was also identified as an opportunity to streamline vaccine production and improve reliability of supply and ‘surge capacity’, if required [CRS, 2004]. Finally, cellular immunity might prove enhanced by the use of an mRNA-based vaccine as compared to classical split-virion vaccines [Divino, 2020; Wei, 2020].

In this first-time-in-human (FTiH) study, GSK will evaluate a formulation containing mRNA sequences encoding 1 antigen (H1N1 hemagglutinin [HA]), encapsulated in lipid nanoparticles (LNPs). This vaccine candidate uses a new iteration of the mRNA backbone developed by CureVac, in which improvements were made to the untranslated regions, expected to increase immunogenicity. Moreover, the mRNA sequences of the vaccine candidate contain modified nucleotides (i.e., N1-methyl-pseudouridine [1mψU]). CCI [redacted]

The present study will comprise an adaptive dose escalation design with staggered enrollment using an active control in younger adults (YAs) and older adults (OAs).

In pivotal clinical trials conducted with the Covid-19 vaccines developed by Moderna and Pfizer/BioNTech, the mRNA vaccine was found to be less reactogenic in the older age groups (defined as >65 years of age for Moderna and >55 years of age for Pfizer/BioNTech) than in the YAs [Baden, 2021; Polack, 2020]. These vaccines also use 1mψU -containing mRNA technology encapsulated in LNPs, comparable to the vaccine candidate assessed in this study. Preliminary Phase 1 data presented by Moderna show a similar trend for a candidate mRNA seasonal influenza vaccine, with a higher incidence of Grade 3 solicited adverse reactions in YAs when administered high doses of vaccines, compared to OAs [Moderna, 2021].

The aim of this study is to collect preliminary data to support progression of the clinical development with a multivalent influenza vaccine in a larger number of participants. Given the higher medical need for an improved influenza vaccine for OAs, a preliminary assessment of the immunogenicity and reactogenicity profile in this age group is clinically important.

Based on the data provided above, it is reasonable to hypothesize that a dose considered too reactogenic in YAs may be suitable for OAs in terms of reactogenicity and immunogenicity. Therefore, it will be important to confirm findings in YAs, also in the OA population. The enrollment of OAs, however, will be limited to a single dose level and not be initiated prior to establishing a safety database in YAs.

The methodology used in this study comprises several measures to minimize the risk for the study participants, namely:

1. Initiation of the dose escalation CCI [redacted] than the dose used in the efficacy trial conducted using the previous generation of CureVac mRNA Covid-19 vaccine CCI [redacted]
2. Initiation of the dosing of OAs not until after the review of the safety/reactogenicity data reported with the 3 first dose levels administered in YAs by an unblinded Safety Review Team (SRT). Note: as the goal of protocol amendment***s*** 3, 4 ***and 5*** are to ***further explore the*** reactogenicity/ immunogenicity profile in YAs (all previous dose levels were tested in this population), no OAs will be enrolled in the CCI [redacted] ***and*** CCI [redacted] ***dose cohort,*** C [redacted] and CCI [redacted] dose cohort, or in the CCI [redacted] ***(***and potential intermediate ***doses) dose*** cohorts***.***

3. Supervision of the dose escalation by SRT. The safety/reactogenicity data reviewed by this team cover 8 days of follow up post-dosing (Day 1 to Day 8 included) of all participants of the current dose level. This time window is sufficient to ensure a reliable evaluation of the reactogenicity of the vaccine, considering that the median onset of solicited systemic events after mRNA Covid-19 vaccines administration is 1 to 2 days, and a median duration of such events is 1 to 2 days [CBER, 2021; CBER, 2022]. Note: CCI [redacted], and CCI [redacted] have shown a CCI [redacted] (incidence of Grade 3 solicited adverse events ranging from CCI [redacted] depending on dose group), this dose escalation step will not be followed for the CCI [redacted] and CCI [redacted], ***or the*** CCI [redacted] ***and*** CCI [redacted] ***dose cohorts***, i.e., participants in these cohorts will be enrolled in parallel.
4. Enrollment of sentinel participants for each dose level, per age group. The safety/reactogenicity data for at least 2 days of follow up post-dosing of 6 sentinel participants will be reviewed by an SRT before enrolling the 18 remaining participants planned in the study group (24 participants/dose level), to reduce the risk of unnecessary exposure to a possibly highly reactogenic dose.

   Note: CCI [redacted], and CCI [redacted] have shown a CCI [redacted] (incidence of Grade 3 solicited adverse events ranging from CCI [redacted] depending on dose group), no sentinel participants will be included in the additional CCI [redacted] and CCI [redacted] ***or*** CCI [redacted] ***and*** CCI [redacted] dose ***cohorts***.
5. Use of a Bayesian Logistic Regression Model (BLRM) to inform and guide the decision to (i) enroll non-sentinel participants and (ii) escalate the dose. Reactogenicity data from both sentinel and non-sentinel participants at current and all previous dose levels will be used by the BLRM along study progression.
6. Possibility to assess intermediate dose level in YAs, should the posterior probability of the BLRM indicate that the reactogenicity of the upper dose level would be too high (adaptive design).
7. Use of an upper age limit (70 years) for sentinel participants in OA groups.
8. Enrollment of OAs with no clinically significant co-morbidities.

GSK's *Flu Dresden- Quadrivalent Influenza Vaccine*, hereafter referred to as Flu D-QIV and commercially available as *α-RIX-Tetra* in Belgium was chosen as active control in this study. It is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. The vaccine is approved for use in 6 months of age and older.

Note: The sample size of the available Control group (N=30) is similar to the sample size of each additional dose group to be tested (N=24). As such, we consider the available Control group sufficiently large for this phase 1 exploratory and descriptive study and will not use an active control for the additional CCI [redacted] ***and*** CCI [redacted] ***dose cohort, and*** CCI [redacted] and CCI [redacted] dose cohort, where an assessment of immunogenicity is the main objective. However, for the additional CCI [redacted], and their potential intermediate dose cohorts (CCI [redacted] and CCI [redacted] where a safety/reactogenicity assessment is the main objective, Flu D-QIV will be reintroduced as active control.

Objectives, endpoints and estimands:

Refer to Section 3 for detailed list of objectives, endpoints and estimands.

1.2. Schema

See Figure 1 in Section 4.

1.3. Schedule of Activities (SoA) *(Amended: 20 June 2023)*

Table 1 Schedule of Activities (SoA) *(Amended: 20 June 2023)*

Type of contact	Screening visit	Visit 1	Contact 1†	Contact 2	Visit 2	Visit 3	Visit 4	Visit 5***	Visit 6***	Notes
Timepoints	**Day -28 to Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 22**	**Day 29**	**Day 62**	**Day 183**	
Informed consent	●									See Section 10.1.3 for details
Check inclusion/exclusion criteria	●	○ [a]								Check clinical status before randomization and/or administration of study intervention. See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Collect demographic data	●									See Section 8.2.1.1 for more information
Medical and vaccination history	●									See Section 8.2.1.2 for more information
Physical examination	●	● [a]			○	○	○	○	○	Physical examination after Day 1 will be performed only if the participant indicates that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate. See Section 8.2.1.3 for more information
Randomization		○ [a]								A randomization procedure will be used with sentinel, age and dose level cohort as stratification factor and with study, country, site, and flu vaccination history during past 2 years as minimization factors. See Section 6.3 for more information

Type of contact	Screening visit	Visit 1	Contact 1†	Contact 2	Visit 2	Visit 3	Visit 4	Visit 5***	Visit 6***	Notes
Timepoints	**Day -28 to Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 22**	**Day 29**	**Day 62**	**Day 183**	
Study intervention										
Check contraindications, warnings and precautions to study intervention administration		○ [a]								See Section 8.2.1.7 for more information
Check criteria for temporary delay for study intervention administration		○ [a]								See Section 5.5 for more information
Urine pregnancy test (only for female participants of childbearing potential)	●	●[a]								Serum pregnancy test can be done as per local requirements if time allows. See Section 8.2.1.4 for more information
Study group and intervention number allocation		● [a]								See Section 6.3 for more information
Body temperature before study intervention administration		● [a]								Fever is defined as temperature ≥38°C/100.4°F regardless the location of measurement. The preferred location for measuring temperature will be axillary. See Section 8.2.1.4 for more information
Study intervention administration		●								See Section 6.1 for more information
Post-dose observation period		○								See Section 6.1 for more information
Recording of administered study intervention number		●								
Distribution of participant card		○								See Section 8.3.5 for more information
Check participant's device compatibility for eDiary data collection	○	○								See Section 8.2.1.6 for more information

Type of contact	Screening visit	Visit 1	Contact 1†	Contact 2	Visit 2	Visit 3	Visit 4	Visit 5***	Visit 6***	Notes
Timepoints	**Day -28 to Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 22**	**Day 29**	**Day 62**	**Day 183**	
Training and installing/assigning eDiaries		○								See Section 8.2.1.6 for more information
Review of eDiary data			○	○	○	○	○			Recording of solicited events (Day 1-Day 7 post-dosing) [b] Reporting of unsolicited adverse events (Day 1-Day 28 post-dosing) [b] Completion of [redacted] (Day 3 and Day 7 post-dosing) [b] See Section 10.3.9 for more information
Return/uninstalling of eDiary							○			See Section 10.3.9 for more information
Laboratory Assessment										
Blood sampling for routine safety panel (~10 mL) All participants	●	●[a]			●		●			If screening occurs within 3 days (Day -3 to Day -1) before Visit 1, the results of safety lab assessments from screening can be used as baseline. Volume of the blood drawn will vary depending on local lab requirements. See Section 10.2.1 for more information
Urine sampling for routine safety panel All participants	●	●[a]			●		●			Volume of urine sample will be defined as per local practice. See Section 10.2.1 for more information.
Blood sampling for antibody determination and characterization (~10 mL) All participants		●[a]				●		●**	●**	For this assessment, serum has to be isolated from blood. See Section 8.1.2 for more information

Type of contact	Screening visit	Visit 1	Contact 1†	Contact 2	Visit 2	Visit 3	Visit 4	Visit 5***	Visit 6***	Notes
Timepoints	**Day -28 to Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 22**	**Day 29**	**Day 62**	**Day 183**	
Blood sampling CCI (~30mL) * CCI subset		●[a]			●			●**	●**	See Section 8.1.2 for more information
Safety assessments										
Record any concomitant vaccinations	●	●	●	●	●	●	●	●	●	See Section 6.8 and Table 12 for more information.
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	See Section 10.3.9 for more information
Record any concomitant medications		●	●	●	●	●	●	●	●	See Section 6.8 and Table 12 for more information.
Recording of unsolicited AEs (Day 1-Day 28 post-dosing)		●	●	●	●	●	●			See Sections 10.3.4 and 10.3.9.1 for more information
Recording of SAEs, AESIs and pregnancies		●	●	●	●	●	●	●	●	See Section 10.3.9 for more information
AEs/SAEs leading to withdrawal from the study		●	●	●	●	●	●	●	●	See Section 10.3.9 for more information
Study conclusion									●	See Section 4.4 for more information
Investigator sign-off on eCRF						●	●		●	

Note: The double-line border after Day 22 (Visit 3) and Day 29 (Visit 4) indicates the schedule of interim analyses. Two initial interim analyses will be conducted upon availability of all primary endpoints up to Day 22 for YA participants in the CCI and CCI cohorts, respectively and ***a*** third interim analysis will be performed upon availability of all primary endpoints up to Day 29 for all study participants. Note: additional interim analyses will be performed upon availability of all primary endpoints up to Day 29 for (i) all participants in the ** and CCI dose cohort, (ii) all participants in the CCI and their potential intermediate dose cohorts CCI and CCI ***), and (iii) all participants in the CCI and CCI dose cohort.***
CCI eDiary: electronic diary (application or electronic device); AE: adverse event; SAE: serious adverse event; AESI: adverse event of special interest.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

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

† Contact 1 (Day 2) will be performed for sentinel participants only. Note that no sentinel participants are included for the CCI ***and*** CCI ***or*** ** and CCI dose cohorts.

* Samples will be collected on sites associated with a CCI Note: for the CCI and their potential intermediate dose cohorts CCI and CCI no blood sampling for CCI response will be performed.

** Sample will be collected only if participants did not receive the standard of care vaccination against seasonal flu since study participation. Note that blood sampling for antibody determination and characterization will be limited to Day 1 and Day 22 for the CCI and their potential intermediate dose cohorts CCI and CCI).

*** Visit 5 (Day 62) and Visit 6 (Day 183) will be replaced by a contact if participant have received the standard of care vaccination against seasonal flu prior to this visit and did not report any adverse events that would require physical examination on site. Note: No blood sampling will be performed at Day 62 and Day 183 for the CCI , and their potential intermediate dose cohorts CCI and CCI). As such, Visit 5 and Visit 6 will be replaced by a contact for all participants in these cohorts unless they reported any adverse events that would require physical examination on site.

[a] is used to indicate a study procedure to be performed prior to study intervention administration.

[b] is used to indicate a study procedure recorded in eDiary.

Table 2 Intervals between study visits *(Amended: 20 June 2023)*

Interval	Planned contact interval	Allowed interval range
Screening* → Visit 1	1-28 days	1 – 28 days
Visit 1 → Contact 1**	20 hours	18-24 hours
Visit 1 → Contact 2	2 days	2 days†
Visit 1 → Visit 2	7 days	6-8 days
Visit 1 → Visit 3	21 days	20-24 days
Visit 1 → Visit 4	28 days	26-35 days
Visit 1 → Visit 5***	61 days	54-68 days
Visit 1 → Visit 6***	182 days	168-196 days

* Screening visit should take place within 28 days before Visit 1, with sufficient time to receive/review the hematology, biochemistry, coagulation and urinalysis results. When applicable, a re-screening visit (including blood and urine sample collection, physical examination and re-checking of inclusion/exclusion criteria) may be scheduled at any time (but only once to assess eligibility) before Visit 1. All screening procedures need to be performed within 28 days before Visit 1. Only laboratory results from the re-screening visit, if it occurs, will be taken into consideration. The participant can only be randomized once the investigator receives the results and confirms the eligibility criteria.
** Contact 1 (Day 2) will be performed for sentinel participants only. Note that no sentinel participants are included for the CCI ***and*** CCI ***or*** [redacted] and CCI dose cohorts.
*** Visit 5 (Day 62) and Visit 6 (Day 183) will be replaced by a contact if participant have received the standard of care vaccination against seasonal flu prior to this visit and did not report any adverse events that would require physical examination on site. Note: No blood sampling will be performed at Day 62 and Day 183 for the CCI [redacted], and their potential intermediate dose cohorts (CCI and CCI [redacted]). As such, Visit 5 and Visit 6 will be replaced by a contact for all participants in these cohorts unless they reported any adverse events that would require physical examination on site.
† For non-sentinel participants, the allowed interval ranges from 1 to 3 days.

2. INTRODUCTION

2.1. Study rationale *(Amended: 20 June 2023)*

Annual influenza vaccination is currently the most effective mean of controlling influenza and preventing its complications and mortality [WHO, 2018].

In the United States of America (USA), the Center for Disease Control and Prevention (CDC) recommends annual immunization for everyone 6 months and older. Vaccination is particularly important for older adults, children younger than 2 years old, pregnant women, and individuals of all ages with certain chronic medical conditions [Grohskopf, 2020].

Influenza viruses constantly change their surface glycoproteins that are the targets of most immune responses, allowing them to escape pre-existing immunity, a process called antigenic drift. Therefore, seasonal influenza vaccines must be reformulated and re-administered on an annual basis [WHO, 2021]. Currently licensed seasonal influenza vaccines are efficacious when they are well-matched with the circulating virus strains. Hence, seasonal influenza vaccine effectiveness ranges from only 10% in years when vaccine strains are mismatched, to maximum 60% when they are highly matched [CDC, 2020].

Moreover, licensed seasonal influenza vaccines are less effective in older adults, since immunity may wane rapidly after immunization. In addition, the egg-based

manufacturing process that requires strain adaptation is thought to negatively impact the immunogenicity [CDC, 2020].

New vaccines have been developed to circumvent those hurdles. High-dose vaccines [DiazGranados, 2014; Dunkle, 2017a; Dunkle, 2017b], adjuvanted vaccines [Novavax, 2021] and non-egg-based vaccines [Divino, 2020; Freyn, 2020] have all demonstrated improved immunogenicity and/or efficacy over classical egg-based standard-dose vaccines.

However, considering the need to improve supply continuity and to develop a more flexible, adaptable vaccine that can provide optimal strain-adapted protection in all age groups in a timely manner, GSK in collaboration with CureVac are developing a new seasonal flu vaccine based on a messenger RNA (mRNA) platform. The use of an mRNA platform circumvents the immunological limitations caused by viral mutations occurring during the egg-adaptation process [CDC, 2020a]. The use of an egg-independent manufacturing process was also identified as an opportunity to streamline vaccine production and improve reliability of supply and 'surge capacity', if required [CRS, 2004]. Finally, cellular immunity might prove enhanced by the use of an mRNA-based vaccine as compared to classical split-virion vaccines [Divino, 2020; Wei, 2020].

In this first-time-in-human (FTiH) study, GSK will evaluate a formulation containing mRNA sequences of 1 antigen (H1N1 hemagglutinin [HA]) encapsulated in lipid nanoparticles (LNPs). This vaccine candidate uses a new iteration of the mRNA backbone developed by CureVac, in which improvements were made to the untranslated regions, expected to increase immunogenicity. Moreover, the mRNA sequences of the vaccine candidate contain modified nucleotides (i.e., N1-methyl-pseudouridine [1mψU]).
CCI [redacted]

The present study will comprise an adaptive dose escalation design with staggered enrollment using an active control in younger adults (YAs) and older adults (OAs).

In pivotal clinical trials conducted with the Covid-19 vaccines developed by Moderna and Pfizer/BioNTech, the mRNA vaccine was found to be less reactogenic in the older age groups (defined as >65 years of age for Moderna and >55 years of age for Pfizer/BioNTech) than in the YAs [Baden, 2021; Polack, 2020]. These vaccines also use 1mψU -containing mRNA technology encapsulated in LNPs, comparable to the vaccine candidate assessed in this study. Preliminary Phase 1 data presented by Moderna show a similar trend for a candidate mRNA seasonal influenza vaccine, with a higher incidence of Grade 3 solicited adverse reactions in YAs when administered high doses of vaccines, compared to OAs [Moderna, 2021].

The aim of this study is to collect preliminary data to support progression of the clinical development with a multivalent influenza vaccine in a larger number of participants. Given the higher medical need for an improved influenza vaccine for OAs, a preliminary assessment of the immunogenicity and reactogenicity profile in this age group is clinically important.

Based on the data provided above, it is reasonable to hypothesize that a dose considered too reactogenic in YAs may be suitable for OAs in terms of reactogenicity and immunogenicity. Therefore, it will be important to confirm findings in YAs, also in the OA population. The enrollment of OAs will be limited to a single dose level and not be initiated prior to establishing a safety database in YAs.

The methodology used in this study comprises several measures to minimize the risk for the study participants, namely:

1. Initiation of the dose escalation with a CCI than the dose used in the efficacy trial conducted using the previous generation of CureVac mRNA Covid-19 vaccine CCI).
2. Initiation of the dosing of OAs not until after the review of the safety/reactogenicity data reported with the 3 first dose levels administered in YAs by an unblinded Safety Review Team (SRT).

   Note: As the goals of protocol amendments 3***, 4 and 5 are*** to ***further explore the*** reactogenicity/immunogenicity profile in YAs (all previous dose levels were tested in this population), no OAs will be enrolled in the CCI ***and*** CCI ***dose cohort, and*** CCI and CCI dose cohort, or in the CCI , and their potential intermediate dose cohorts (CCI and CCI).
3. Supervision of the dose escalation by SRT. The safety/reactogenicity data reviewed by this team cover 8 days of follow up post-dosing (Day 1 to Day 8 included) of all participants of the current dose level. This time window is sufficient to ensure a reliable evaluation of the reactogenicity of the vaccine, considering that the median onset of solicited systemic events after mRNA Covid-19 vaccines administration is 1 to 2 days, and a median duration of such events is 1 to 2 days [CBER, 2021; CBER, 2022].

   Note: CCI , and CCI have shown a CCI (incidence of Grade 3 solicited adverse events ranging from CCI depending on dose group) this dose escalation step will not be followed for the CCI and CCI , ***or the*** CCI ***and*** CCI ***dose cohorts***, i.e., participants in these cohorts will be enrolled in parallel. Enrollment of sentinel participants for each dose level, per age group. The safety/reactogenicity data for at least 2 days of follow up post-dosing of 6 sentinel participants will be reviewed by an SRT before enrolling the 18 remaining participants planned in the study group (24 participants/dose level), to reduce the risk of unnecessary exposure to a possibly highly reactogenic dose.

   Note: CCI , and CCI have shown a CCI (incidence of Grade 3 solicited adverse events ranging from CCI depending on dose group), no sentinel participants will be included in the additional CCI ***and*** CCI ***dose cohort and*** CCI and CCI dose cohort.
4. Use of a Bayesian Logistic Regression Model (BLRM) to inform and guide the decision to (i) enroll non-sentinel participants and (ii) escalate the dose. Reactogenicity data from both sentinel and non-sentinel participants at current and all previous dose levels will be used by the BLRM along study progression.

5. Possibility to assess intermediate dose level in YAs, should the posterior probability of the BLRM indicate that the reactogenicity of the upper dose level would be too high (adaptive design).
6. Use of an upper age limit (70 years) for sentinel participants in OA groups.
7. Enrollment of OAs with no clinically significant co-morbidities.

GSK's *Flu Dresden- Quadrivalent Influenza Vaccine*, hereafter referred to as Flu D-QIV and commercially available as *α-RIX-Tetra* in Belgium was chosen as active control in this study. It is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. The vaccine is approved for use in 6 months and older.

Note: The sample size of the available Control group (N=30) is similar to the sample size of each additional dose group to be tested (N=24). As such, we consider the available Control group sufficiently large for this phase 1 exploratory and descriptive study and will not use an active control for the additional CCI ***and*** CCI ***dose cohort and*** CCI and CCI dose cohort, where an assessment of immunogenicity is the main objective. However, for the additional CCI, and their potential intermediate dose cohorts (CCI and CCI), where a safety/reactogenicity assessment is the main objective, Flu D-QIV will be reintroduced as active control.

2.2. Background

Influenza is an infectious disease caused by influenza viruses, enveloped negative-sense RNA viruses belonging to the Orthomyxoviridae family. Four types of influenza viruses have been identified, of which type A and B are primarily responsible for human disease.
CCI

Influenza causes variable but often high rates of seasonal disease in the human population, with consequent significant morbidity and mortality. Uncomplicated influenza is characterized by the abrupt onset of general and respiratory symptoms which usually resolve within a week. However, in vulnerable populations such as the elderly and young children, influenza can aggravate existing medical conditions and potentially lead to life-threatening complications. During seasonal epidemics, 5-15% of the population is typically infected, resulting in 3-5 million cases of severe illness. Up to 650 000 deaths annually are associated with seasonal influenza [WHO, 2017].

Please refer to the current Investigator's Brochure (IB) for information regarding pre-clinical studies of Flu Seasonal mRNA.

2.3. Benefit/Risk assessment

Detailed information about the known and expected benefits and risks and expected adverse events of Flu Seasonal mRNA can be found in the IB.

Detailed information about the known and expected benefits and risks and expected adverse events of Flu D-QIV can be found in the Summary of Product Characteristics (SmPC).

As for any vaccine, administration site (e.g., pain, swelling, redness) and systemic (e.g., fever, fatigue, headache, myalgia) post-dosing events may occur within the first 3 days of study intervention administration, and are anticipated to resolve within a few days of onset.

2.3.1. Risk assessment *(Amended 20 June 2023)*

Potential risks	Data/Rationale for risk	Mitigation strategy
All study vaccines		
Hypersensitivity including allergic reactions such as anaphylaxis	Acute allergic reactions are serious, but rare occurrences estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied [Rüggeberg, 2007].	Participants with history of hypersensitivity or severe allergic reaction to any previous vaccine or any component of the study intervention are excluded from the study enrollment. All participants will remain under observation with appropriate medical treatment readily available, if needed. Participants will be instructed to contact the study site immediately for occurrence of any possible hypersensitivity reaction within 1 day following study intervention administration.
Bleeding following intramuscular injection	As with other intramuscular injections, study intervention should be given with caution in individuals with bleeding disorders, such as hemophilia or on anticoagulant therapy, to avoid the risk of hematoma following the injection.	To minimize the risk of bleeding, study intervention should be given with caution in individuals with thrombocytopenia or any coagulation disorder. Participants with any medical condition that in judgment of the investigator would make intramuscular injection unsafe will be excluded from study enrollment.
Flu Seasonal mRNA vaccine		
Due to the lack of experience in human participants, there is currently not enough information available about the relationship of AEs and the administration of the Flu Seasonal mRNA investigational vaccines		The first sentinel participants in each age category (both in Flu mRNA and in Control groups) will be dosed in the morning of the first day. There will be an interval of at least 60 minutes between dosing of all sentinel participants. The next day, if no holding rule has been met in the sentinel participants dosed at the first day, the remaining sentinel participants in each age category (in Flu mRNA and in Control groups) will be dosed. All the participants (including non-sentinel) will be observed on site for 60 minutes after dosing. Refer to Section 8.2.3.1 for more information on safety monitoring.

Potential risks	Data/Rationale for risk	Mitigation strategy
Bell's palsy	Previous studies have shown controversial results on the risk of Bell's palsy after influenza vaccination [Ozonoff, 2021; Bardage, 2011; Huang, 2012; Wijnans, 2017; Baxter, 2017; Mutsch, 2004]. The risk of reporting facial paralysis following an influenza vaccination seems to be higher compared with that following the administration of other vaccines [Kamath, 2020]. Although literature is sparse on specific mechanism involved, given the potential association between influenza infection and incidence of facial palsy, Bell's palsy is proposed as an important potential risk for this candidate vaccine.	Participants with a recurrent history of neurological disorders or seizures, including Bell's palsy, will be excluded from the study enrollment. Moreover, pIMDs including Bell's palsy will be collected as AESIs (refer to Section 10.3.6).
Guillain-Barré Syndrome (GBS)	An association between the onset of GBS and influenza vaccination was suggested in late 70's during swine flu immunization program [Langmuir, 1979; Schonberger, 1979] and was confirmed by results of 39 studies published between 1981 and 2014 [Martín Arias, 2015; Greene, 2012; Wise, 2012]. Given the potential association, GBS is proposed as an important potential risk for this candidate vaccine.	Participants with a recurrent history of neurological disorders or seizures, including GBS, will be excluded from the study enrollment. Moreover, pIMDs including GBS will be collected as AESIs (refer to Section 10.3.6).
Study procedures		
Pain and bruising	Pain or bruising at the site where blood is drawn.	A topical analgesic may be applied to the site where blood will be taken.
Syncope and vasovagal reactions to study intervention administration	Syncope (fainting) and other anxiety related reactions can occur as a psychogenic response to the needle injection following or before blood draw or dosing.	To minimize the risk of injury associated with syncope before/after dosing or blood draw, all participants will be seated or lying down during study intervention administration/blood draw and will remain under observation after the procedure. The decision to dose the participant will be dependent on the clinical judgment of the investigator.

Note: no sentinel participants are included for the CCI ***and*** CCI ***or*** CCI and CCI dose cohorts

2.3.2. Benefit assessment

Participants may gain information and medical advice about their general health status through medical evaluations/assessments associated with this study (i.e., physical examinations, urine analysis and blood testing [hematology, biochemistry and coagulation data]).

2.3.3. Overall benefit/risk conclusion

The investigational Flu Seasonal mRNA vaccine is currently in an early stage of clinical development and vaccine efficacy, immunogenicity, and safety have not yet been demonstrated in humans. Considering the measures to minimize the risk to participants in this Phase 1 clinical study, the potential risks are justified by the potential benefits linked to the development of this Flu Seasonal mRNA vaccine.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3 Study objectives, endpoints and estimands

Objectives	Endpoint(s) and estimand(s)
Co-primary	
To evaluate the safety and reactogenicity profile of the study interventions	Solicited events: • Percentage of participants reporting each solicited administration site and systemic events within 7 days (i.e., from Day 1 to Day 7) after study intervention administration Unsolicited adverse events (AEs): • Percentage of participants reporting unsolicited AEs within 28 days (i.e., from Day 1 to Day 28) after study intervention administration Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI*): • Percentage of participants reporting SAEs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration • Percentage of participants reporting AESIs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration Safety laboratory: • Percentage of participants reporting a shift from non-clinically significant laboratory value on Day 1 (pre-dose) to clinically significant abnormal laboratory value on Day 8 (post-dose) or on Day 29 (post-dose) for hematology, clinical chemistry, coagulation and urine analysis.
To evaluate the humoral immune response induced by the study interventions	CCI [redacted] antibody titer: • Geometric mean titers (GMT) at Day 1 and Day 22 • Geometric mean increase (GMI) from Day 1 to Day 22 • CCI [redacted] from Day 1 to Day 22 • CCI [redacted]) at Day 22
Secondary	
To evaluate the humoral immune response induced by the study interventions	CCI [redacted] antibody titer**: • GMT at Day 62 and Day 183 • GMI from Day 1 to Day 62 • GMI from Day 1 to Day 183 • CCI [redacted] at Day 62 and Day 183
CCI [redacted]	

Objectives	Endpoint(s) and estimand(s)
CCI	

CCI

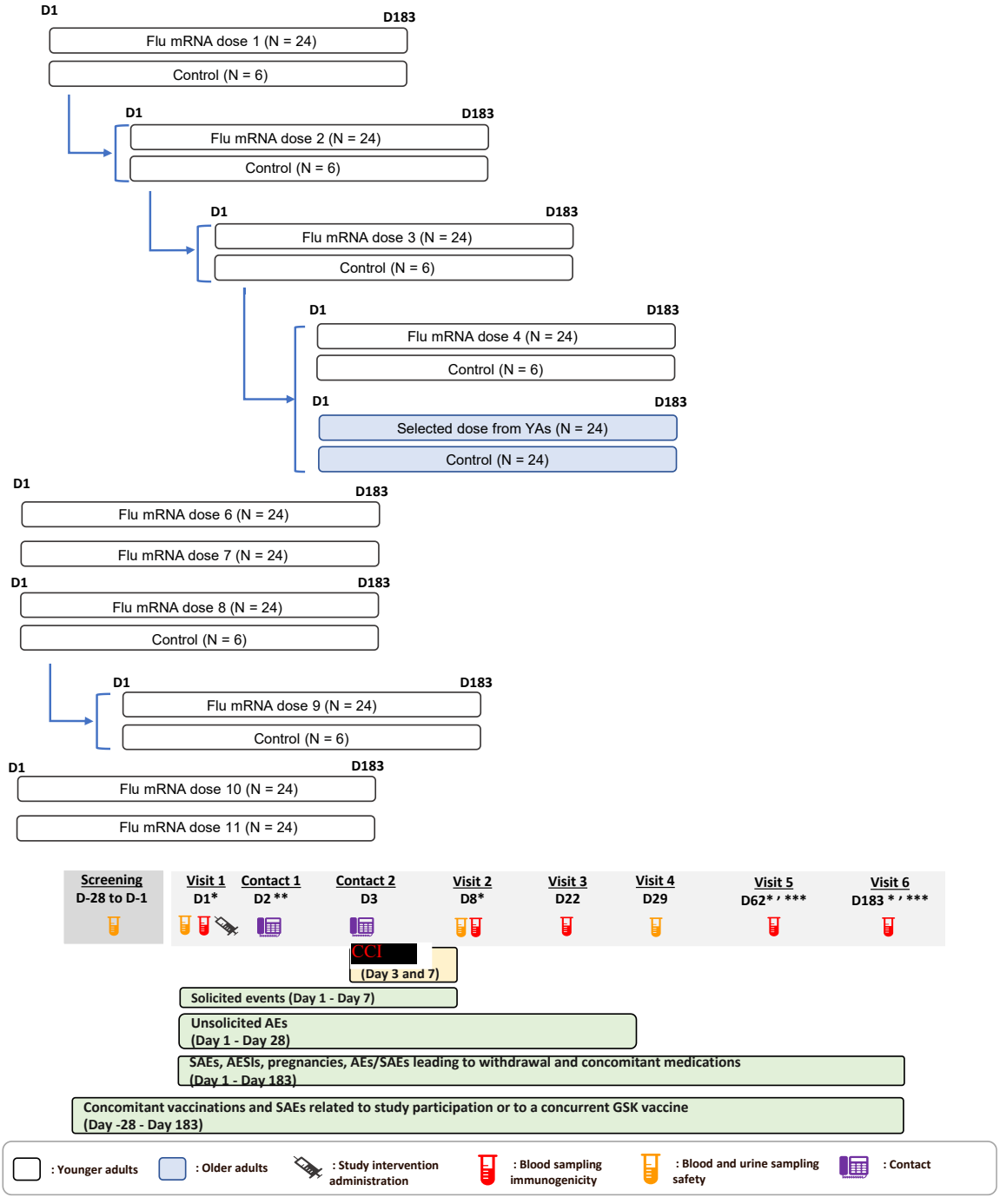
* Refer to Sections 10.3.3 and 10.3.6 for the list of solicited events and events considered as AESI, respectively.
** Note: for the CCI, and their potential intermediate dose cohorts CCI and CCI no analysis for CCI response will be performed, and humoral immune response determination will be limited to Day 1 and Day 22.

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

4. STUDY DESIGN

4.1. Overall design *(Amended: 20 June 2023)*

Figure 1 Study design overview *(Amended: 20 June 2023)*



AE: adverse event; SAE: serious adverse event; AESI: adverse event of special interest; D: day; CCI [redacted] Control: Flu D-QIV (*Flu Dresden-Quadrivalent Influenza Vaccine*; GlaxoSmithKline; season 2021-2022 Northern Hemisphere [NH] for the CCI [redacted] dose cohorts, and season 2022-2023 NH for the CCI

CCI dose cohorts, and their potential intermediate dose cohorts CCI and CCI); commercially available as α-RIX-Tetra in Belgium).
Doses of study intervention for YAs are coded as follows: dose 1: CCI dose 2: CCI dose 3: CCI , dose 4: CCI dose 6: CCI dose 7: CCI , dose 8 CCI , dose 9: CCI ***dose 10:*** CCI ***dose 11:*** CCI Potential intermediate dose levels CCI , and CCI may be evaluated with the total number of dose levels not exceeding ***12*** in YAs and 1 in OAs. In OAs, dose of study intervention will be selected based on safety/reactogenicity data up to dose 3 in YAs. Refer to Section 4.3 for more information. Refer to Section 4.3.2, ***4.3.4, and 4.3.4*** for rationale for addition of the CCI and their potential intermediate dose cohorts (CCI) respectively.
* Blood sample for CCI will be collected from a subset of participants. CCI will be assessed in 50% of participants of each group (Flu mRNA and Control) to be enrolled at the selected sites.
Note: for the CCI and their potential intermediate dose cohorts CCI) no blood sampling for CCI response will be performed.
** Contact 1 (Day 2) will be performed for sentinel participants only. Note that no sentinel participants are included for the CCI dose ***cohorts***.
*** Visit 5 (Day 62) and Visit 6 (Day 183) will be replaced by a contact if participant have received the standard of care vaccination against seasonal flu prior to this visit and did not report any adverse events that would require physical examination on site. Note: No blood sampling will be performed at Day 62 and Day 183 for the CCI , and their potential intermediate dose cohorts CCI). As such, Visit 5 and Visit 6 will be replaced by a contact for all participants in these cohorts unless they reported any adverse events that would require physical examination on site.
Note: Each dose group consists of sentinel and non-sentinel participants, except for the CCI dose ***groups***.

- First-time-in-human (FTiH)
- Phase 1 study with adaptive design that will be conducted in the following way:
  - Safety of and immune response to 1 formulation at different dose levels of study intervention will be assessed in YAs using an active controlled and dose escalation design. Unless safety concerns are identified by SRT after dosing sentinel participants, remaining participants at the current dose level will be administered the study intervention. SRT will also review data from all participants from a current dose level and advise on dosing of sentinel participants for the next dose level.
  - Safety of and immune response to 1 formulation at 1 dose level of study intervention will be assessed in OAs using an active control. Unless safety concerns are identified by SRT after dosing sentinel participants, remaining participants at the current dose level will be administered the study intervention.
  - For the additional CCI dose ***cohorts***, no sentinel participants will be enrolled; no dose escalation design applies; the dose levels ***in each cohort*** will be enrolled in parallel; no control vaccine will be used.

YA				OA			
Flu mRNA		**Control**		**Flu mRNA**		**Control**	
Sentinel participants	Non-sentinel participants	Sentinel participants	Non-sentinel participants	Sentinel participants	Non-sentinel participants	Sentinel participants	Non-sentinel participants
N = 6 /group	N = 18/group	N = 3 /group	N = 3/group	N = 6 /group	N = 18/group	N = 6 /group	N = 18/group

Note: No sentinel participants will be enrolled for the additional CCI dose ***cohorts***, hence all participants in ***these cohorts*** will be considered as non-sentinel. No control vaccine will be used for ***the*** CCI ***or*** CCI dose cohorts, where a randomization ratio of 1:1 will be applied between the CCI ***dose levels, and between the*** CCI dose levels, for a total of 48 participants ***per cohort***.

- Staggered enrollment for the CCI cohorts and their potential intermediate dose cohorts CCI refer to Section 8.2.3.1 and Table 10 for details.
- Parallel enrollment for the CCI ***, and the*** CCI dose cohorts.
- Planned (approximate) number of participants to be enrolled is ***354***:
  - ***306*** YA participants (24 participants per dose level and a total number of 42 participants receiving the active control)
  - 48 OA participants (24 participants receiving a dose of investigational study intervention and 24 participants receiving the active control)
  - Due to the adaptive design, the actual number of participants enrolled might be lower than the target number or up to ***384*** participants in case a ***12th*** dose level is evaluated in YAs.
- Study intervention: single dose intramuscular (IM) administration of different dose levels of the study intervention:
  - YAs: 1 formulation at 6 dose levels (CCI). Depending on the reactogenicity/safety findings after dosing with these dose levels, potential intermediate dose levels may be assessed (i.e., CCI and CCI . Refer to Section 8.2.3.1 for details on dose escalation management.

    Furthermore, 2 additional doses of CCI of the vaccine candidate will be assessed in 48 YAs under Protocol Amendment 3***; and 2 additional doses of*** CCI ***will be assessed in 48 YAs under Protocol Amendment 5.*** Refer to Section 4.3.2, 4.3.4***, and 4.3.4*** for rationale for addition of the CCI , and their potential intermediate dose cohorts respectively. In any case, the total number of dose levels assessed will not exceed ***12.***
  - OAs: 1 formulation at 1 dose level (up to CCI The dose level will be selected after review by SRT of the safety/reactogenicity data obtained in YAs dose levels 1 to 3 (up to CCI
- Active control: Flu D-QIV (*Flu Dresden- Quadrivalent Influenza Vaccine*; GlaxoSmithKline; season 2021-2022, Northern Hemisphere [NH], commercially available as *α-RIX-Tetra* in Belgium) will be used as the active control for the CCI , and their potential intermediate dose cohorts in both YAs and OAs, while Flu D-QIV season 2022-2023 will be used as active control for the CCI , and their potential intermediate dose cohorts (CCI No active control will be used for the CCI ***, or*** CCI dose ***cohorts.***
- Study groups:
  - 2 parallel groups, Flu mRNA versus Control in YAs.
  - 2 parallel groups, Flu mRNA versus Control in OAs.
  - For the CCI dose cohort: 2 parallel groups, Flu mRNA CCI versus Flu mRNA CCI in YAs.
  - ***For the*** CCI ***dose cohort: 2 parallel groups, Flu mRNA*** CCI ***versus Flu mRNA*** CCI ***in YAs.***

A CCI subset will be defined, where CCI will be assessed in 50% of participants of each group (Flu mRNA and Control) to be enrolled at the selected sites.

- Note: no CCI response will be assessed for the CCI, and their potential intermediate dose cohorts (CCI).
- Method of study intervention allocation: for each dose level and age group separately, randomization, using study, country, site and influenza vaccination history for the past 2 years as minimization factors for all participants.
  - YA participants will be randomized to receive either 1 of the dose levels, or the active control.
  - OA participants will be randomized to receive either 1 dose level or the active control.
  - For the CCI dose cohort, YA participants will be randomized to receive either the Flu mRNA CCI or CCI dose.
  - ***For the CCI and CCI dose cohort, YA participants will be randomized to receive either the Flu mRNA CCI or CCI dose.***
- Study type: primary vaccination.
- Level of blinding: for participants and investigators, the study will be observer-blind with regards to the study intervention, but open-label with regards to the dose level. For the sponsor, the study will be open-label. For the CCI***, and*** CCI dose ***cohorts,*** the study will be single-blind.
- Multi-country, multi-center. However, sentinel participants will be preferably recruited at a single site.
- Self-contained.
- Aspects of data collection: blood and urine samples, safety events, CCI
- Intended duration of the study per participant: up to 8 months.
- Method of data collection:
  - Standardized electronic Case Report Form (eCRF)
  - Solicited AEs, the occurrence of unsolicited AEs and responses to CCI will be collected using electronic Diary (eDiary).
- Safety monitoring: refer to Section 8.2.3 for the review of safety data by SRT.

Table 4 Study groups, intervention and blinding *(Amended: 20 June 2023)*

Study groups	Number of participants	Age (Min-Max)	Study interventions (IM use)	Blinding Visit 1→Visit 6
YA				
Flu mRNA dose 1	24	18 – 45 years	CCI	Observer-blind*
Flu mRNA dose 2	24	18 – 45 years		Observer-blind*
Flu mRNA dose 3	24	18 – 45 years		Observer-blind *
Flu mRNA dose 4	24	18 – 45 years		Observer-blind *
Flu mRNA dose 6	24	18 – 45 years		Single-blind*
Flu mRNA dose 7	24	18 – 45 years		Single-blind*
Flu mRNA dose 8	24	18 – 45 years		Observer-blind *
Flu mRNA dose 9	24	18 – 45 years		Observer-blind *
Flu mRNA dose 10	***24***	***18 – 45 years***		***Single-blind****
Flu mRNA dose 11	***24***	***18 – 45 years***		***Single-blind****
Control**	24	18 – 45 years	FDQ21A-NH	Observer-blind*
Control**	12	18 – 45 years	FDQ22A-NH	Observer-blind*
OA				
Selected dose from YAs	24	60 – 80 years	Selected dose from YAs***	Observer-blind*
Control	24	60 – 80 years	FDQ21A-NH	Observer-blind*

YA: younger adult; OA: older adult; NH: Northern Hemisphere.
Control: Flu D-QIV (*Flu Dresden- Quadrivalent Influenza Vaccine*; GlaxoSmithKline; season 2021-2022 NH for the CCI dose cohorts, and season 2022-2023 NH for the CCI dose cohorts; commercially available as *α-RIX-Tetra* in Belgium)
Doses of vaccine candidate are coded as follows: dose 1: CCI dose 2: CCI dose 3: CCI ; dose 4: CCI , dose 6: CCI dose 7: CCI , dose 8: CCI , dose 9: CCI ***, dose 10:*** CCI ***, dose 11:*** CCI Potential intermediate dose levels CCI may be evaluated with the total number of dose levels not exceeding ***12*** in YAs and 1 in OAs. Refer to Section 4.3.2, ***4.3.4, and 4.3.4*** for rationale for addition of the CCI and their potential intermediate dose cohorts CCI respectively.
* For participants and investigators, the study will be observer-blind with regards to the study intervention, but open-label with regards to the dose level. For the sponsor, the study will be open-label. For the CCI ***and*** CCI dose ***cohorts***, the study will be single-blind. Refer to Section 6.3.5 for more information.
** In YAs, 6 participants are enrolled in the control group per dose level of the investigational study intervention, except for the CCI ***and*** CCI dose ***cohorts***, where no control vaccine will be used.
*** Study intervention dose will be selected based on the safety/reactogenicity data obtained up to dose 3 in YAs. Refer to Section 4.3 for more information.
Note: Hereafter, name of the study groups for YAs will be only referred to as Flu mRNA dose 1-***11***. Details on the study intervention administered are shown in Table 5.

4.1.1. Enrollment rules *(Amended: 20 June 2023)*

Overall, participants will be enrolled in 2 age categories (YAs and O***A***s) with at least 35% of either sex to ensure balance between males and females. Note: To allow a higher enrollment flexibility in the study and since sex is not considered an important prognosis factor, the sex enrollment rule will not be applied to the additional CCI ***dose cohort, or the*** CCI and their potential intermediate dose cohorts (CCI).

4.2. Scientific rationale for study design

4.2.1. Choice of active comparator *(Amended: 20 June 2023)*

To completely characterize the immunogenicity of the candidate vaccine compared with a licensed vaccine, Flu D-QIV has been selected as active control in this study. This vaccine is indicated for active immunization for prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine and is approved for use in adults.

Note: The sample size of the available Control group (N=30) is similar to the sample size of each additional dose group to be tested (N=24). As such, we consider the available Control group sufficiently large for this phase 1 exploratory and descriptive study and will not use an active control for the additional CCI ***or*** CCI dose ***cohorts,*** where an assessment of immunogenicity is the main objective. However, for the additional CCI, and their potential intermediate dose cohorts (CCI), where a safety/reactogenicity assessment is the main objective, Flu D-QIV will be reintroduced as active control.

4.2.2. Rationale for study blinding *(Amended: 20 June 2023)*

CCI the study will be blinded for participants and investigators with regards to the formulation (Flu mRNA versus Control) but open-label with regards to the dose level.

For the CCI ***and*** CCI dose ***cohorts***, 2 different Flu mRNA doses are to be used, therefore the persons reconstituting the interventions will be aware of the dose of the allocated Flu mRNA vaccine. This requires unblinding the randomization system for this cohort and accordingly all users of the randomization system, including the investigator, will be unblinded and only the participant will remain blinded.

The study will be open-label for the sponsor to allow continuous review of data by the SRT for dose level determination and escalation and monitoring of holding rules.

Please refer to Glossary of terms for the definition of observer-blind and single-blind.

Further information on blinding and unblinding is provided in Section 6.3.

4.3. Justification for dose *(Amended: 20 June 2023)*

Six dose levels CCI) and 1 dose level (up to CCI) are planned to be evaluated in YAs and OAs, respectively, in this study. Depending on the outcomes of safety and reactogenicity evaluations, intermediate dose levels (YAs: CCI; OAs: CCI) may be used. Furthermore, 2 additional doses of CCI of the vaccine candidate will be evaluated in YAs under Protocol Amendment 3***, and 2 additional doses of*** CCI ***of the vaccine candidate will be evaluated in YAs under Protocol Amendment 5.*** Refer to Section 4.3.2, 4.3.4***, and 4.3.4*** for rationale for

addition of the CCI [redacted], and CCI [redacted] and their potential intermediate dose cohorts CCI [redacted] respectively. The total number of dose levels will not exceed ***12*** in YAs and 1 in OAs.

4.3.1. Justification for dose for YAs

In the Phase 3 efficacy trial of the Covid-19 vaccine (first generation mRNA vaccine of the same platform with unmodified nucleotides) conducted by CureVac in approximately 20 000 participants, the safety profile of CCI [redacted] was CCI [redacted] [Kremsner, 2021a]. As the reactogenicity profile of modified nucleotides formulations is expected to be improved as compared to the unmodified formulations, a starting dose of CCI [redacted] in YAs is considered appropriate.

For dose escalation in YAs, CCI [redacted]-fold increases will be implemented (option to decrease to lower than CCI [redacted]-fold increases with intermediate dose levels). A CCI [redacted]-fold dose escalation increase will be implemented for the higher dose levels (i.e., CCI [redacted]). Although earlier studies [Aldrich, 2021; Kremsner, 2021b] showed that reactogenicity increased even after modest dose increments, dose-finding studies of mRNA vaccines based on modified nucleotides have adopted CCI [redacted] incremental dose escalation schemes: 10-20-30-100 µg for Pfizer/BioNTech Covid-19 vaccine and 25-100-250 µg for Moderna's Covid-19 vaccine [Jackson, 2020; Walsh, 2020].

Data from CCI [redacted], a GSK-sponsored FTiH dose escalation study in adults evaluating an investigational SARS-CoV-2 vaccine using the same mRNA platform as in the Flu SV mRNA-003 study, have shown a CCI [redacted].

In addition, as competitors' experience suggests CCI [redacted] as the maximum tolerable dose [Jackson, 2020; Walsh, 2020], and the test vaccines in this study use comparable LNPs as the Pfizer/BioNTech Covid-19 vaccine [Walsh, 2020], CCI [redacted] tested in that program.

4.3.2. Justification for additional doses in YAs, evaluated in Amendment 5 (Amended: 20 June 2023)

Available data from the CCI [redacted] dose cohorts in this study CCI [redacted] In this amendment, we will therefore further assess the immunogenicity of CCI [redacted] dose levels in order to CCI [redacted]. Data from this amendment will be used to further characterize the mRNA platform, and may CCI [redacted]

4.3.3. Justification for additional doses in YAs, evaluated in Amendment 3

Preliminary immunogenicity data from the CCI [redacted] cohorts in this study suggest that the most immunogenic dose of the study intervention in YAs CCI [redacted] In this amendment, we will therefore further assess the immunogenicity of C [redacted] dose levels in order to better define the optimal dose for this monovalent H1 vaccine candidate. These data will be used to inform the selection of dose levels of influenza vaccine candidates in upcoming clinical studies.

4.3.4. Justification for additional doses in YAs, evaluated in Amendment 4

Available data from the CCI [redacted] dose cohorts in this study show C [redacted]. In addition, data from CCI [redacted] a GSK-sponsored FTiH dose escalation study in adults evaluating an investigational SARS-CoV-2 vaccine using the same mRNA platform as in the Flu SV mRNA-003 study, have shown CCI [redacted]. The aim of the current protocol amendment is to CCI [redacted] and specifically to explore the reactogenicity/immunogenicity profile at CCI [redacted] and their potential CCI [redacted] Data from this amendment will not only be used to further characterize the mRNA platform, but also to support CCI [redacted].

4.3.5. Justification for dose for OAs

To limit overall exposure in OAs, CCI [redacted] will be evaluated for safety/reactogenicity and immunogenicity for comparison with YAs. Dosing in OAs will be initiated after the review of safety/reactogenicity from CCI [redacted] in YAs.

The dose level in OAs will be selected from the dose levels evaluated in YAs CCI [redacted] and will be limited to dose levels CCI [redacted] with no safety/reactogenicity concerns (including a posterior probability estimate of Grade 3 solicited event rate <18% based on the BLRM) in YAs.

4.4. End of Study definition

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

End of Study (EOS): Last subject last visit (LSLV) (Visit 6) or Date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

5. STUDY POPULATION

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

5.1. Inclusion criteria

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

1. A male or female between and including 18 and 45 years of age (YAs) or between and including 60 and 80 years of age (OAs) at the time of the study intervention administration. The age of sentinel participants in OA category will be limited to maximum 70 years.
2. Healthy or medically stable participants as established by medical history, safety laboratory assessments and clinical examination.
3. Body mass index $\geq$ 18 kg/m^2 and $\leq$ 32 kg/m^2.
4. Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the eDiary, return for follow up visits).
5. Written informed consent obtained from the participant prior to performing any study-specific procedure.
6. Female participants of non-childbearing potential may be enrolled in the study. Refer to Section 10.4.1 for definitions of women of childbearing potential, menarche and menopause.
7. Female participants of childbearing potential may be enrolled in the study if the participant:
   - has practiced adequate contraception for 28 days prior to study intervention administration, and
   - has a negative pregnancy test on the day of study intervention administration, and
   - has agreed to continue adequate contraception for at least 1 month after study intervention administration.

   Refer to Section 10.4.1 for definitions of woman of childbearing potential and adequate contraception.

5.2. Exclusion criteria

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

5.2.1. Medical conditions

1. Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or review of the participant's medical record.
2. Any clinically significant* hematological, biochemical, coagulation or urine analysis laboratory abnormality. Refer to Section 10.2.1 for the list of safety laboratory assessments to be considered in this study.

   * The investigator should use his/her clinical judgment to decide which abnormalities are clinically significant.
3. Current or past malignancy, unless completely resolved without sequelae for >5 years.
4. Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection, based on medical history and physical examination (no laboratory testing required).
5. History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention (including latex, poly-ethylene-glycol, egg-protein and aminoglycoside antibiotics).
6. Recurrent history or uncontrolled neurological disorders or seizures, including Guillain-Barré syndrome and Bell's palsy, with the exception of febrile seizures during childhood.
7. Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
8. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.
9. Significant exposure to persons with influenza or laboratory-confirmed SARS-CoV-2 within 7 days prior to Visit 1 (Day 1) and for whom a SARS-CoV-2 PCR test has not (yet) been confirmed as negative.

5.2.2. Prior/Concomitant therapy

10. Administration of seasonal influenza vaccine, within 180 days before enrollment or planned administration up to Visit 4 (Day 29).
11. Administration of a vaccine not foreseen by the study protocol in the period starting 28 days before the study intervention administration, or planned administration within 28 days after the study intervention administration*, with the exception of vaccines authorized or approved for the prevention of Covid-19 (regardless of the type of vaccine).

    **In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by public health authorities outside the routine immunization program, the time period described above can be reduced to 7 days, if necessary, for that mass vaccination vaccine, provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly*.

12. Use of any investigational or non-registered product (drug, vaccine or invasive medical device) other than the study intervention during the period beginning 30 days before the study intervention administration, or their planned use during the study period.
13. Administration of long-acting immune-modifying drugs within 90 days before enrollment or planned use at any time during the study period (e.g., infliximab).
14. Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the study intervention administration, or planned administration during the study period. Administration of monoclonal antibodies specifically directed against the spike protein of SARS-CoV-2 virus, for treatment of Covid-19 disease is allowed.
15. 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 study intervention administration. For corticosteroids, this will mean prednisone equivalent ≥ 20 mg/day. Inhaled, topical and intraarticular steroids are allowed.

5.2.3. Other exclusions

16. Pregnant or lactating female.
17. Female planning to become pregnant or planning to discontinue contraceptive precautions within the 1-month post-dosing period.
18. History of abusive alcohol and/or drug consumption in the past 5 years.
19. Any study personnel or their immediate dependents, family, or household members.
20. Participants with extensive tattoos covering deltoid region on both arms that would preclude the assessment of local reactogenicity.
21. Previous enrollment in this study.

5.3. Lifestyle considerations

Section is not applicable.

5.4. Screening failures

A screening failure is an individual who consents to participate in this study but is not entered in the study/randomized to a study intervention.

Limited data for screening failures (including informed consent date, demographic data, eligibility criteria check, reason for screening failure and any SAEs related to study participation or concurrent GSK medication/vaccine) will be collected and reported in the eCRF.

5.5. Criteria for temporarily delaying randomization/study intervention administration

For participants who have not been randomized, randomization may be postponed within the screening period of 28 days interval until transient conditions cited below are resolved.

For participants who have been randomized, study intervention administration may be postponed within the 3 days interval until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of randomization and/or study intervention administration. Refer to the SoA (Section 1.3) for definition of fever and preferred location for measuring temperature in this study.
- Use of antipyretics and/or analgesics within 24 hours prior to study intervention administration, with exception of use of low dose of acetyl salicylic acid for prevention of cardiovascular disease.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

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

6.1. Study intervention(s) administered

Table 5 Study intervention(s) administered *(Amended: 20 June 2023)*

Study intervention name:	**Flu mRNA vaccine**							
Study intervention formulation:	CCI [redacted]							
Presentation:	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)
Manufacturer:	GSK Biologicals	B BRAUN****	GSK Biologicals	B BRAUN****	GSK Biologicals	B BRAUN****	GSK Biologicals	B BRAUN****
Type:	Investigational							
Product category:	Biologic							
Route of administration:	IM							
Location	Deltoid							
• **Directionality**	Upper							
• **Laterality ****	Non-Dominant							
Number of doses to be administered:	1							
Volume to be administered by dose *:**	Refer to the Study Procedures Manual (SPM) for more details							
Packaging and labeling:	Refer to the SPM for more details							

Study intervention name:	**Flu mRNA vaccine**							
Study intervention formulation:	CCI [redacted]							
Presentation:	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)
Manufacturer:	GSK Biologicals	B BRAUN*** *	GSK Biologicals	B BRAUN*** *	GSK Biologicals	B BRAUN*** *	GSK Biologicals	B BRAUN*** *
Type:	Investigational							
Product category:	Biologic							
Route of administration:	IM							
Location	Deltoid							
• **Directionality**	Upper							
• **Laterality ****	Non-Dominant							
Number of doses to be administered:	1							
Volume to be administered by dose *:**	Refer to the Study Procedures Manual (SPM) for more details							
Packaging and labeling:	Refer to the SPM for more details							

Study intervention name:	**Flu mRNA vaccine**							
Study intervention formulation:	CCI [redacted]							
Presentation:	***Concentrate for dispersion for injection (Vials)***	***Solution for dispersion for injection (Ampoule or other)***	***Concentrate for dispersion for injection (Vials)***	***Solution for dispersion for injection (Ampoule or other)***	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)
Manufacturer:	***GSK Biologicals***	***B BRAUN****	***GSK Biologicals***	***B BRAUN****	GSK Biologicals	B BRAUN*	GSK Biologicals	B BRAUN*
Type:	Investigational							
Product category:	Biologic							
Route of administration:	IM							
Location	Deltoid							
• **Directionality**	Upper							
• **Laterality****	Non-Dominant							
Number of doses to be administered:	1							
Volume to be administered by dose *:**	Refer to the Study Procedures Manual (SPM) for more details							
Packaging and labeling:	Refer to the SPM for more details							

Study intervention name:	**Flu mRNA vaccine**					
Study intervention formulation:	CCI [redacted]					
Presentation:	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)
Manufacturer:	GSK Biologicals	B BRAUN****	GSK Biologicals	B BRAUN****	GSK Biologicals	B BRAUN****
Type:						
Product category:	Biologic					
Route of administration:	IM					
Location	Deltoid					
• **Directionality**	Upper					
• **Laterality ****	Non-Dominant					
Number of doses to be administered:	1					
Volume to be administered by dose *:**	Refer to the Study Procedures Manual (SPM) for more details					
Packaging and labeling:	Refer to the SPM for more details					

Study intervention name:	**FDQ21A-NH†**	**FDQ22A-NH‡**
Study intervention formulation:	A/Victoria/2570/2019 (H1N1), IVR-215 (15 µg HA); A/Tasmania/503/2020 (H3N2), IVR-221 (15 µg HA); B/Washington/02/2019 (15 µg HA); B/Phuket/3073/2013 (15 µg HA); Water for injections	A/Victoria/2570/2019 (H1N1), IVR-215 (15 µg HA); A/Darwin/06/2021 (H3N2), IVR-227 (15 µg HA); B/Austria/1359417/2021, BVR-26 (15 µg HA); B/Phuket/3073/2013 (15 µg HA); Water for injections
Presentation:	Suspension for injection (Syringe)	Suspension for injection (Syringe)
Manufacturer:	GSK Biologicals	GSK Biologicals
Type:	Active control	Active control
Product category:	Combination product	Combination product
Route of administration:	IM	IM
Location	Deltoid	Deltoid
• **Directionality**	Upper	Upper
• **Laterality ****	Non-Dominant	Non-Dominant
Number of doses to be administered:	1	1
Volume to be administered by dose *:**	Refer to the Study Procedures Manual (SPM) for more details	Refer to the Study Procedures Manual (SPM) for more details
Packaging and labeling:	Refer to the SPM for more details	Refer to the SPM for more details

IM: intramuscular; TBD: to be defined.
† FDQ21A-NH: Flu D-QIV (*Flu Dresden- Quadrivalent Influenza Vaccine*, GlaxoSmithKline; 2021-2022 NH for the CCI [redacted] dose cohorts).
‡ FDQ22A-NH: Flu D-QIV (Flu Dresden- Quadrivalent Influenza Vaccine, GlaxoSmithKline; 2022-2023 NH for the CCI [redacted], and their potential intermediate dose cohorts (CCI [redacted]).
* Potential intermediate dose levels that may be evaluated, with the total number of dose levels not exceeding ***12*** in YAs and 1 in OAs.
** The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed.
*** Refer to the SPM for the volume after reconstitution.
**** Another manufacturer might be used depending on study site.

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

Refer to Section 4 for more information on study groups and enrollment strategy.

6.2. Preparation, handling, storage, and accountability

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

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

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

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

6.3.2. Randomization to study intervention *(Amended: 20 June 2023)*

Planned (approximate) number of participants to be enrolled is ***354***:

- ***306*** YA participants (24 participants per dose level and a total number of 42 participants receiving the active control)
- 48 OA participants (24 participants receiving a dose of investigational study intervention and 24 participants receiving the active control)

Due to the adaptive design, the actual number of participants enrolled might be lower or higher (up to ***384*** participants in total) in case a ***12th*** dose level is evaluated in YAs.

Planned number of participants to be enrolled for the CCI [redacted] dose cohort is 48 (24 participants per dose level). ***Planned number of participants to be enrolled for the*** CCI [redacted] ***dose cohort is 48 (24 participants per dose level).***

The randomization of supplies within blocks will be performed at GSK, using MATerial Excellence (MatEx), a program developed for use in Statistical Analysis System (SAS) (Cary, NC, US) by GSK. Entire blocks will be shipped to the study centers/warehouse(s). ***For the*** CCI [redacted] ***dose cohort, the active control arm will be blocked at randomization.*** For the CCI [redacted] dose ***cohort***, partial block sizes, not including active control, will be shipped.

To allow GSK to take advantage of greater rates of recruitment than anticipated at individual centers in this multi-center study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

6.3.3. Intervention allocation to the participant

An automated Internet-based system, Source data Base for Internet Randomization (e.g., SBIR) will be used for randomization and for identification of study intervention.

Once a participant identification number is allocated, the randomization system will determine study group and will provide the study intervention number to be used.

When SBIR is not available, please refer to the SBIR user guide or SPM for specific instructions.

The randomization algorithm will use a stratification procedure accounting for sentinel, age and dose level cohort as stratification factor and a minimization procedure accounting for study, country, site, and flu vaccination history during past 2 years as minimization factors.

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

6.3.4. Allocation of participants to assay subsets

A CCI subset will be defined, where CCI will be assessed in 50% of participants of each group (Flu mRNA and Control). Participants will be enrolled at selected sites.

Note: no CCI response will be assessed for the CCI, and their potential intermediate dose cohorts CCI).

6.3.5. Blinding and unblinding *(Amended: 20 June 2023)*

Data will be collected in an observer-blind manner. The participant and the site personnel involved in the clinical evaluation of the participants are blinded while the sponsor and other study personnel may be aware of the treatment assignment. To do so, study interventions will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review or the entry of any study endpoint (i.e., reactogenicity, safety and immunogenicity).

However, for the additional CCI ***dose cohort and*** CCI dose cohort, data will be collected in a single-blind manner. The investigator(s) and/or their staff are aware of the study intervention assignment, but the participant is not. The study intervention will be prepared and administered by qualified study personnel who can be aware of the intervention assignment.

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant.

6.3.5.1. Emergency unblinding

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

In case of emergency, the investigator can have unrestricted, immediate and direct access to the participant's study intervention information via an automated Internet-based system (e.g., SBIR). The investigator may contact a GSK Helpdesk (refer to Table 6) if help is needed to access participant's study intervention information (i.e., if the investigator is unable to access SBIR).

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

Table 6 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Belgium 00 800 4344 1111 Canada 1 833 541 0263 Spain 00 800 4344 1111 Fax: +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com

6.3.5.2. Unblinding prior to regulatory reporting of SAEs

GSK Global Safety staff may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction (SUSAR). GSK Global Safety is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to Section 10.3.11.1). For SAEs requiring expedited reporting to 1 or more regulatory agencies, a copy of the report containing participant's intervention assignment may be sent to investigators in accordance with

local regulations and/or GSK policy. GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study interventions, prior to regulatory reporting.

6.4. Study intervention compliance

Study intervention administration will be performed on site by authorized personnel under medical supervision. The date of the dose administration will be recorded in the source documents and in the eCRF.

6.5. Dose modification

Section is not applicable.

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

Section is not applicable.

6.7. Treatment of overdose and management of anaphylaxis

An overdose is any dose of study vaccine given to a participant that exceeds the planned randomized dose for an individual within a given dose group.

There is no specific treatment recommended for an overdose.

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

The appropriate medical treatment to be administered for any episodes of anaphylaxis or other immediate AEs, including those associated with overdose, will be based on the judgment of the medical team/physician attending to the participant.

6.8. Concomitant therapy

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

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

- All concomitant medications, except vitamins and dietary supplements, administered during the study (Day 1 to Day 183).
- Any concomitant vaccination administered in the period starting 28 days before study intervention administration and ending at the last study visit (Day -28 to Day 183).

- All concomitant medication which may explain/cause/be used to treat an SAE/AESI including vaccines/products, as defined in Sections 8.3.1 and 10.3.9.1. These must also be recorded in the Expedited Adverse Event report.
- Prophylactic medication (i.e., medication administered in the absence of any symptom and in anticipation of a reaction to the vaccination).

The Local Medical Lead (LML) should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Section is not applicable.

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

The participant will be permanently discontinued from the study at that time.

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

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

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

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

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

- AEs requiring expedited reporting to GSK (refer to Section 10.3.11.1 for the details)
- Unsolicited non-serious adverse events
- Solicited AEs
- Withdrawal by participant, not due to an AEs*

- Physician decision
- Migrated/Moved from the study area
- Lost to follow up
- Sponsor study/site termination
- Other (specify)

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

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.9.2).

7.3. Lost to follow up

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

All screening evaluations must be completed and the results reviewed before confirming that potential participants meet all eligibility criteria. When applicable, a re-screening visit (including blood and urine sample collection, physical examination and re-checking of inclusion/exclusion criteria) may be scheduled at any time (but only once to assess eligibility) before Visit 1 (Day 1).

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

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

In exceptional situations (e.g., pandemic) and if allowed by local regulation, the following procedures can be performed remotely/virtually, provided approved tools and infrastructures are used, as per local requirements (refer to the Glossary of terms for the definitions of telemedicine, remote and virtual visits):

- Safety follow up may be performed by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with the participant and monitoring the participant's progress. In addition, qualified study staff/health care professionals (HCPs) may also identify AEs and report them to the investigator for evaluation.
- If allowed by local regulation, blood samples may be collected remotely* by qualified study staff/HCPs. Blood samples should be collected only if they can be processed in a timely manner and appropriately stored until the intended use.

  **It is the investigator's responsibility to ensure that the alternate location for collection of samples meets the International Council for Harmonization (ICH) GCP requirements, such as adequate facilities to perform study procedures/data collection, appropriate training of the staff and documented delegation of responsibilities in this location. This location should be covered by proper insurance for the conduct of study by investigator/study staff at a site other than the designated study site.*

Details of how these visits will be conducted are outlined in the SPM.

Study participants may decide to assign a caregiver to help them fulfilling the study procedures. Please refer to the Glossary of terms for the definition of a caregiver.

A caregiver can be appointed by the participant at any time during the study, when the participant feels it is necessary. Caregiver should receive the caregiver information letter before providing support to the study participant. Ideally, a single caregiver should be appointed by the participant but, in some situations, it may happen that several caregivers will support a study participant throughout the conduct of the study. This should be recorded in the source documents. However, every effort should be done to ensure that only one caregiver enters the data into eDiary to allow for timely completion.

Caregivers may help the study participants perform some study procedures such as receiving or making phone call(s) to site staff, planning study visits, transcribing responses to eDiaries, transportation to and from the study site etc. However, at no time, the caregiver should evaluate the participant's health status while answering diaries or make decisions on behalf of the participant.

During the screening visit, the site staff should inform the participant of the possibility of appointing a caregiver. Then at subsequent study visit(s), the site staff should check again with the participant if he/she wishes to appoint a caregiver or if there were or will be changes of caregiver.

Please refer to the SPM for additional information on the appointment of a caregiver.

8.1. Immunogenicity assessments

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

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

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

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

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

8.1.1. Biological samples

Approximate maximum volumes of blood collected from each participant in each subset over the duration of the study are summarized in Table 7.

Refer to SoA (Section 1.3) for details of volumes collected for different assessments.

Table 7 Biological samples

Sample type	Quantity*	Unit	Timepoint	Subset name**
Blood	200	mL	Screening	Participants in CCI subset
			Day 1	
			Day 8	
			Day 22	
			Day 29	
			Day 62	
			Day 183	
Blood	80	mL	Screening	Other participants
			Day 1	
			Day 8	
			Day 22	
			Day 29	
			Day 62	
			Day 183	
Urine	As per local practice		Screening	All participants
			Day 1	

		Day 8 Day 29	

CCI

*Approximate maximum total volume collected throughout the study.
** Refer to Section 6.3.4 for subset description.
Note: for the CCI and their potential intermediate dose cohorts (CCI), no blood sampling for CCI response will be performed, and blood sampling for antibody determination and characterization will be limited to Day 1 and Day 22. For the participants in these cohorts, the total quantity of blood collected will be approximately 60 mL.

8.1.2. Laboratory assays

All laboratory testing will be performed at GSK laboratory or in a laboratory designated by GSK, with the exception of the routine blood and urine panel for safety monitoring which will be performed by the site's local laboratory according to their standard practices.

Table 8 Laboratory assays

Test Classification	System	Component	Challenge	Method	Laboratory *
Humoral Immunity (Antibody determination and characterization)	Serum	CCI		CCI	GSK** or GSK designated laboratory
CCI					GSK** or GSK designated laboratory

Ab: antibody; CCI.
* Refer to the list of clinical laboratories for details.
** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; CLS may designate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Siena, Italy

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

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

Additional exploratory testing to characterize the immune response of the vaccine/vaccine components or to characterize the disease may be performed on the serum and CCI if deemed necessary for accurate interpretation of the data and/or should such test(s) become available in the GSK Biologicals' laboratory, or a laboratory designated by GSK Biologicals. These additional assays may not be represented in the objectives/endpoints of the study protocol. Serum/CCI might also be

used for other Influenza-related assay development/validation purpose outside of this protocol.

8.1.3. Immunological read-outs *(Amended: 20 June 2023)*

Table 9 Immunological read-outs *(Amended: 20 June 2023)*

Blood sampling timepoint		Subset name*	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-dose	All enrolled participants	***354***	CCI [redacted]
		Participants in CCI subset	***147***	
Visit 2 (Day 8)	Post-dose	Participants in CCI subset	***147***	
Visit 3 (Day 22)	Post-dose	All enrolled participants	***354***	
Visit 5 (Day 62)	Post-dose	All enrolled participants	***294***	
		Participants in CCI subset	***147***	
Visit 6 (Day 183)	Post-dose	All enrolled participants	***294***	
		Participants in CCI subset	***147***	

* Refer to Section 6.3.4 for subset description.
Ab: antibody; CCI [redacted].

CCI

[redacted]

8.2. Safety assessments

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

8.2.1. Pre-intervention administration procedures

8.2.1.1. Collection of demographic data

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

8.2.1.2. Medical and vaccination history

Obtain the participant's medical/vaccination history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the study intervention administration and flu vaccination history for the past 2 years in the eCRF.

8.2.1.3. Physical examination

During the screening visit and prior to dosing at Visit 1 (Day 1), the investigator will perform a physical examination of the participant including assessment of resting vital signs: systolic/diastolic blood pressure, pulse oximetry, heart rate and respiratory rate after at least 10 minutes of rest, body weight and height. Vital signs are to be taken before blood collection for laboratory tests.

If the participant reported any pre-existing medical condition, the investigator would extend the physical examination according to his/her medical judgment to ensure that the participant meets all the inclusion/exclusion criteria.

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

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

8.2.1.4. Pre-dosing body temperature

The body temperature of each participant needs to be measured prior to the study vaccine administration and recorded in the eCRF. If the participant has fever on the day of dosing, the study intervention administration visit will be rescheduled. Refer to the SoA (Section 1.3) for the definition of fever for this study and preferred location for body temperature measurement.

8.2.1.5. Pregnancy test

Only women with negative pregnancy test result at the screening visit will be included in the study. The study intervention may only be administered if the pregnancy test result is negative at Visit 1 (Day 1).

Female participants of childbearing potential must perform a urine pregnancy test before the administration of the study intervention. If time allows, serum pregnancy test can be done as per local requirements. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

Refer to Section 10.4.3.1 for the information on study continuation for participants who become pregnant during the study.

8.2.1.6. Distribution of eDiary or installing the application for devices

Participants will be encouraged to bring their own devices at screening visit, or if not feasible, at Visit 1 (Day 1). The study staff will check the compatibility of participant's device (e.g., smart phone or tablet) with respect to eDiary application.

At Visit 1 (Day 1), participant will download the eDiary application on his/her own electronic device or will receive an electronic device to record information related to his/her health and participation in the study. The participant will also be trained on the use of eDiary.

The same procedures should apply to a caregiver, if identified by the study participant.

Refer to Section 8.3.1 for details of collection of safety information and Section 10.3.9 for guidelines.

8.2.1.7. Warnings and precautions to administration of study intervention

Warnings and precautions to administration of study intervention must be checked at Visit 1 (Day 1), as specified in SoA (Section 1.3).

Refer to the approved product label/package insert.

8.2.2. Clinical safety laboratory tests

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

Analyses will be performed at the local laboratory using local standards, and the results will be encoded by the investigator into the eCRF.

Laboratory data will be graded according to the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007 [FDA, 2007]. These laboratory values serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Only clinically significant laboratory findings, as judged by the investigator, should be reported as AE.

8.2.3. Study holding rules and safety monitoring

Safety monitoring is specified in the SoA (Section 1.3), Section 8.2.3.1 and Table 11.

8.2.3.1. Staggered enrollment and safety monitoring

During this study, recruitment will be progressive to allow careful monitoring of the participants. At each dose level, early participants in each group will be referred to as 'sentinel participants'. Enrollment of sentinel and non-sentinel participants will be managed as described below. Refer to Table 10 for a visual representation of the process.

8.2.3.1.1. Staggered enrollment of YAs (Amended: 20 June 2023)

Enrollment of sentinel and non-sentinel participants in YA for each dose level:

- Sentinel participants will be the first 9 participants (6 in Flu mRNA group and 3 in Control group) to be randomized at each dose level and will be enrolled over 2 days.
  - In the morning of the first day, the first 3 sentinel participants (2 in Flu mRNA group and 1 in Control group) will be dosed. There will be an interval of at least 60 minutes between dosing of each of the 3 sentinel participants. A safety follow up contact with each sentinel participant in each dose group will be performed approximately 20 hours post-dosing and prior to dosing of the next sentinel participants.
  - The second day, the next 6 sentinel participants (4 in Flu mRNA group and 2 in Control group) can be dosed, if no holding rule has been met in the sentinel participants dosed the first day.

- After at least 2 days of follow up of sentinel participants, all available safety data will be analyzed, and the BLRM will be run. Results will be provided to and reviewed by the SRT during scheduled meetings. The SRT will decide whether to allow the dosing of non-sentinel participants at the current dose level. Screening procedures may be initiated prior to SRT meeting to facilitate the enrollment of remaining participants.
- If obtaining favorable decision from SRT, non-sentinel participants at the current dose level will be dosed without restriction.
- After 8 days of follow up of non-sentinel participants (Day 1 to Day 8 included), all safety data collected until this point (from both sentinel and non-sentinel participants) will be analyzed and the BLRM will be run. Results will be provided to and reviewed by the SRT during scheduled meetings. The SRT will decide whether to allow the initiation of dosing of new sentinel participants at the next higher (or intermediate) dose level (until the maximum dose level of CCI has been reached and/or a maximum of 8 dose levels have been tested in sentinel participants). Screening procedures may be initiated prior to SRT meeting to facilitate the enrollment of sentinel participants at the next dose level.
- Note: No sentinel participants will be enrolled for the additional CCI ***dose cohort, or*** CCI dose cohort. The rationale for this is that CCI have showed a CCI (incidence of Grade 3 solicited AEs ranging from CCI depending on dose group), and CCI . The CCI dose ***cohorts*** will be enrolled in parallel.
- All the participants will be observed on site for 60 minutes after dosing.

8.2.3.1.2. Staggered enrollment of OAs

Enrollment of sentinel and non-sentinel participants in OA for 1 dose level:

- Enrolled of OAs will be initiated once the analysis of safety data (for 8 days follow up post-dosing) for 3 dose levels in YAs is completed and an OA dose level has been recommended by the SRT. Refer to Section 4.3 for dose justification.
- Sentinel participants will be the first 12 participants (6 in Flu mRNA group and 6 in Control group) to be randomized and will be enrolled over 2 days. The age of sentinel participants will be limited to maximum 70 years.
  - In the morning of the first day, the first 4 sentinel participants (2 in Flu mRNA group and 2 in Control group) will be dosed. There will be an interval of at least 60 minutes between dosing of each of the 4 sentinel participants. A safety follow up contact with each sentinel participant will be performed approximately 20 hours post-dosing and prior to dosing of the next sentinel participants.
  - The second day, the next 8 sentinel participants (4 in Flu mRNA group and 4 in Control group) can be dosed, if no holding rule has been met in the sentinel participants dosed the first day.

- After at least 2 days of follow up of sentinel participants, all available safety data will be analyzed, and the BLRM will be run. Results will be provided to and reviewed by the SRT during scheduled meetings. The SRT will decide whether to allow the dosing of non-sentinel participants at the current dose level. Screening procedures may be initiated prior to SRT meeting to facilitate the enrollment of remaining participants.
- If obtaining favorable decision from SRT, non-sentinel participants at the current dose level will be dosed without restrictions.
- All the participants will be observed on site for 60 minutes after dosing.

Table 10 Staggered enrollment and safety monitoring *(Amended: 20 June 2023)*

YA						OA	
Dose 1	**Control**	**Dose 2**	**Control**	**Dose 3**	**Control**	**Dose 4**	**Control**	**Selected dose from YAs**	**Control**
2 p*	1 p*	2 p*	1 p*	2 p*	1 p*	2 p*	1 p*	2 p*	2 p*
1 day follow up**		1 day follow up**		1 day follow up**					
4 p*	2 p*	4 p*	2 p*	4 p*	2 p*				
2 days follow up		2 days follow up		2 days follow up					
SRT review***		SRT review***		SRT review***					
18	3	18	3	18	3				
8 days follow up		8 days follow up		8 days follow up					
SRT review****		SRT review****		SRT review*****					

1 day follow up**		1 day follow up**	
4 p*	2 p*	4 p*	4 p*
2 days follow up		2 days follow up	
SRT review***		SRT review***	
18	3	18	18

Dose 8	Control
2 p*	1 p*
1 day follow up**	
4 p*	2 p*
2 days follow up	
SRT review***	
18	3
8 days follow up	
SRT review****	

Dose 9	Control
2 p*	1 p*
1 day follow up**	
4 p*	2 p*
2 days follow up	
SRT review***	
18	3
8 days follow up	
SRT review****	

P: participant; SRT: Safety Review Team. Dose 1-4 and dose 8 and 9: Flu mRNA dose 1-4 and 8 and 9. Potential intermediate dose levels may be evaluated with the total number of doses not exceeding ***12*** in YAs and 1 in OAs.

* Sentinel participants

** Participants will be followed-up to the next day post-dosing. If any holding rule is met or any Grade 3 AE is reported within follow up post-dosing period, the SRT will be consulted before continuation of enrollment of the next sentinel participants.

*** Safety review of at least 2-days post-dosing data from sentinel participants by SRT to decide on enrollment of non-sentinel participants.

**** Safety review of 8-days post-dosing data from all sentinel and non-sentinel participants by SRT to decide on enrollment of sentinel participants for next dose level in YAs.

***** Safety review of 8-days post-dosing data from all sentinel and non-sentinel participants by SRT to decide on enrollment of sentinel participants for next dose level in YA and enrollment of sentinel OAs.

Refer to Section 10.1.5 for the definition and roles of the SRT.

8.2.3.2. Outcome of safety evaluation

Outcome of safety evaluations will be documented and provided in a written way to the investigator. Refer to Appendix 1 on Safety Oversight of Phase I study for more details.

8.2.3.3. Study holding rules

The safety holding rules are defined in the Table 11. Holding rules 1a-d will be assessed by the investigator on a continuous basis. Meeting any of these holding rules will trigger a hold of study intervention administration irrespective of number of participants enrolled and/or timing of the event. Holding rules 2a-c will be assessed by the SRT during the safety evaluations on unblinded data.

Of note, no formal holding rules will be applied for other safety data such as non-life-threatening SAEs, missed visits due to study intervention related AEs, Grade 1 and Grade 2 solicited and unsolicited AEs in the 7-day follow up period (Day 1 to Day 7) and unsolicited AEs collected from Day 8 to Day 28 after study intervention administration. However, if available, these data will also be reviewed by the SRT to allow an overall assessment of the benefit/risk ratio of study intervention administration.

Table 11 Study holding rules

Holding rule	Events, per dose and per individual study group	Number of participants to pause dosing in all groups, pending further evaluation by the SRT
1a	Death or any life-threatening SAE regardless of causality	≥ 1
1b	Any non-life-threatening SAE that cannot reasonably be attributed to a cause other than study intervention administration as per Investigator or Sponsor assessment	≥ 1
1c	Any withdrawal from the study (by investigator or participant request) due to a Grade 3 AE that cannot reasonably be attributed to a cause other than study intervention administration	≥ 1
1d	Any administration site or systemic solicited AE leading to hospitalization, or necrosis at the injection site, each with an event onset within the 7-day (Day 1-7) post-dosing period	≥ 1
2a	Any Grade 3 solicited local or systemic AE in an investigational vaccine group, within the 7-day (Day 1-7) post-dosing period	BLRM
2b	Any occurrence in an investigational vaccine group, of a same or similar Grade 3 unsolicited AE, including events with an identical MedDRA High Level Term and events assessed as clinically similar, and that cannot reasonably be attributed to a cause other than study intervention administration, within the 7-day (Day 1-7) post-dosing period	≥ 2
2c	Any Grade 3 unsolicited AE that can be reasonably attributed to the study intervention administration as per Investigator or Sponsor assessment, with an event onset within the 7-day (Day 1-7) post-dosing period OR Any Grade 3 or above abnormality in pre-specified hematological or biochemical laboratory parameters* that are reported as AEs with onset within the 8-day (Day 1-8) post-dosing period	≥ 3

* 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".

Rule 2a will be analyzed on a regular basis and reviewed during the scheduled SRT meetings to manage (i) initiation of dosing of non-sentinel participants at current dose level (ii) initiation of randomization of the sentinel participants at the next dose level in YAs (iii) initiation of randomization of the sentinel participants in OA age group (see Section 8.2.3.1). The adaptive BLRM evaluates the posterior probability for the percentage of severe solicited events at the current and the next dose levels (Section 10.8). A greater than 50% posterior probability that the percentage is below the 18% (i.e., the maximal tolerable rate), will be favorable to progress with the enrollment of non-sentinel participants in the current dose or sentinel participants in the next dose.

More details on the composition, objectives, and responsibilities of the SRT, and the schedule and conduct of the SRT meetings will be described in the Appendix 1 on Safety Oversight of Phase I study.

If the investigator becomes aware of a holding rule being met, he/she must suspend administration of the study intervention and inform GSK immediately (e.g., holding rules 1a-1d). Refer to 8.3.3.1 for contact information. GSK will inform the investigator if holding rules 2a-2c are met.

The following communication sequence must be followed, when an investigator becomes aware of a holding rule (1a-1d) being met:

- The concerned site staff have to put study intervention administration on hold.
- The concerned site staff must immediately inform their local GSK contact defined in Section 8.3.3.1.
- Local GSK contact will immediately inform the study Clinical Research and Development Lead (CRDL) and LML. The study CRDL will ensure that other sites are notified.
- All informed site staff will confirm to their local contact that action has been taken providing appropriate documentation to GSK.
- GSK Central will further evaluate the case with the SRT and GSK Global Safety Board (GSB) and will take the decision to stop or to restart the study intervention administration or to amend the protocol. All site staff will be informed about that final decision by their local GSK contact.

The following communication sequence must be followed when a holding rule (2a-2c) is being met:

- The study CRDL will ensure that all LMLs and local GSK contacts are notified upon meeting holding rules 2a-2c.
- The LMLs and local GSK contacts will inform all the sites of their country that a holding rule is met. Following this notification, the study intervention administration should be put on hold.
- All informed site staff will confirm to their local contact that action has been taken providing appropriate documentation to GSK.
- GSK Central will further evaluate the case with the SRT and GSK GSB and will take the decision to stop or to restart the study intervention administration or to amend the protocol. All site staff will be informed about that final decision by their local GSK contact.

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

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

Table 12 Timeframes for collecting and reporting of safety information

Event	Pre-dose* D-28 to D-1	Dose D1	D7	D28	Study conclusion D183
SAEs related to study participation** or concurrent GSK medication/vaccine					
Record any concomitant vaccinations					
Administration site and systemic solicited events					
Unsolicited AEs					
AEs/SAEs leading to withdrawal from the study					
SAEs					
Record any concomitant medications					
Pregnancy					
AESIs					

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

The investigator or designee will record and immediately report all SAEs in enrolled participants to the sponsor or designee via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes

aware of an SAE, as indicated in Section 10.3.11. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 12. Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and if the investigator considers the event to be reasonably related to the study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in the Table 14.

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

Detection and recording of AE/SAE/AESI/pregnancies are detailed in Section 10.3.9.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.10.

Open-ended and non-leading verbal questioning of participants is the preferred method of acquiring information related to an AE/SAE/AESI/pregnancy.

8.3.2.1. Clinically significant abnormal laboratory findings

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

- All clinically significant abnormal laboratory test values reported during the study should be repeated until the values return to normal/baseline, or until they are no longer considered significantly abnormal by the investigator or LML. Refer to Section 10.3.7 for more information on clinically abnormal laboratory assessments that qualify as an AE or SAE.
- If such values do not return to normal/baseline after an interval judged reasonable by the investigator, the etiology of the abnormal value should be identified, and the sponsor notified.

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

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/AESI/pregnancy, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 13. This is essential for GSK to meet legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/AESIs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.10.2.

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

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

Please refer to Section 10.3.11 for further details regarding the reporting of SAEs/AESIs/pregnancies.

Table 13 Timeframes for submitting SAE, pregnancy and other events reports to GSK

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

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI.
‡ Paper Expedited Adverse Events Report will be dated and signed by the investigator (or designee)
‡‡ For each SAE/AESI, the investigator(s) must document in the medical notes that they have reviewed the SAE/AESI and have provided an assessment of causality.

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

Table 14 Contact information for reporting SAEs, AESIs, pregnancies and study holding rules

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

8.3.4. Treatment of expedited adverse events (SAE/AESI)

Any medication administered for the treatment of an SAE/AESI should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to Section 10.3.11.1).

8.3.5. Participant card

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

8.3.6. Medical device deficiencies

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

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

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

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

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

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

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

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

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

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

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

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers

This section is not applicable.

8.7. Immunogenicity assessments

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

Health outcomes data (e.g., CCI data) will be collected as an outcome of this study. This data will be collected in the eDiary. Statistical analyses must be adjusted for protocol-mandated procedures, tests, and encounters.

CCI [redacted] All participants of the study are expected to complete the CCI as part of the eDiary. If necessary, the CCI may be administered by an interviewer (e.g., a caregiver). Interviewer instructions are provided in the CCI on how to record the participant's answers exactly as reported and without any interpretation from the interviewer.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

There is no formal hypothesis testing in this study; where statistical methods are applied, the emphasis will be on estimation with 95% cIs.

9.2. Analysis sets

Table 15 Analysis sets

Analysis set	Description
Screened	All participants who were screened for eligibility
Enrolled	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study
Exposed Set (ES)	All participants who received a study intervention. Analysis per group is based on the study intervention administered
Per Protocol Set (PPS)	All eligible participants who received a dose of study intervention as per protocol, had CCI [redacted] results pre- and post-dose, without intercurrent conditions (influenza disease) that may interfere with immunogenicity and without prohibited concomitant medication/vaccination before Day 22. The analysis will be done according to the study intervention that participants received. Results from blood sample deviating from the dosing/blood draw intervals (refer to Table 2) as well as results obtained after intercurrent conditions (influenza disease) that may interfere with immunogenicity or after prohibited concomitant medication/vaccination during this period will be excluded from the PPS.

9.3. Statistical analyses

The statistical analysis plan (SAP) will be finalized prior to the first subject first visit (FSFV) and it will include a more technical and detailed description of the statistical analyses including demography, tertiary endpoint analyses and supporting analyses, if applicable. This section is a summary of the planned statistical analyses of the most important endpoints, i.e., the primary endpoints.

The co-primary and secondary endpoints are described in Section 3. The primary analyses of immunogenicity endpoints will be based on the per protocol set (PPS). The analysis of safety endpoints will be based on the ES. All analyses will be done separately for OAs and YAs, unless specified otherwise.

9.3.1. Co-primary safety endpoints

The percentage of participants reporting each individual solicited administration site event (any grade, Grade 2 or 3, Grade 3 and medically attended events) and solicited systemic event (any grade, Grade ≥2, Grade ≥3 and medically attended events) within the 7-day follow up period (i.e., Day 1-Day 7 post-dose) will be tabulated for each group.

The verbatim reports of unsolicited AEs will be reviewed by a qualified person and the signs and symptoms will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate preferred term (PT). The percentage of participants with any unsolicited AEs within the 28-day follow up period (i.e., Day 1-Day 28 post-dose) with its exact 95% confidence interval (CI) will be tabulated by group and by MedDRA PT and System Organ Class (SOC). Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.

The percentage of participants with at least 1 report of SAE, and with at least 1 report of AESI respectively, classified by the MedDRA SOC and PT and reported from Dose 1 up to study end will be tabulated with exact 95% CI.

The percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 28-day follow up period (i.e., Day 1-Day 28 post-dose) will be summarized by group.

9.3.1.1. Analysis of reactogenicity for dose escalation: BLRM

An adaptive BLRM guided by the escalation with overdose control (EWOC) principle will be used to inform on the dose escalation part of the study. The use of Bayesian response adaptive models for Phase 1 studies has been advocated by the European Medicines Agency (EMA) adopted guideline on small populations [EMA, 2006] and by Rogatko et al., 2007 [Rogatko, 2007] and is 1 of the key elements of the FDA's Critical Path Initiative.

The dose escalation will be based on a modified version of the 2-parameter BLRM described by Neuenschwander et al., 2008 [Neuenschwander, 2008] and will account for all doses and age groups. The modification will be the addition of age-specific slope to account for a potential difference in safety profile between the 2 age groups. This approach allows the results of 1 age group to inform the decisions in the other group, which increases statistical power. The decisions will still be done separately for each age group, but this approach allows the use of all the available information as well as the assessment of whether there is a relevant difference in the solicited Grade 3 event rate between groups.

Standardized dose level will be used such that 1 of the doses (d*) equals 1, e.g., doses are rescaled as d/d*. Consequently, α is equal to the odds of the probability of intolerance at d*. This model was shown to be fit for purpose in the context of Phase I mRNA vaccine dose range [Walsh, 2020; Kremsner, 2021b]. The prior distribution will be updated after each group of participants with all the data available in the Safety Set from the current study. Once updated, the distribution summarizes the posterior probability that the true Grade 3 solicited event rate for each dose level lies in the following categories:

- 0% to <18%: targeted tolerance; and
- ≥18% to 100%: intolerance.

The EWOC principle mandates that any dose of the study vaccine candidates that has more than a 50% chance of being in the intolerance category is not considered for the next dose administrations [Neuenschwander, 2008; Babb, 1998].

Section 10.8 provides additional details on the model and data scenarios.

A clinical synthesis of the available safety and reactogenicity information (including symptoms that are not Grade 3), and, if available, laboratory values as well as the recommendations from the Bayesian model and the SRT will be used to determine the dose level(s) for the next group at a dose escalation teleconference. The frequency of each safety event associated to holding rules (see Table 11) will be tabulated by study group (i.e., by dose level). Individual data will also be available.

9.3.2. Co-primary and secondary immunogenicity endpoints

The group difference between the investigational study intervention and control group (pooled for YAs) will be assessed at each dose level separately as follows:

- At each post-dosing timepoint and in each age group separately, the 2-sided CI for group GMT ratio between Flu mRNA dose and (over) the control group (pooled across dose cohorts for YAs) will be derived from an ANCOVA model on $\log_{10}$ transformed concentration. The ANCOVA model will be based on the data from all age groups and will include group (i.e., each of the Flu mRNA doses and the (pooled) control group), country, flu vaccination history and log-transformed concentration at pre-dosing as fixed effects. The adjusted GMT and GMI in each group will be obtained from the same model with 95% CI. Missing data will not be replaced. Concentrations below the assay cut-off will be replaced by half the assay cut-off.

- For a given age group, the 2-sided 95% CI on group difference in CCI between a mRNA dose and (minus) the control group (pooled across dose cohorts for YAs) will be computed at day 22 based on the method of Miettinen and Nurminen [Miettinen, 1985].
- The percentage of participants achieving CCI, defined as having post-dose CCI for CCI will be summarized by age group with associated exact 95% CI.

Abbreviation/term	Definition
CCI GMI	The geometric mean of the ratios of the post-dose CCI over the Day 1 CCI.
CCI	The percentage of dosed participants who have either a CCI pre-dose CCI and a post-dose CCI or a pre-dose CCI and at least a 4-fold increase in post-dose CCI
	The percentage of dosed participants with a CCI.

9.4. Interim analyses

9.4.1. Sequence of planned analyses *(Amended: 20 June 2023)*

In addition to the analyses detailed below, safety analyses will be conducted to support SRT decisions as described in Section 8.2.3.

Two initial interim analyses will be conducted upon availability of all primary endpoints up to Day 22 for YA participants in the CCI cohorts, respectively. A***n*** interim analysis will be performed upon availability of all primary endpoints up to Day 29 for all study participants in the CCI cohorts**.**

Additional interim analyses will be performed upon availability of all primary endpoints up to Day 29 for ***(i)*** all participants in the CCI dose cohort**,*(ii)*** all participants in the CCI, and and their potential intermediate dose cohorts (CCI) and ***(iii) all participants in the*** CCI ***dose cohort***,.

For all interim analyses, the GSK study team will have access to all unblinded individual data while the investigator, participants and site personnel will remain blinded.

An analysis with all primary and secondary endpoints obtained until the last visit (Visit 6 [Day 183]) will be performed and made available to the investigators and submitted to regulatory authorities, as appropriate.

Analysis of tertiary endpoints may be performed later and described in an annex report. Tertiary analyses deemed futile due to the other study results will not be analyzed nor reported.

Note: If there is a delay in availability of the immunogenicity data, leading to a window between 2 analyses shorter than what is planned at the time of protocol writing, statistical analyses may be combined.

9.4.2. Statistical considerations for interim analysis

As this study is descriptive and each analysis will be completed on expected final immunogenicity data, there will be no type I error adjustment for the different analyses.

9.5. Sample size determination

Enrolled participants who withdraw from the study will not be replaced.

9.5.1. Sample size determination for reactogenicity and safety

The study is designed to provide a reasonable precision for the rate of Grade 3 solicited events and to describe the safety profile of an mRNA-based monovalent seasonal influenza vaccine.

For each dose cohort, it is expected that up to 24 participants will be enrolled per age group. Assuming a maximum acceptable rate of Grade 3 solicited events of 18%, it is possible to calculate the probability of a lower true Grade 3 solicited event rate given a different number of participants with Grade 3 solicited event(s). Table 16 provides the estimate and 95% credibility interval for a given observed number of participants for a sample size of 24 participants per age group in a dose level cohort (assuming a Beta [0.5,0.5] prior distribution). For example, if 4 participants report Grade 3 solicited event(s) among 24 exposed participants, the posterior probability that the true Grade 3 solicited event rate is <18% is 54.5%.

Table 16 Posterior probability estimates of Grade 3 solicited event rate <18% for different observed numbers of participants with Grade 3 solicited event(s) and 95% credibility interval for the rate

Number of participants with Grade 3 solicited event(s)	Estimate (95% credibility interval) in %	Probability Grade 3 solicited event rate <18%
0	2 (0 - 9.8)	99.8
1	6 (0.5 - 17.9)	97.6
2	10 (1.8 - 24.1)	89.9
3	14 (3.6 - 29.7)	74.8
4	18 (5.9 - 34.9)	54.5

A further description of the BLRM, including prior, hypothetical data scenarios of number of Grade 3 solicited events that could occur in the actual study, and the decision guides are presented in Section 10.8.

9.5.2. Sample size determination for immunogenicity

The primary objective is to explore how the different dose levels of mRNA-based monovalent seasonal influenza vaccine compare to standard of care control group.

The sample size is based on clinical considerations to inform dose regimen decisions for continued clinical development. With 24 participants in each dose level cohort and age group, a 10% unevaluable rate for immunogenicity results, and a standard deviation of 0.61 for log10-transformed titer, assuming that all doses will progress with enrollment, the ratio of the upper limit of a 2-sided 95% CI and the point estimate of the group GMT ratio between a mRNA dose level and the control group (pooled across dose cohorts for YAs) is 2.5.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/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.

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

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

Participant must be informed that their participation is voluntary.

Freely given and written informed consent must be obtained from each participant prior to participation in the study.

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

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. If a caregiver is assigned by the participant to help with the study procedures, the caregiver must receive an information letter that describes his/her roles prior to supporting study participant.

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

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

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

10.1.4. Data protection

Participants will be assigned a unique identifier by the investigator. Any participant records or datasets transferred to the sponsor will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.

The participants must be informed that:

- Their personal study-related data will be used by the sponsor in accordance with local data protection law.
- Their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The participants must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF.

10.1.5. Committees structure

The SRT will be an internal team, with representatives from both GSK and CureVac.

The role of the SRT in deciding dose escalation is described in Section 8.2.3.1. In addition, the SRT will review safety and immunogenicity data during the planned interim analyses and whenever any study holding rules are met (Section 8.2.3.3). According to its charter, the SRT may also recommend to permanently stop enrollment in a group. Based on SRT review and recommendations, the sponsor may drop dose groups at any time during the study if an unfavorable safety profile is observed in that group or based on safety or immunogenicity data from other groups.

More details on the composition, objectives, and responsibilities of the SRT, and the schedule and conduct of the SRT meetings will be described in the Appendix 1 on Safety Oversight of Phase I study.

10.1.6. Dissemination of clinical study data

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

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

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

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

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

Essential study documents may be added or removed where justified (in advance of study initiation) based on their importance and relevance to the study. When a copy is used to replace an original document (e.g., source documents, case report form [CRF]), the copy should fulfill the requirements for certified copies (see Glossary of terms for the exact definition of certified copies).

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

The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants (see Glossary of terms for the exact definition of source documents) that supports information entered in the eCRF.

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

The sponsor or designee is responsible for the data management of this study including quality checking of the source data (see Glossary of terms for the exact definition of source documents).

Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure

the original entry, and be fully explained if necessary (e.g., via an audit trail). The safety and rights of participants must be protected, and the study conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

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

10.1.8. Source documents

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

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

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

10.1.9. Study and site start and closure

First act of recruitment

The start of study is defined as FSFV at a country-level.

Study/Site termination

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

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

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

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

- 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 participants by the investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected

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

10.1.10. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Protocol required safety laboratory assessments

Table 17 Protocol required safety laboratory assessments

Laboratory assessments	Parameters
Hematology	White Blood Cell (WBC) count with differential: Lymphocytes, Neutrophil, Eosinophils, Basophils, Monocytes Red Blood Cell (RBC) count Platelet count Hemoglobin Hematocrit
Clinical chemistry/Biochemistry	Creatinine, CRP, BUN/Urea, AST, ALT, cardiac troponin (Troponin I and/or Troponin T)
Coagulation	INR
Urinalysis*	Leukocytes, Blood, Proteins, Glucose, Ketones, Bilirubin, Urobilinogen, Nitrite, Specific gravity, pH

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; INR: international normalized ratio.
*Urinalysis will be done by dipstick.

The tests detailed in Table 17 will be performed by the local laboratory.

10.2.2. FDA Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (September 2007)

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 18 FDA toxicity grading scales for biochemistry parameters evaluated in the current study

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
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

ULN is the upper limit of the normal range.
* 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 participant had a new seizure associated with the low sodium value.

Table 19 FDA toxicity grading scales for hematology parameters evaluated in the current study

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.

Table 20 FDA toxicity grading scales for urinalysis parameters evaluated in the current study

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

*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.

10.3. Appendix 3: AEs: definitions and procedures for recording, evaluating, follow up, and reporting

10.3.1. Definition of an AE

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

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits).
- Significant failure of an expected pharmacologic or biological action.

- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

10.3.1.2. 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 participant before the study intervention administration. These events will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

10.3.2. Definition of an SAE

An SAE is any untoward medical occurrence that:	
a.	Results in death.
b.	Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c.	Requires hospitalization or prolongation of existing hospitalization Note: In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any

	other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
d.	Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, 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.
f.	defect in the offspring of a study participant.
g.	Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
h.	Other situations Medical or scientific judgment must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should be considered serious. Examples of such events are invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; and convulsions that do not result in hospitalization.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited:

Table 21 Solicited administration site events

Pain
Redness
Swelling
Lymphadenopathy*

* Lymphadenopathy, defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the injection arm

b. Solicited systemic events

The following systemic events will be solicited:

Table 22 Solicited systemic events

Fever
Headache
Myalgia
Arthralgia
Fatigue
Chills

Note: Participants will be instructed to measure and record the axillary temperature in the evening. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the eDiary.

10.3.4. Unsolicited AEs

An unsolicited AEs is an AEs that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow up for solicited events. Unsolicited AEs must have been communicated by a participant who has signed the informed consent or through his/her caregiver.

Unsolicited AEs include both serious and non-serious AEs. The participants will be instructed to report the occurrence of unsolicited AEs using the eDiary from Day 1 to Day 28. If the participant is unable to fill out the eDiary, he/she may contact the site directly.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or an emergency room visit, or visit to/by a health care provider). Upon notification from eDiary system to the investigator of the occurrence of unsolicited AEs that are medically attended or perceived as a concern by the participant, the site should contact the participant to collect the safety information. Refer to the SPM for details.

Unsolicited AEs that are not medically attended or perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next scheduled visit/contact or earlier, if deemed necessary by the investigator or delegate.

As of Day 29, the participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

10.3.5. SAEs related to study participation

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

10.3.6. AESIs

10.3.6.1. 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 etiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 23. Refer to Section 10.3.9.1 for reporting details.

The investigator(s) must exercise their medical/scientific judgment to determine 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.

When there is enough evidence to make any of the diagnoses mentioned in Table 23, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

To facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of PTs and PT codes corresponding to the above diagnoses will be available to investigators at study start.

Once a pIMD is diagnosed (serious or non-serious) in a study participant, the investigator (or designate) must complete, date and sign an electronic Expedited Adverse Events Report.

Table 23 List of potential immune-mediated diseases (pIMDs)

Medical Concept	Additional Notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura (ITP)”, “idiopathic immune thrombocytopenia”, “primary immune thrombocytopenia”.
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• Also known as “Moschcowitz-syndrome” or “microangiopathic hemolytic anemia”
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	Including but not limited to: • Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis
Idiopathic pulmonary fibrosis	Including but not limited to: • Idiopathic interstitial pneumonia (frequently used related terms include “Interstitial lung disease”, “Pulmonary fibrosis”, “Immune-mediated pneumonitis”) • Pleuroparenchymal fibroelastosis (PPFE)
Pulmonary alveolar proteinosis (PAP)	• Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”
Endocrine disorders	
Addison’s disease	
Autoimmune / Immune-mediated thyroiditis	Including but not limited to: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis

Medical Concept	Additional Notes
Autoimmune diseases of the testis and ovary	• Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow's disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to: • Crohn's disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis

Medical Concept	Additional Notes
	• Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic lupus Erythematosus	• Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)
Systemic Scleroderma (systemic sclerosis)	• Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory demyelinating variants	Includes the following: • Acute necrotizing myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)

Medical Concept	Additional Notes
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis), including Bell's palsy	Including but not limited to: • Cranial nerve neuritis (e.g., Optic neuritis) • Idiopathic nerve palsies/paresis (e.g., Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis (TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome

Medical Concept	Additional Notes
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localized Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-johnson syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis

Medical Concept	Additional Notes
	• Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Wegener's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• Frequently used related terms include: “systemic capillary leak syndrome (SCLS)” or “Clarkson's Syndrome”
Goodpasture syndrome	• Frequently used related terms include: “pulmonary renal syndrome” and “anti-Glomerular Basement Membrane disease (anti-GBM disease)”
Immune-mediated enhancement of disease	• Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include “vaccine-mediated enhanced disease (VMED)”, “enhanced respiratory disease (ERD)”, “vaccine-induced enhancement of infection”, “disease enhancement”, “immune enhancement”, and “antibody-dependent enhancement”
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki’s disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud’s phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
Susac's syndrome	

10.3.6.2. Other AEs of special interest

The following events are considered as AESI in this study.

- Severe hypersensitivity reactions within 24 hours after study intervention administration
- Myocarditis/Pericarditis

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

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

In the absence of a diagnosis, abnormal laboratory findings assessments described in Table 17 or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Sections 10.3.1 and 10.3.2).

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

10.3.8. Events or outcomes not qualifying as AEs or SAEs

10.3.8.1. Pregnancy

Female participants who become pregnant after administration of the study intervention may continue the study at the discretion of the investigator.

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

10.3.9. Recording and follow up of AEs, SAEs, AESIs and pregnancies

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

When an AE/SAE occurs, it is the investigator's responsibility to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE on the paper Expedited Adverse Events Report/in eCRF. The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the paper Expedited Adverse Events Report/eCRF.

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

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

Electronic Diary (eDiary) will be used in this study to capture solicited administration site or systemic events and inform the site staff of the occurrence of an unsolicited event. The participant/caregiver should be trained on how and when to complete the eDiary.

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

Collect and verify completed eDiary during discussions with the participant on all contacts and visits up to Day 29. eDiary device should be returned to the site after the end of the relevant data collection period on Day 29 (Visit 4). If eDiary application was installed on participant's/caregiver's own device, it must be uninstalled after Day 29.

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

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

10.3.9.1. Time period for collecting and recording AEs, SAEs, AESIs and pregnancies

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

All unsolicited AEs that occur within 28 days after administration of the study intervention (Day 1 to Day 28) must be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

SAEs related to study participation or to a concurrent GSK medication/vaccine will be collected from the time the consent is obtained until the participant is discharged from the study.

The time period for collecting and recording SAEs and AESIs will begin at the day of study intervention administration (Day 1) and will end 6 months after (study end [Day 183]).

all AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study intervention until the participant is discharged from the study.

See Section 10.3.9 for instructions on reporting of pregnancies.

10.3.9.2. Follow up of AEs, SAEs, AESIs, pregnancies or any other events of interest

After the initial AE/SAE/AESI/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs

and AESIs (as defined in the Section 10.3.6), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow up.

Other non-serious AEs must be followed for 6 months (until Day 183) or until the participant is lost to follow up.

10.3.9.2.1. Follow up during the study

AEs/AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study or the participant is lost to follow up.

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

10.3.9.2.2. Follow up after the participant is discharged from the study

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

10.3.9.2.3. Follow up of pregnancies

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

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

Furthermore, the investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.11.

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

When additional SAE, AESI or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the study contact for reporting SAEs (refer to Section 8.3.3.1 or to GSK Global Safety department within the defined reporting timeframes specified in the Table 13).

10.3.10. Assessment of intensity and causality

10.3.10.1. Assessment of intensity

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

Table 24 Intensity scales for solicited events in participants of 6 years of age or more

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

* Defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the administration arm.
** Refer to the SoA (Section 1.3) for the definition of fever and the preferred location for temperature measurement.

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

	Redness/Swelling	Fever
0:	< 25 mm	< 38.0°C (100.4°F)
1:	≥ 25 - ≤ 50 mm	≥ 38.0°C (100.4°F) - ≤ 38.4°C (101.1°F)
2:	≥ 51 - ≤ 100 mm	≥ 38.5°C (101.2°F) - ≤ 38.9°C (102.0°F)
3:	> 100 mm	≥ 39.0°C (102.1°F)

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

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

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

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

10.3.10.2. Assessment of causality

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

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

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

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

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

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

Possible contributing factors include:

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

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

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

10.3.10.3. Medically attended visits

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

10.3.10.4. Assessment of outcomes

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

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

10.3.11. Reporting of SAEs, AESIs, pregnancies and other events

10.3.11.1. Events requiring expedited reporting to GSK

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

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

Refer to the Table 13 for the details on timeframes for reporting of SAEs/AESIs/pregnancies.

Refer to Section 10.3.11.2 for information on back up systems in case the electronic reporting system does not work.

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

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

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

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

10.4.1. Definitions

10.4.1.1. Woman of childbearing potential (WOCBP)

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

10.4.1.1.1. Women not considered as women of childbearing potential

- Premenarchal

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

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

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Current bilateral tubal ligation or occlusion

Note: Documentation can come from the site personnel's: review of participant'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 a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 25).

Table 25 Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent ***Failure rate of <1% per year when used consistently and correctly.****
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – Oral – Intravaginal – Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation – Injectable – Oral (if allowed by local regulation or if it is part of standard medical practice in the country)
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/ligation.
Vasectomized partner *(A vasectomized 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 sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant, *(The information on the male sterility can come from the site personnel's review of the participant'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 participant.)*

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

10.4.3. Collection of pregnancy information

10.4.3.1. Female participants who become pregnant

Refer to Sections 8.3.1, 8.3.2, 10.3.9.1, 10.3.9.2 and 10.3.9.3 for further information on detection, recording, reporting and follow up of pregnancies.

Since this is a single dose study, a female participant who becomes pregnant during the study will be allowed to continue the study until the end unless she withdraws consent or the investigator decides that it is in the participant's best interest to be discontinued from the study.

10.5. Appendix 5: Genetics

Not applicable.

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

10.6.1. Definition of medical device AE and ADE

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

10.6.2. Definition of medical device SAE, SADE and USADE

A medical device SAE is any SAE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: – A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. – A permanent impairment of a body structure or a body function. – Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. – Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an ADE that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the IB.

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

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

10.6.4. Reporting of medical device deficiencies for associated person

- If an associated person (e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the safety reporting information and authorization to contact physician letter.
- If follow up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent.
- Medical device deficiencies should be reported using the medical device deficiency report form.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for Medical device Deficiency reporting can be found in the medical device deficiency report form.

10.7. Appendix 7: Country-specific requirements

Not applicable.

10.8. Appendix 8: Statistical appendix including model performance and data scenarios

Study holding rules will be applied independently to each dose group. Rule 2a relates to any Grade 3 solicited events in an investigational group, with an event onset within the 7-day (Days 1 to 7) post-dose period. The threshold of the holding decision is determined by a mixed BLRM, described below:

$\text{logit}(p_i(d)) = \log(\alpha) + \beta_1 * \log(d/d^*) + \beta_2 * \text{age group}$

where

- $p_i(d)$ represents the probability of having a Grade 3 solicited event at dose d
- $\text{logit}(p) = \log(p/(1-p))$
- $d^* =$ CCI is the reference dose
- α is the intercept parameter
- β_1 is a dose effect
- β_2 is age group effect.

Since no prior information is available, the uncertainty about the dose-tolerance relationship (parameters α and β1) is expressed by a mixture of 2 bivariate normal distributions as follows:

1. 80% weight for minimally informative component: log(α) ≈ normal (mean= -1.516, var=1) and log(β_1) ≈ normal (mean= -1.553, var=1), *a priori* assuming 10% and 18% Grade 3 solicited event rate at [redacted], respectively.
2. 20% weight for toxicity component: log(α) ≈ normal (mean= -0.708, var=1) and log(β1) ≈ normal (mean= -***1***.143, var=1), *a priori* assuming 15% and 33% Grade 3 solicited event rate at [redacted], respectively.

The age group parameter, β_2, will be assigned a half-normal prior, normal (mean = 0, var = 0.25) with $\beta_2<0$ to reflect a priori lower adverse reaction (AR) rate in the OA group.

A zero covariance between priors is assumed.

Holding rule 2a will be based on a greater than 50% posterior probability that the Grade 3 solicited event rate ≥ 18% at the next dose. This will be applied by dose.

Hypothetical scenarios that illustrate when a study hold could occur is presented in Table 26.

Table 26 Hypothetical data scenarios for study holds

Scenario	Age group	Dose	#Events	#Participants	CD – P(OD)	Next Dose	ND – P(TD)	ND – P(OD)
1	YA	[redacted]	0	24	0	[redacted]	0.990	0.010
			0	24	0		0.976	0.024
			0	24	0		0.959	0.041
			0	24	0	NA		
	OA		0	24	0	[redacted]	0.998	0.002
			0	24	0		0.996	0.004
			0	24	0		0.989	0.011
			0	24	0	NA		
2	YA		0	24	0	[redacted]	0.990	0.010
			3	24	0.026		0.706	0.294
			5	24	0.607*		0.104	0.896*
			8	24	*0.999**	*NA*		
	OA		0	24	0	[redacted]	0.998	0.002
			3	24	0.002		0.877	0.123
			5	24	0.270		0.259	0.741*
			8	24	*0.975**	*NA*		
3	YA		0	24	0	[redacted]	0.990	0.010
			0	24	0.002		0.922	0.078
			4	24	0.764*		0.023	0.977*
			9	24	*1**	NA		
	OA		0	24	0	[redacted]	0.999	0.001
			2	24	0		0.974	0.026
			9	24	0.565*		0.050	0.950*
			14	24	*1**	NA		

*Holding rule met, i.e., ND – P(OD) >0.5
CD = Current dose; NA = not applicable; ND = Next dose; P(TD) = Probability of target dose; and P(OD) = Probability of overdose.

When fitting the model, 0 events (#events) are replaced by 1 event (i.e., assume 1 event in the younger adult group); this is done to prevent results from being overinfluenced by rates of events (=0%) being on the boundary of the parameter space.
Rows in red should not be in the table since the holding rule would have been met at the previous dose; however, the rows are included for illustration purposes only.

10.9. Appendix 9: Abbreviations and glossary of terms

10.9.1. List of abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
BLRM	Bayesian Logistic Regression Model
BUN	Blood Urea Nitrogen
CCI [redacted]	
CDC	Center for Disease Control and Prevention
CCI [redacted]	
CRDL	Clinical Research and Development Lead
CCI [redacted]	
CSR	Clinical Study Report
eCRF	electronic Case Report Form
EoS	End of Study
EWOC	Escalation with Overdose Control
FDA	Food and Drug Administration, United States of America
FSFV	First Subject First Visit

FTiH	First-Time-in-Human
GCP	Good Clinical Practice
GMI	Geometric Mean Increase
GMT	Geometric Mean Titers
GSB	GSK Global Safety Board
GSK	GlaxoSmithKline
GSK-[redacted]	GSK[redacted]
HA	Hemagglutinin
HCP	Health Care Professional
[redacted]	
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICS	Intracellular Cytokine Staining
IEC	Independent Ethics Committee
[redacted]	
IgA	Immunoglobulin A
[redacted]	
IM	Intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
LLOQ	Lower Limit of Quantification
LML	Local Medical lead
LNP	Lipid Nanoparticles

LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
OA	Older Adult
PCD	Primary Completion Date
PI	Prescribing Information
pIMD	Potential Immune-Mediated Disease
PPS	Per Protocol Set
PT	Preferred Term
QTL	Quality Tolerance Limit
RNA	Ribonucleic Acid
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SBIR	Source data Base for Internet Randomization
CCI [redacted]	
SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOC	System Organ Class
SPM	Study Procedures Manual
CCI [redacted]	
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
CCI [redacted]	
USADE	Unanticipated Serious Adverse Device Effect

VCSP	Vaccines Clinical Safety and Pharmacovigilance
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential
YA	Younger Adult

10.9.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In a single-blind study, the investigator(s) and/or their staff are aware of the intervention assignment, but the participant is not. In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment. Refer to Section 6.3.5 for more information on blinding applied in this study.
Caregiver:	A ‘caregiver’ is someone who – lives in the close surroundings of a participant and has a continuous caring role or – has substantial periods of contact with a participant and is engaged in their daily health

	care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified procedures.
Child in care:	A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Combination product:	Combination product comprises any combination of – drug – device – biological product Each drug, device and biological product included in a combination product is a constituent part.
eDiary	Electronically registered patient data and automated data entries on, for example, a handheld mobile device, tablet or computer.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrollment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
eTrack:	GSK’s tracking tool for clinical studies.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.

Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Invasive medical device	EEC directive 93/42/EEC defines an invasive medical device as 'A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body'
Investigational vaccine	A pharmaceutical form of an active ingredient being tested in a clinical study, including a product with a marketing authorization 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. Synonym: Investigational Medicinal Product
Investigator:	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions
Medical device deficiency:	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject

Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical study was concluded according to the pre-specified protocol or was terminated.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit:	This term refers to the visit conducted in the place other than the study site.
Self-contained study:	Study with objectives not linked to the data of another study.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical study).
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.

Study monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Telemedicine:	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, patient and professional health-related education, public health and health administration.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow up for solicited symptoms will be reported as an unsolicited AE.
Virtual visit:	This term refers to study visits conducted using multimedia or technological platforms.

10.10. Appendix 10: Protocol amendment history

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

DOCUMENT HISTORY	
Document	Date of issue
Amendment 5	20 June 2023
Amendment 4	14 February 2023
Amendment 3	12 January 2023
Amendment 2	08 July 2022
Amendment 1	19 May 2022
Final protocol	15 April 2022

Amendments summary of changes table:

Document	Date of issue	Section # and title	Description of change	Brief rationale
Amendment 1	19 May 2022	Title page	'Observer-blind' was removed from the title of the study	To avoid confusion: the study remains observer-blind for the study participant and investigator, but will be open-label for the sponsor
		1.1 Synopsis	Rationale for the study has been updated	The description of methodology used in this study and measures to minimize the risk for the study participants have been updated to reflect the study design revisions based on recommendations from the Belgian Competent Authority
		1.3 Schedule of Activities (SoA)	Contact 3 (Day 29) has been transformed into a visit to enable sample collection for safety laboratory assessments. Numbering of visits has been adjusted throughout the document.	Modifications made based on the recommendation from the Belgian Competent Authority
			Urine analysis was added into the list of safety assessments.	
			Possibility to replace Visit 5 and 6 by a contact has been added.	To reduce burden on study participants and improve compliance and participants retention
			Table 2 'Intervals between study visits' has been updated	To reflect updated schedule of study visits and contacts
		2.1. Study rationale	Updated to align with Section 1.1 Synopsis	The description of methodology used in this study and measures to minimize the risk for the study participants were aligned with synopsis

Document	Date of issue	Section # and title	Description of change	Brief rationale
		2.3.1. Risk assessment	Wording for mitigation strategy applicable to Flu Seasonal mRNA vaccine has been updated	Updated to reflect the changes in safety follow up strategy for younger adults (YAs) versus older adults (OAs) implemented based on the recommendations from the Belgian Competent Authority
		2.3.2. Benefit assessment 3. Objectives, endpoints, and estimands 4.1 Overall design 5.2.1. Medical conditions 8. Study assessments and procedures 8.1.1. Biological samples 8.1.2. Laboratory assays Table 17 Protocol required safety laboratory assessments	Urinalysis was added into the list of safety assessments made at different timepoints of the study	To comply with the recommendation from the Belgian Competent Authority

Document	Date of issue	Section # and title	Description of change	Brief rationale
		4.1. Overall design Table 5 Study intervention(s) administered 8.2.3.1. Staggered enrollment and safety monitoring 8.2.3.2. Outcome of safety evaluation 8.2.3.3. Study holding rules 9.3.1.1. Analysis of reactogenicity for dose escalation: Bayesian logistic regression model 9.4.1. Sequence of planned analyses 10.1.5. Committees structure	Wording of several sections has been modified to implement following changes in study design: Dose escalation in YAs will depend on safety/reactogenicity data from all (sentinel and non-sentinel) participants at a given dose level Enrollment of OAs will start only after a reasonable database (i.e., from several dose levels in YAs) is available Only 1 dose will be assessed in OA. This dose will be assessed after the doses of CCI [redacted] are evaluated in YAs To maximize the efficiency of the review of the safety data by the sponsor, the blinding is maintained for the investigator and participants, but the study becomes open-label for the sponsor. This alleviates the need for an internal Safety Review Committee (iSRC) and therefore, the safety data will be reviewed in an unblinded fashion by the Safety Review Team (SRT), in line with GSK processes.	Several sections of the document have been updated to comply with the recommendations from the Belgian Competent Authority and to enhance safety of participants
		4.3. Justification for dose	Wording on dose selection for OAs has been updated	To limit overall exposure in OAs to investigational study intervention
		6.3.2. Randomization to study intervention Table 9 Immunological read-outs	Total number of participants in the study has been updated	To limit overall exposure in OAs to investigational study intervention

Document	Date of issue	Section # and title	Description of change	Brief rationale
		9.3.2. Co-primary and secondary immunogenicity endpoints 9.5.1. Sample size determination for reactogenicity and safety 9.5.2. Sample size determination for immunogenicity		
		4.2.2. Rationale for study blinding 6.3.5. Blinding and unblinding	Blinding was updated to open-label for the sponsor	To maximize the efficiency of the safety data review by SRT for providing recommendations on dosing of non-sentinel participants at the current dose level, dose escalation for the next dose level in YAs and selection of dose for OAs
		5.1. Inclusion criteria	Safety laboratory assessments were added	To comply with the recommendation from the Belgian Competent Authorities
		Prior/Concomitant therapy	Timing for administration of seasonal influenza vaccine has been changed	To avoid biased reporting of AEs due to seasonal flu vaccination and its impact on safety and immunogenicity data within time period for collection of unsolicited adverse events
		6.8. Concomitant therapy	Time-periods for recording of administration of concomitant medications and vaccinations have been updated	To align with study design and GSK process
		8.2.1.5. Pregnancy test	Wording updated to include pregnancy test at screening	To clarify that 2 pregnancy tests will be required prior to enrollment and study intervention administration

Document	Date of issue	Section # and title	Description of change	Brief rationale
		10.2.1. Protocol required safety laboratory assessments (Table 17)	Troponin I and/or Troponin T was added as options for cardiac troponin assessment	To allow flexibility for local labs when performing this assessment
		10.2.2. FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007)	Table 20 was added	To provide FDA toxicity grading scales for urinalysis parameters evaluated in the study
		10.3.10.1. Assessment of intensity	Scales for redness, swelling and fever measurements have been updated	To align with FDA toxicity grading scales.
Amendment 2	08 July 2022	5.1. Inclusion criteria	'Before entering the study' was removed from inclusion criterion N°2 to clarify that this inclusion criterion will be checked along with all other eligibility criteria prior to enrolment/study intervention administration	To comply with the recommendation from the Belgian Competent Authorities
		6.7. Treatment of overdose	Section title and content were modified to include the management of anaphylaxis	To comply with the recommendation from the Canadian Competent Authorities
		7.2. Participant discontinuation/withdrawal from the study	Additional wording was added to provide a more exhaustive list of criteria for participant's withdrawal from the study	To comply with the recommendation from the Canadian Competent Authorities
		10.2.1. Protocol required safety laboratory assessments (Table 17)	Urea has been added as option for clinical chemistry/biochemistry assessment	To allow flexibility for local labs when performing this assessment
		10.3.10.1 Assessment of intensity (Table 24)	Definition of Grade 0 for 'Fatigue' has been updated from 'Normal' to 'None'	Grading aligned with current GSK standard definition and definition of grading provided in the participant diary

Document	Date of issue	Section # and title	Description of change	Brief rationale
Amendment 3	12 January 2023	4.1. Overall design 4.3. Justification for dose 4.3.2. Justification for additional doses in YAs, evaluated in Amendment 3	Addition of 2 dose levels to the study CCI [redacted]	To define the optimal dose for the monovalent H1 vaccine candidate
		1.1. Synopsis 2.1. Study rationale	Clarification that only younger adults will be enrolled in the CCI [redacted] dose cohort	To optimize the dose level in younger adults (all previous dose levels were tested in this population)
		1.1 Synopsis 1.3. Schedule of Activities (SoA) 2.1. Study rationale 2.3. Benefit/Risk assessment 4.1. Overall design 8.2.3.1.1. Staggered enrollment of OAs	Removal of sentinel participants for the CCI [redacted] dose cohort	As (i) CCI [redacted] dose cohorts, and (ii) CCI [redacted] have showed a CCI [redacted] (incidence of Grade 3 solicited adverse events ranging from CCI [redacted] depending on dose group)
		1.1. Synopsis 2.1. Study rationale 4.1. Overall design	No dose escalation and parallel enrollment for the CCI [redacted] dose cohort	CCI [redacted] dose levels are CCI [redacted] than the CCI [redacted] dose levels that have been tested previously in this study with a CCI [redacted] (incidence of Grade 3 solicited adverse events ranging from CCI [redacted] depending on dose group)
		1.1. Synopsis 2.1. Study rationale 4.1. Overall design 4.2.1. Choice of active comparator	No active control for the CCI [redacted] dose cohort	The sample size of the available control group (N=30) is already similar to the sample size of each additional dose group to be tested (N=24)

Document	Date of issue	Section # and title	Description of change	Brief rationale
		1.3. Schedule of Activities (SoA) 9.4.1. Sequence of planned analyses	Addition of a planned interim analysis upon availability of all primary endpoints up to Day 29 for the CCI dose cohort	To allow an interim analysis of primary endpoints for this cohort
		1.3. Schedule of Activities (SoA)	Expansion of the allowed interval range for Visit 1 → Contact 2 for non-sentinel participants	To provide more flexibility for study sites to ensure participant compliance with study procedures
		5.2.2. Prior/Concomitant therapy	"Previous enrollment in this study" added to the exclusion criteria	To mitigate the risk of having the same participant enrolling more than once in the study
		8.1.2. Laboratory assays 8.1.3. Immunological read-outs	Replacement of cell-propagated CCI with CCI	Due to strain production issue, the CCI strain was used for the validation of the CCI assay instead of the CCI strain. Both strains are per WHO recommendation considered as "like virus" and belong to the same clade/sub-clade, i.e., CCI
		8.1.3. Immunological read-outs	Revision of the number of participants included for each immunological readout	To reflect the 5 dose levels enrolled to date and the additional number of participants planned in the CCI dose cohort
		6.1. Study intervention(s) administered	Addition of the CCI Flu mRNA vaccine in the study intervention table	To reflect all the dose levels used in this study
		4.1. Overall design 4.2.2. Rationale for study blinding 6.3.5. Blinding and unblinding	Clarification that the blinding level for CCI dose cohort will be single-blind	Two different Flu mRNA doses will be used, therefore the persons reconstituting the interventions will be aware of the dose of the allocated Flu mRNA vaccine. This requires unblinding the randomization system for this cohort and accordingly all users of the

Document	Date of issue	Section # and title	Description of change	Brief rationale
				randomization system will be unblinded and only the participant will remain blinded
		10.8. Appendix 8: Statistical appendix including model performance and data scenarios	Correction of a typographical error for the mean of the second component of the mixture prior from -0.143 to -1.143. An updated description of the prior of the age group parameter to reflect what was actually used for the hypothetical data scenario in Table 26	To account for feedback received from FDA statistician
		10.9.2. Glossary of terms	Single-blind definition added to the Glossary	Since the blinding level for CCI [redacted] dose cohort will be single-blind
		8.2.1.1. Collection of demographic data	Clarification that year of birth, and not date of birth, is recorded in the participant's eCRF	To correct for error in protocol that date of birth is collected in the eCRF
		8.3.3. Regulatory reporting requirements for SAEs, pregnancies and other events	Administration and systemic solicited events and Unsolicited events were removed from Table 13	As these are not events that would require expedited reporting within 24 hours unless they meet the definition of SAE or AESI as per section 8.3.3. and Appendix 3
		6.3.2. Randomization to study intervention	Clarification that partial block sizes without active control will be shipped for the CCI [redacted] dose cohort	As no active control is used for the CCI [redacted] dose cohort
Amendment 4	14 February 2023	4.1. Overall design 4.3. Justification for dose 4.3.2. Justification for additional doses in YAs, evaluated in Amendment 4	Addition of 2 dose levels CCI [redacted]), and 2 potential intermediate dose levels (CCI [redacted]) to the study	To widen the dose range of the monovalent Flu Seasonal mRNA vaccine candidate in younger adults, and explore the reactogenicity/immunogenicity profile at these dose levels

Document	Date of issue	Section # and title	Description of change	Brief rationale
		8.2.3.1 Staggered enrolment and safety monitoring		
		1.1. Synopsis 2.1. Study rationale	Clarification that only younger adults will be enrolled in the CCI [redacted] and their potential intermediate dose cohorts (CCI [redacted]	To allow comparisons of reactogenicity/immunogenicity between dose levels in younger adults, as all previous dose levels were also tested in this population
		4.4. Enrollment rules	Removal of the enrolment rule for sex	To allow a higher enrollment flexibility in the study and since sex is not considered an important prognosis factor. The study conclusions are not expected to be impacted by sex distribution.
		1.1. Synopsis 2.1. Study rationale 4.1. Overall design 4.2.1. Choice of active comparator	New active control (Flu seasonal QIV vaccine 2022-2023) for the CCI [redacted], and their potential intermediate dose cohorts (CCI [redacted])	Added due to expiry of the previous active control (Flu seasonal QIV vaccine 2021-2022)
		1.3. Schedule of Activities (SoA) 3. Objectives, Endpoints, and Estimands 4.1. Overall design 6.3.4 Allocation of participants to assay subsets 8.1.1. Biological samples	No blood sampling for CCI [redacted] response for CCI [redacted] and their potential intermediate dose cohorts (CCI [redacted])	As safety/reactogenicity assessment is the main objective for these additional dose cohorts, immunogenicity endpoints will be restricted to the most critical (Day 1 and Day 22 antibody determination).
		1.3. Schedule of Activities (SoA) 3. Objectives, Endpoints, and Estimands 4.1. Overall design	Removal of blood sampling at Day 62 and Day 183	As safety/reactogenicity assessment is the main objective for these additional dose cohorts, immunogenicity endpoints will be

Document	Date of issue	Section # and title	Description of change	Brief rationale
		8.1.1. Biological samples		restricted to the most critical (Day 1 and Day 22 antibody determination).
		1.3. Schedule of Activities (SoA) 9.4.1. Sequence of planned analyses	Addition of a planned interim analysis upon availability of all primary endpoints up to Day 29 for the CCI [redacted], and their potential intermediate dose cohorts (CCI [redacted])	To allow an interim analysis of primary endpoints for these dose cohorts.
		8.1.3. Immunological read-outs	Revision of the number of participants included for each immunological readout	To reflect the additional number of participants planned in the CCI [redacted] dose cohorts, as well as the changes in blood sampling schedule for these cohorts
		6.1. Study intervention(s) administered	Addition of the CCI [redacted] Flu mRNA vaccine and new active control (Flu seasonal QIV vaccine 2022-2023) in the study intervention table	To reflect all the Flu mRNA dose levels and control vaccines used in this study
		8.2.3.2. Outcome of safety evaluation 8.2.3.3. Study holding rules 10.1.5. Committees structure	Replacement of term SRT charter with Appendix 1 on Safety Oversight of Phase I study	This Appendix 1 on Safety Oversight of Phase I study has replaced the SRT charter and contains same information.
		9.3.1. Co-primary safety endpoints	Addition of grade 4 (grade ≥ 3) solicited systemic events (fever)	To make it clearer that Grade 4 solicited systemic events as defined by FDA's Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, in particular fever, are captured and accounted for in this study.
		5.2. Exclusion criteria 5.2.3. Other exclusions	Exclusion criteria "Previous enrollment in this study" moved to number 21 under "Other exclusions".	To avoid needing to implement eCRF coding changes that would impact already enrolled study participants

Detailed description of the current Protocol amendment:

Sections 1.1. Synopsis

[…]

2. Initiation of the dosing of OAs not until after the review of the safety/reactogenicity data reported with the 3 first dose levels administered in YAs by an unblinded Safety Review Team (SRT). Note: as the goal of protocol amendment***s*** 3, ~~and~~ 4 ***and 5*** are to ~~***optimize***~~***further explore the*** reactogenicity/ immunogenicity profile ~~***the dose level between*** CCI ***and to explore the reactogenicity/immunogenicity profile of*** CCI ***dose cohorts respectively***~~ in YAs (all previous dose levels were tested in this population), no OAs will be enrolled in the CCI ***dose cohort,*** CCI dose cohort, or in the CCI ***dose*** cohorts CCI

[…]

3. Supervision of the dose escalation by SRT. The safety/reactogenicity data reviewed by this team cover 8 days of follow up post-dosing (Day 1 to Day 8 included) of all participants of the current dose level. This time window is sufficient to ensure a reliable evaluation of the reactogenicity of the vaccine, considering that the median onset of solicited systemic events after mRNA Covid-19 vaccines administration is 1 to 2 days, and a median duration of such events is 1 to 2 days [CBER, 2021; CBER, 2022]. Note: CCI -have shown a CCI (incidence of Grade 3 solicited adverse events ranging from CCI depending on dose group), this dose escalation step will not be followed for the CCI , ***or the*** CCI ***dose cohorts***, i.e., participants in these cohorts will be enrolled in parallel.

[…]

Note: CCI , and CCI have shown a CCI (incidence of Grade 3 solicited adverse events ranging from CCI depending on dose group), no sentinel participants will be included in the additional CCI ***or*** CCI dose ***cohorts***.

[…]

Note: The sample size of the available Control group (N=30) is similar to the sample size of each additional dose group to be tested (N=24). As such, we consider the available Control group sufficiently large for this phase 1 exploratory and descriptive study and will not use an active control for the additional CCI ***dose cohort, and*** CCI dose cohort, where an assessment of immunogenicity is the main objective. However, for the additional CCI , and their potential intermediate dose cohorts (CCI), where a safety/reactogenicity assessment is the main objective, Flu D-QIV will be reintroduced as active control.

Section 1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities (SoA)

[…]

Note: The double-line border after Day 22 (Visit 3) and Day 29 (Visit 4) indicates the schedule of interim analyses. Two initial interim analyses will be conducted upon availability of all primary endpoints up to Day 22 for YA participants in the CCI cohorts, respectively and ***a*** third interim analysis will be performed upon availability of all primary endpoints up to Day 29 for all study participants. Note: additional interim analyses will be performed upon availability of all primary endpoints up to Day 29 for (i) all participants in the CCI dose cohort ~~and~~, (ii) all participants in the CCI and their potential intermediate dose cohorts (CCI ***and (iii) all participants in the*** CCI ***dose cohort.***

CCI ; eDiary: electronic diary (application or electronic device); AE: adverse event; SAE: serious adverse event; AESI: adverse event of special interest.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

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

† Contact 1 (Day 2) will be performed for sentinel participants only. Note that no sentinel participants are included for the CCI ***or*** CCI dose ***cohorts***.

* Samples will be collected on sites associated with a CCI . Note: for the CCI and their potential intermediate dose cohorts (CCI no blood sampling for CCI response will be performed.

** Sample will be collected only if participants did not receive the standard of care vaccination against seasonal flu since study participation. Note that blood sampling for antibody determination and characterization will be limited to Day 1 and Day 22 for the CCI , and their potential intermediate dose cohorts (CCI).

*** Visit 5 (Day 62) and Visit 6 (Day 183) will be replaced by a contact if participant have received the standard of care vaccination against seasonal flu prior to this visit and did not report any adverse events that would require physical examination on site. Note: No blood sampling will be performed at Day 62 and Day 183 for the CCI , and their potential intermediate dose cohorts CCI). As such, Visit 5 and Visit 6 will be replaced by a contact for all participants in these cohorts unless they reported any adverse events that would require physical examination on site.

[a] is used to indicate a study procedure to be performed prior to study intervention administration.

[b] is used to indicate a study procedure recorded in eDiary.

[…]

Table 2 Intervals between study visits

[…]

* Screening visit should take place within 28 days before Visit 1, with sufficient time to receive/review the hematology, biochemistry, coagulation and urinalysis results. When applicable, a re-screening visit (including blood and urine sample collection, physical examination and re-checking of inclusion/exclusion criteria) may be scheduled at any time (but only once to assess eligibility) before Visit 1. All screening procedures need to be performed within 28 days before Visit 1. Only laboratory results from the re-screening visit, if it occurs, will be taken into consideration. The participant can only be randomized once the investigator receives the results and confirms the eligibility criteria.

** Contact 1 (Day 2) will be performed for sentinel participants only. Note that no sentinel participants are included for the CCI ***or*** CCI dose cohorts.

*** Visit 5 (Day 62) and Visit 6 (Day 183) will be replaced by a contact if participant have received the standard of care vaccination against seasonal flu prior to this visit and did not report any adverse events that would require physical examination on site. Note: No blood sampling will be performed at Day 62 and Day 183 for the CCI , and their potential intermediate dose cohorts (CCI). As such, Visit 5 and Visit 6 will be replaced by a contact for all participants in these cohorts unless they reported any adverse events that would require physical examination on site.

† For non-sentinel participants, the allowed interval ranges from 1 to 3 days.

[…]

Section 2.1. Study rationale

[…]

Note: As the goals of protocol amendments 3 ~~***and 4 and 5 are***~~ to ***further*** ~~optimize ***the dose level between*** CCI ***and to explore the*~~ reactogenicity/immunogenicity profile ~~***of*** CCI ***dose cohorts respectively***~~ in YAs (all previous dose levels were tested in this population), no OAs will be enrolled in the CCI ***dose cohort, and*** CCI dose cohort, or in the CCI and their potential intermediate dose cohorts (CCI ~~).~~

[…]

Note: CCI , and CCI have shown a CCI (incidence of Grade 3 solicited adverse events ranging from CCI depending on dose group ***this dose escalation step will not be followed for the*** CCI , ***or the*** CCI ***dose cohorts***, i.e., ***participants in these cohorts will be enrolled in parallel.*** ~~), this dose escalation step will not be followed for the~~ CCI ~~dose groups will be enrolled in parallel.~~ […]

Note: CCI and CCI have shown a CCI (incidence of Grade 3 solicited adverse events ranging from CCI depending on dose group), no sentinel participants will be included in the additional ***or*** CCI ***dose cohort and*** CCI dose cohort.

[…]

Note: The sample size of the available Control group (N=30) is similar to the sample size of each additional dose group to be tested (N=24). As such, we consider the available Control group sufficiently large for this phase 1 exploratory and descriptive study and will not use an active control for the additional CCI ***dose cohort and*** CCI dose cohort, where an assessment of immunogenicity is the main objective. However, for the additional CCI , and their potential intermediate dose cohorts (CCI), where a safety/reactogenicity assessment is the main objective, Flu D-QIV will be reintroduced as active control.

Section 2.3.1. Risk assessment

[…]

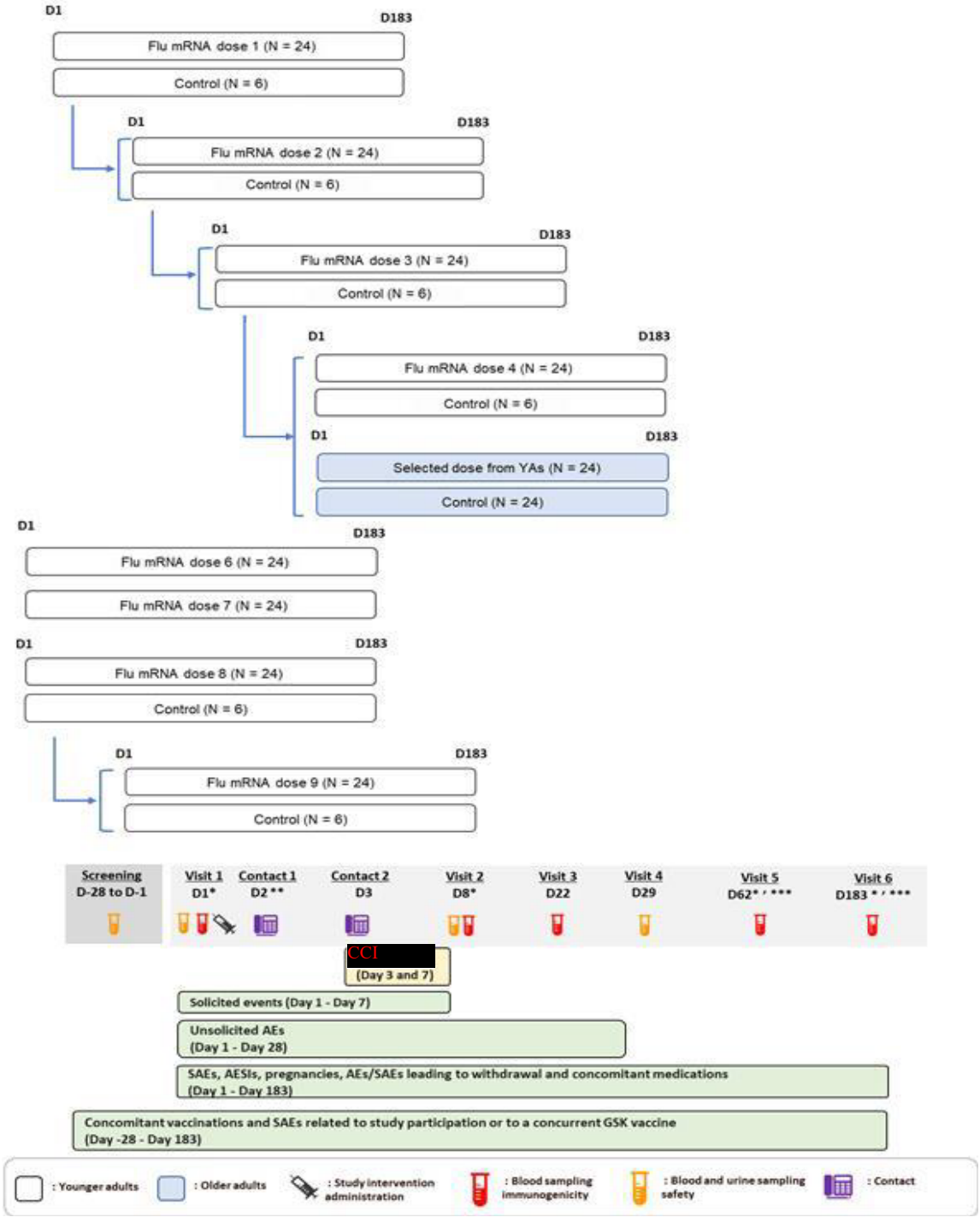
Note: no sentinel participants are included for the CCI ***or*** CCI dose cohorts

[…]

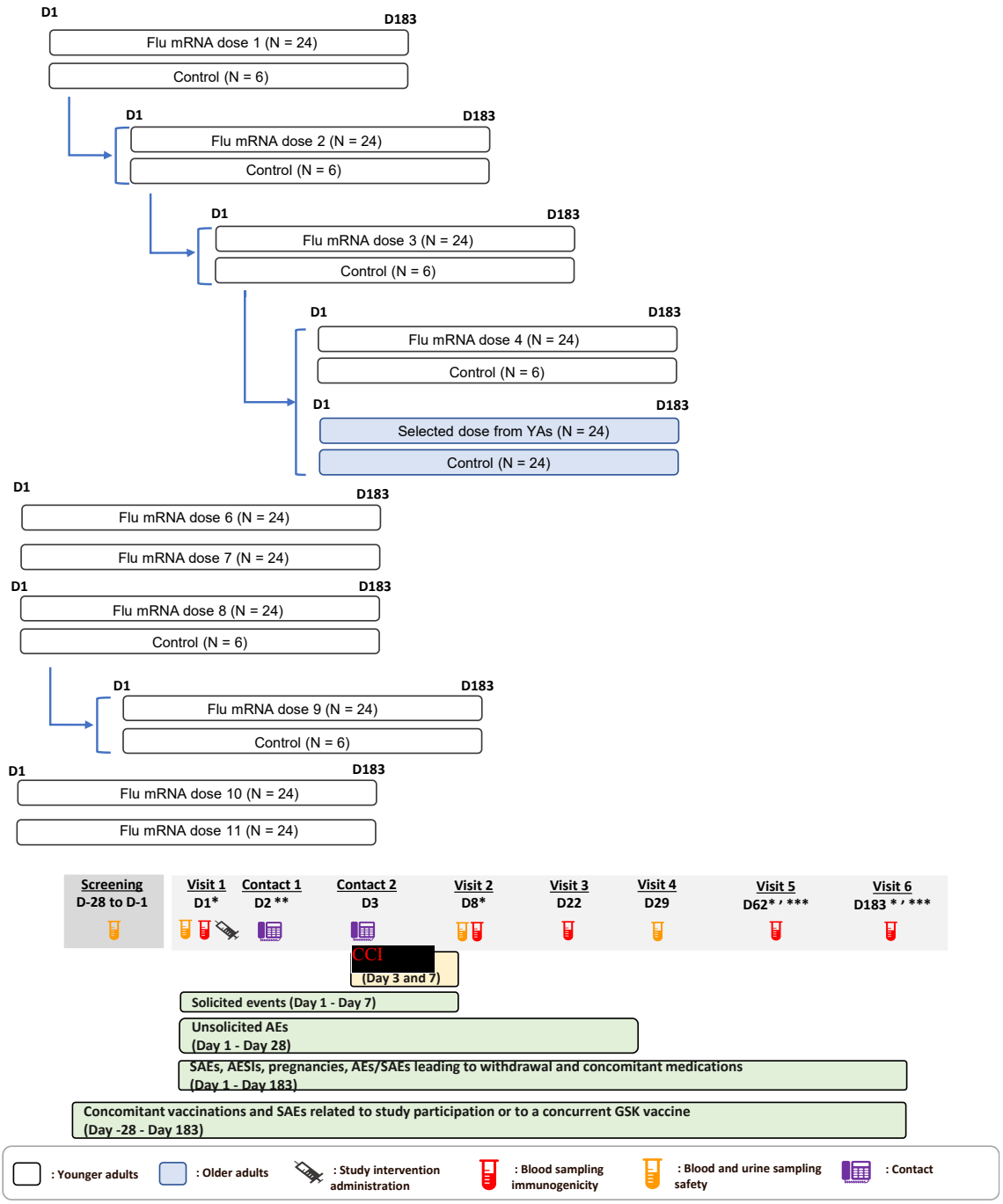
Section 4.1 Overall design

Figure 1 Study design overview

Old figure:



New figure:



AE: adverse event; SAE: serious adverse event; AESI: adverse event of special interest; D: day; CCI [redacted]; Control: Flu D-QIV (*Flu Dresden-Quadrivalent Influenza Vaccine*; GlaxoSmithKline; season 2021-2022 Northern Hemisphere [NH] for the CCI [redacted] dose cohorts, and season 2022-2023 NH for the CCI [redacted] dose cohorts, and their potential intermediate dose cohorts CCI [redacted]); commercially available as α-RIX-Tetra in Belgium).

Doses of study intervention for YAs are coded as follows: dose 1: CCI [redacted], dose 2: CCI [redacted], dose 3: CCI [redacted], dose 4: CCI [redacted] dose 6: CCI [redacted], dose 7: CCI [redacted], dose 8: CCI [redacted], dose 9: CCI [redacted], ***dose 10:*** CCI [redacted], ***dose 11:*** CCI [redacted] Potential intermediate dose levels CCI [redacted] may be evaluated with the total number of dose levels not exceeding ~~***10***~~***12*** in YAs and 1 in OAs. In OAs, dose of study intervention will be selected based on safety/reactogenicity data up to dose 3 in YAs. Refer to Section 4.3 for more information. Refer to Section 4.3.2, 4.3.4,

and 4.3.4 for rationale for addition of the CCI and CCI and their potential intermediate dose cohorts CCI) respectively.
* Blood sample for CCI will be collected from a subset of participants. CCI will be assessed in 50% of participants of each group (Flu mRNA and Control) to be enrolled at the selected sites.
Note: for the CCI and their potential intermediate dose cohorts (CCI) no blood sampling for CCI response will be performed.
** Contact 1 (Day 2) will be performed for sentinel participants only. Note that no sentinel participants are included for the CCI dose ***cohorts***.
*** Visit 5 (Day 62) and Visit 6 (Day 183) will be replaced by a contact if participant have received the standard of care vaccination against seasonal flu prior to this visit and did not report any adverse events that would require physical examination on site. Note: No blood sampling will be performed at Day 62 and Day 183 for the CCI , and their potential intermediate dose cohorts (CCI). As such, Visit 5 and Visit 6 will be replaced by a contact for all participants in these cohorts unless they reported any adverse events that would require physical examination on site.
Note: Each dose group consists of sentinel and non-sentinel participants, except for the CCI dose ***cohorts***.

[…]

For the additional CCI dose cohorts, no sentinel participants will be enrolled; no dose escalation design applies;-CCI the dose levels ***in each cohort*** will be enrolled in parallel; no control vaccine will be used.

[…]

Note: No sentinel participants will be enrolled for the additional CCI dose ***cohorts***, hence all participants in ~~that~~***these cohorts*** will be considered as non-sentinel. No control vaccine will be used for ***the*** CCI dose cohorts, where a randomization ratio of 1:1 will be applied between the CCI ***dose levels, and between the*** CCI dose levels, for a total of 48 participants ***per cohort***.

[…]

- Parallel enrollment for the CCI ***, and the*** CCI dose cohorts.
- Planned (approximate) number of participants to be enrolled is ~~***306***~~***354***:
  - ~~***258***~~***306*** YA participants (24 participants per dose level and a total number of 42 participants receiving the active control)
  - 48 OA participants (24 participants receiving a dose of investigational study intervention and 24 participants receiving the active control)
  - Due to the adaptive design, the actual number of participants enrolled might be lower than the target number or up to ~~***336***~~***384*** participants in case a ~~***10***~~$^{\textbf{\textit{th}}}$ ***12***$^{\textbf{\textit{th}}}$ dose level is evaluated in YAs.

[…]

Furthermore, 2 additional doses of CCI of the vaccine candidate will be assessed in 48 YAs under Protocol Amendment 3***; and 2 additional doses of*** CCI ***will be assessed in 48 YAs under Protocol Amendment 5.*** Refer to Section 4.3.2, ~~and~~ 4.3.4***, and 4.3.4***for rationale for addition of the CCI , and their potential intermediate dose cohorts respectively. In any case, the total number of dose levels assessed will not exceed ~~10~~***12.***

[…]

Flu D-QIV season 2022-2023 will be used as active control for the CCI and their potential intermediate dose cohorts (CCI No active control will be used for the CCI dose ***cohorts.***

[…]

- Study groups:
  - 2 parallel groups, Flu mRNA versus Control in YAs.
  - 2 parallel groups, Flu mRNA versus Control in OAs.
  - For the CCI dose cohort: 2 parallel groups, Flu mRNA CCI versus Flu mRNA CCI in YAs.
  - ***For the*** CCI ***dose cohort: 2 parallel groups, Flu mRNA*** CCI ***versus Flu mRNA*** CCI ***in YAs.***

[…]

- Level of blinding: for participants and investigators, the study will be observer-blind with regards to the study intervention, but open-label with regards to the dose level. For the sponsor, the study will be open-label. For the CCI ***, and*** CCI dose ***cohorts,*** the study will be single-blind.

[…]

Table 27 Study groups, intervention and blinding

Study groups	Number of participants	Age (Min-Max)	Study interventions (IM use)	Blinding Visit 1→Visit 6
YA				
Flu mRNA dose 1	24	18 – 45 years	CCI [redacted]	Observer-blind*
Flu mRNA dose 2	24	18 – 45 years		Observer-blind*
Flu mRNA dose 3	24	18 – 45 years		Observer-blind *
Flu mRNA dose 4	24	18 – 45 years		Observer-blind *
Flu mRNA dose 6	24	18 – 45 years		Single-blind*
Flu mRNA dose 7	24	18 – 45 years		Single-blind*
Flu mRNA dose 8	24	18 – 45 years		Observer-blind *
Flu mRNA dose 9	24	18 – 45 years		Observer-blind *
Flu mRNA dose 10	***24***	***18 – 45 years***		***Single-blind****
Flu mRNA dose 11	***24***	***18 – 45 years***		***Single-blind****
Control**	24	18 – 45 years	FDQ21A-NH	Observer-blind*
Control**	12	18 – 45 years	FDQ22A-NH	Observer-blind*
OA				
Selected dose from YAs	24	60 – 80 years	Selected dose from YAs***	Observer-blind*
Control	24	60 – 80 years	FDQ21A-NH	Observer-blind*

YA: younger adult; OA: older adult; NH: Northern Hemisphere.
Control: Flu D-QIV (*Flu Dresden- Quadrivalent Influenza Vaccine*; GlaxoSmithKline; season 2021-2022 NH for the CCI [redacted] dose cohorts, and season 2022-2023 NH for the CCI [redacted] dose cohorts; commercially available as *α-RIX-Tetra* in Belgium)
Doses of vaccine candidate are coded as follows: dose 1: CCI [redacted]; dose 2: CCI [redacted]; dose 3: CCI [redacted] dose 4: CCI [redacted], dose 6: CCI [redacted], dose 7: CCI [redacted] dose 8: CCI [redacted], dose 9: CCI [redacted] ***dose 10:*** CCI [redacted] ***dose 11:*** CCI [redacted]. Potential intermediate dose levels CCI [redacted]) may be evaluated with the total number of dose levels not exceeding ~~**10**~~***12*** in YAs and 1 in OAs. Refer to Section 4.3.2,~~***and***~~ ***4.3.4, and 4.3.4*** for rationale for addition of the CCI [redacted] ***and their potential intermediate dose cohorts*** (CCI [redacted]) [1] ***respectively.***
* For participants and investigators, the study will be observer-blind with regards to the study intervention, but open-label with regards to the dose level. For the sponsor, the study will be open-label. For the CCI [redacted]***, and*** CCI [redacted] dose cohorts, the study will be single-blind. Refer to Section 6.3.5 for more information.
** In YAs, 6 participants are enrolled in the control group per dose level of the investigational study intervention, except for the CCI [redacted]***, and*** CCI [redacted] dose ***cohorts***, where no control vaccine will be used.
*** Study intervention dose will be selected based on the safety/reactogenicity data obtained up to dose 3 in YAs. Refer to Section 4.3 for more information.
Note: Hereafter, name of the study groups for YAs will be only referred to as Flu mRNA dose 1-~~***11***~~***9***. Details on the study intervention administered are shown in Table 5.

[…]

Section 4.1.1 Enrollment rules

Overall, participants will be enrolled in 2 age categories (YAs and O*A*s) with at least 35% of either sex to ensure balance between males and females. Note: To allow a higher enrollment flexibility in the study and since sex is not considered an important prognosis factor, the sex enrollment rule will not be applied to the additional CCI [redacted] ***dose cohort, or the*** CCI [redacted], and their potential intermediate dose cohorts (CCI [redacted]).

[…]

Table 28 Study groups, intervention and blinding *(Amended:20 June 2023)*

Study groups	Number of participants	Age (Min-Max)	Study interventions (IM use)	Blinding Visit 1→Visit 6
YA				
Flu mRNA dose 1	24	18 – 45 years	CCI [redacted]	Observer-blind
Flu mRNA dose 2	24	18 – 45 years		Observer-blind
Flu mRNA dose 3	24	18 – 45 years		Observer-blind
Flu mRNA dose 4	24	18 – 45 years		Observer-blind
Flu mRNA dose 6	24	18 – 45 years		Single-blind
Flu mRNA dose 7	24	18 – 45 years		Single-blind
Flu mRNA dose 8	***24***	***18 – 45 years***		***Observer-blind***
Flu mRNA dose 9	***24***	***18 – 45 years***		***Observer-blind***
Control**	24	18 – 45 years	FDQ21A-NH	Observer-blind
Control*	***12***	***18 – 45 years***	***FDQ22A-NH***	***Observer-blind****
OA				
Selected dose from YAs	24	60 – 80 years	Selected dose from YAs***	Observer-blind
Control	24	60 – 80 years	FDQ21A-NH	Observer-blind

YA: younger adult; OA: older adult; NH: Northern Hemisphere.
Control: Flu D-QIV (*Flu Dresden- Quadrivalent Influenza Vaccine*; GlaxoSmithKline; season 2021-2022 NH for the CCI [redacted], CCI [redacted] dose cohorts, and season 2022-2023 NH for the CCI [redacted] dose cohorts; commercially available as *α-RIX-Tetra* in Belgium)
Doses of vaccine candidate are coded as follows: dose 1: CCI [redacted] dose 2: CCI [redacted]; dose 3: CCI [redacted]; dose 4: CCI [redacted] dose 6: CCI [redacted], dose 7: CCI [redacted], dose 8: CCI [redacted], dose 9: CCI [redacted] ***, dose 10:*** CCI [redacted] ***, dose 11:*** CCI [redacted]. Potential intermediate dose levels CCI [redacted] may be evaluated with the total number of dose levels not exceeding ***12*** in YAs and 1 in OAs. Refer to Section 4.3.2, ***4.3.4, and 4.3.4*** for rationale for addition of the CCI [redacted] CCI [redacted] ***and their potential intermediate dose cohorts*** CCI [redacted] ***) respectively.***
* For participants and investigators, the study will be observer-blind with regards to the study intervention, but open-label with regards to the dose level. For the sponsor, the study will be open-label. For the CCI [redacted] dose cohorts, the study will be single-blind. Refer to Section 6.3.5 for more information.
** In YAs, 6 participants are enrolled in the control group per dose level of the investigational study intervention, except for the CCI [redacted] dose ***cohorts***, where no control vaccine will be used.
*** Study intervention dose will be selected based on the safety/reactogenicity data obtained up to dose 3 in YAs. Refer to Section 4.3 for more information.
Note: Hereafter, name of the study groups for YAs will be only referred to as Flu mRNA dose 1-***11***. Details on the study intervention administered are shown in Table 5.

Section 4.2.1 Choice of active comparator

[…]

Note: The sample size of the available Control group (N=30) is similar to the sample size of each additional dose group to be tested (N=24). As such, we consider the available Control group sufficiently large for this phase 1 exploratory and descriptive study and will not use an active control for the additional CCI dose ***cohorts,*** where an assessment of immunogenicity is the main objective. However, for the additional CCI, and their potential intermediate dose cohorts (CCI), where a safety/reactogenicity assessment is the main objective, Flu D-QIV will be reintroduced as active control.

[…]

Section 4.2.2 Rationale for study blinding

[…]

For the CCI dose ***cohorts***, 2 different Flu mRNA doses are to be used, therefore the persons reconstituting the interventions will be aware of the dose of the allocated Flu mRNA vaccine. This requires unblinding the randomization system for this cohort and accordingly all users of the randomization system, including the investigator, will be unblinded and only the participant will remain blinded.

[…]

Section 4.3 Justification for dose

Six dose levels (CCI) and 1 dose level (up to CCI are planned to be evaluated in YAs and OAs, respectively, in this study. Depending on the outcomes of safety and reactogenicity evaluations, intermediate dose levels (YAs: CCI; OAs: CCI) may be used. Furthermore, 2 additional doses of CCI of the vaccine candidate will be evaluated in YAs under Protocol Amendment 3***, and 2 additional doses of*** CCI ***of the vaccine candidate will be evaluated in YAs under Protocol Amendment 5.*** Refer to Section 4.3.2, 4.3.4***, and 4.3.4*** for rationale for addition of the CCI, and CCI and their potential intermediate dose cohorts (CCI) respectively. The total number of dose levels will not exceed ***10 12*** in YAs and 1 in OAs.

Section 4.3.2 ***Justification for additional doses in YAs, evaluated in Amendment 5***

Available data from the CCI ***dose cohorts in this study show*** CCI ***. In this amendment, we will therefore further assess the immunogenicity of*** CCI ***dose levels in order to expand the therapeutic window of this monovalent H1 vaccine candidate in younger adults. Data from this amendment will be used to further characterize the mRNA platform, and may inform the dose selection for future mRNA-based vaccine candidates and/or vaccine combinations.***

[…]

Section 6.1. Study intervention(s) administered

Table 5 Study intervention(s) administered

Study intervention name:	**Flu mRNA vaccine**							
Study intervention formulation:	CCI [redacted]							
Presentation:	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)
Manufacturer:	GSK Biologicals	B BRAUN*** *	GSK Biologicals	B BRAUN*** *	GSK Biologicals	B BRAUN*** *	GSK Biologicals	B BRAUN*** *
Type:	Investigational							
Product category:	Biologic							
Route of administration:	IM							
Location	Deltoid							
• **Directionality**	Upper							
• **Laterality ****	Non-Dominant							
Number of doses to be administered:	1							
Volume to be administered by dose *:**	Refer to the Study Procedures Manual (SPM) for more details							
Packaging and labeling:	Refer to the SPM for more details							

Study intervention name:	**Flu mRNA vaccine**							
Study intervention formulation:	CCI [redacted]							
Presentation:	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)
Manufacturer:	GSK Biologicals	B BRAUN****	GSK Biologicals	B BRAUN****	GSK Biologicals	B BRAUN****	GSK Biologicals	B BRAUN****
Type:	Investigational							
Product category:	Biologic							
Route of administration:	IM							
• **Location**	Deltoid							
• **Directionality**	Upper							
• **Laterality ****	Non-Dominant							
Number of doses to be administered:	1							
Volume to be administered by dose *:**	Refer to the Study Procedures Manual (SPM) for more details							
Packaging and labeling:	Refer to the SPM for more details							

Study intervention name:	**Flu mRNA vaccine**							
	CCI [redacted]							
Study intervention formulation:								
Presentation:	***Concentrate for dispersion for injection (Vials)***	***Solution for dispersion for injection (Ampoule or other)***	***Concentrate for dispersion for injection (Vials)***	***Solution for dispersion for injection (Ampoule or other)***	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)
Manufacturer:	***GSK Biologicals***	***B BRAUN****	***GSK Biologicals***	***B BRAUN****	GSK Biologicals	B BRAUN***	GSK Biologicals	B BRAUN**
Type:	Investigational							
Product category:	Biologic							
Route of administration:	IM							
Location	Deltoid							
• **Directionality**	Upper							
• **Laterality** **	Non-Dominant							
Number of doses to be administered:	1							
Volume to be administered by dose *:**	Refer to the Study Procedures Manual (SPM) for more details							
Packaging and labeling:	Refer to the SPM for more details							

Study intervention name:	**Flu mRNA vaccine**					
Study intervention formulation:	CCI [redacted]					
Presentation:	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)	Concentrate for dispersion for injection (Vials)	Solution for dispersion for injection (Ampoule or other)
Manufacturer:	GSK Biologicals	B BRAUN****	GSK Biologicals	B BRAUN****	GSK Biologicals	B BRAUN****
Type:						
Product category:	Biologic					
Route of administration:	IM					
Location	Deltoid					
• **Directionality**	Upper					
• **Laterality ****	Non-Dominant					
Number of doses to be administered:	1					
Volume to be administered by dose *:**	Refer to the Study Procedures Manual (SPM) for more details					
Packaging and labeling:	Refer to the SPM for more details					

Study intervention name:	**FDQ21A-NH†**	**FDQ22A-NH‡**
Study intervention formulation:	A/Victoria/2570/2019 (H1N1), IVR-215 (15 µg HA); A/Tasmania/503/2020 (H3N2), IVR-221 (15 µg HA); B/Washington/02/2019 (15 µg HA); B/Phuket/3073/2013 (15 µg HA); Water for injections	A/Victoria/2570/2019 (H1N1), IVR-215 (15 µg HA); A/Darwin/06/2021 (H3N2), IVR-227 (15 µg HA); B/Austria/1359417/2021, BVR-26 (15 µg HA); B/Phuket/3073/2013 (15 µg HA); Water for injections
Presentation:	Suspension for injection (Syringe)	Suspension for injection (Syringe)
Manufacturer:	GSK Biologicals	GSK Biologicals
Type:	Active control	Active control
Product category:	Combination product	Combination product
Route of administration:	IM	IM
Location	Deltoid	Deltoid
• **Directionality**	Upper	Upper
• **Laterality ****	Non-Dominant	Non-Dominant
Number of doses to be administered:	1	1
Volume to be administered by dose *:**	Refer to the Study Procedures Manual (SPM) for more details	Refer to the Study Procedures Manual (SPM) for more details
Packaging and labeling:	Refer to the SPM for more details	Refer to the SPM for more details

IM: intramuscular; TBD: to be defined.
† FDQ21A-NH: Flu D-QIV (*Flu Dresden- Quadrivalent Influenza Vaccine*, GlaxoSmithKline; 2021-2022 NH ***for the*** CCI [redacted] ***dose cohorts)***.
‡FDQ22A-NH: Flu D-QIV (Flu Dresden- Quadrivalent Influenza Vaccine, GlaxoSmithKline; 2022-2023 NH for the CCI [redacted] ***, and their potential intermediate dose cohorts (***CCI [redacted]***).***
* Potential intermediate dose levels that may be evaluated, with the total number of dose levels not exceeding ***12*** in YAs and 1 in OAs.
** The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed.
*** Refer to the SPM for the volume after reconstitution.
**** Another manufacturer might be used depending on study site

[…]

Section 6.3.2 Randomization to study intervention

- Planned (approximate) number of participants to be enrolled is ~~***306***~~***354***:
  - ~~***258***~~***306*** YA participants (24 participants per dose level and a total number of ***42*** participants receiving the active control)
  - 48 OA participants (24 participants receiving a dose of investigational study intervention and 24 participants receiving the active control)
  - Due to the adaptive design, the actual number of participants enrolled might be lower or higher (up to ~~***336***~~***384*** participants in total) in case a ~~***10th***~~***-12th*** dose level is evaluated in YAs.

Planned number of participants to be enrolled for the CCI [redacted] dose cohort is 48 (24 participants per dose level). ***Planned number of participants to be enrolled for the*** CCI [redacted] ***dose cohort is 48 (24 participants per dose level).***

The randomization of supplies within blocks will be performed at GSK, using MATerial Excellence (MatEx), a program developed for use in Statistical Analysis System (SAS) (Cary, NC, US) by GSK. Entire blocks will be shipped to the study centers/warehouse(s). ***For the*** CCI [redacted] ***dose cohort, the active control arm will be blocked at randomization***. For the CCI [redacted] dose cohort, partial block sizes, not including active control, will be shipped.

To allow GSK to take advantage of greater rates of recruitment than anticipated at individual centers in this multi-center study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

[…]

Section 6.3.5. Blinding and unblinding

[…]

However, for the additional CCI [redacted] ***dose cohort and*** CCI [redacted] dose cohort, data will be collected in a single-blind manner. The investigator(s) and/or their staff are aware of the study intervention assignment, but the participant is not. The study intervention will be prepared and administered by qualified study personnel who can be aware of the intervention assignment.

[…]

Section 8.1.3. Immunological read-outs

Table 9 Immunological read-outs

Blood sampling timepoint		Subset name*	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-dose	All enrolled participants	~~***306***~~***354***	CCI [redacted]
		Participants in CCI subset	~~***123***~~***147***	
Visit 2 (Day 8)	Post-dose	Participants in CCI subset	~~***123***~~***147***	
Visit 3 (Day 22)	Post-dose	All enrolled participants	~~***306***~~***354***	
Visit 5 (Day 62)	Post-dose	All enrolled participants	~~***246***~~***294***	
		Participants in CCI subset	~~***123***~~***147***	
Visit 6 (Day 183)	Post-dose	All enrolled participants	~~***246***~~***294***	
		Participants in CCI subset	~~***123***~~***147***	

* Refer to Section 6.3.4 for subset description.
Ab: antibody; CCI [redacted].

[…]

Section 8.2.3.1.1. Staggered enrollment of YAs

[…]

- Note: No sentinel participants will be enrolled for the additional CCI [redacted] ***dose cohort, or*** CCI [redacted] dose cohort. The rationale for this is that all dose cohorts, ~~including the higher dose levels~~ CCI [redacted] ~~, and~~ ***upto*** CCI [redacted] have showed a CCI [redacted] (incidence of Grade 3 solicited AEs ranging from CCI [redacted] depending on dose group), and no safety signal has been observed. The CCI [redacted] ***, and*** CCI [redacted] dose ~~groups~~ cohorts will be enrolled in parallel.

[…]

P: participant; SRT: Safety Review Team. Dose 1-4 and dose 8 and 9: Flu mRNA dose 1-4 and 8 and 9. Potential intermediate dose levels may be evaluated with the total number of doses not exceeding ***12*** in YAs and 1 in OAs.

[…]

Section 9.4.1. Sequence of planned analyses

[…]

Additional interim analyses will be performed upon availability of all primary endpoints up to Day 29 for ***(i)*** all participants in the CCI [redacted] dose cohort***,(ii)*** all participants in the CCI [redacted] and their potential intermediate dose cohorts (CCI [redacted]). and ***(iii) all participants in the*** CCI [redacted] ***dose cohort***,

[…]

11. REFERENCES

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