CLINICAL TRIAL PROTOCOL

Immunogenicity after a prime dose and revaccination with adjuvanted RSVPreF3 vaccine in the most elderly and frail population – an open-labeled phase IIIb-trial

RSV Immunogenicity Study in the Elderly (RISE)

Trial ID:	RISE
EU Trial number:	2024-520141-23-01
Version number:	2.0
Date:	12-June-2025
Sponsor:	[redacted]
Sponsor representative:	[redacted]

Table of Contents

Revision history

Protocol version	Date of Issue	Summary of changes *Describe all changes since the first final protocol.*
V1.0	24-03-2025	
V2.0	12-06-2025	- Updated version number and EU clinical trial number - Updated pIMD list under section 18 - More defined primary endpoint (measurement) - Clear mentioning of GSK subcontracted laboratories

Signature page

Sponsor

I am responsible for ensuring that this protocol includes all essential information to be able to conduct this trial. I will submit the protocol and all other important trial-related information to the responsible investigator(s) so that they can conduct the trial correctly. I am aware that it is my responsibility to hold the staff members who work with this trial informed and trained.

Signature of sponsor's representative Date

Printed name

Principal Investigator

I have read this protocol and agree that it includes all essential information to be able to conduct the trial. By signing my name below, I agree to conduct the trial in compliance with this clinical trial protocol, the EU Regulation on clinical trials of medicinal products for human use (EU 536/2014), the Declaration of Helsinki, ICH-GCP (Good Clinical Practice) guidelines and the current national regulations governing the conduct of this clinical trial.

I will submit this protocol and all other important trial-related information to the staff members and investigators who participate in this trial, so that they can conduct the trial correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this trial informed and trained.

I am aware that quality control of this trial will be performed in the form of monitoring and eventual audit and inspection.

Principal Investigator's signature Date

Printed name

Contact information

Responsibility in the clinical trial	
Sponsor representative Responsibility: • Ensure adherence to Good Clinical Practices and EMA regulatory requirements • Monitor trial progress to ensure compliance with study protocols and local regulations	[redacted]
Principal Investigators	[redacted]
Karolinska Trial Alliance (internal non-profit facility for applications, CTIS submission and monitoring)	[redacted]

List of used acronyms and abbreviations

Abbreviation	**Term/Explanation**
AE	Adverse Event = Any untoward medical occurrence in a participant to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

SAE	Serious Adverse Event = Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death
AESI	Adverse Events of Special Interest
AR	Adverse Reaction = any unfavourable and unintended reaction to an investigational medicinal product, regardless of dose
ASR	Annual Safety Report = the annual safety report for reporting to authorities. In Sweden this is the Swedish Medical Products Agency via CTIS.
ATCC	American Type Culture Collection
BCR	B cell receptor
CA	Competent Authorities
CD	Cluster of Differentiation
CFS	Clinical Frailty Scale
CIOMS	Council for International Organizations of Medical Sciences
CMI	Cell-mediated immunity
CRF/eCRF	Case Report Form/electronic Case Report Form
CTIS	Clinical Trials Information System = Centralized EU database/portal for application and communication with authorities concerning clinical trials. In Sweden this includes the Swedish Medical Products Agency and the Swedish Ethical Review Authority.
CTR	EU Regulation 536/2014, also called CTR, Clinical Trials Regulation
DOPC	Dioleoyl phosphatidylcholine
DSUR	Development Safety Update Report = the standard which should be used for annual safety reporting to authorities
ELISA	Enzyme-linked immunosorbent assay

EMA	European Medicines Agency
EU/EEA	European Union/European Economic Area
FACS	Fluorescence-activated cell sorting
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMT	Geometric mean titer
GSK	GlaxoSmithKline Biologicals S.A.
GVHD	Graft-versus-host disease
[redacted]	[redacted]
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IgG	Immunoglobulin G
IL	Interleukin
ITT	Intention-to-treat = including all data from all participants who have participated in the trial
Läkemedelsverket	Swedish Medical Products Agency – the national authority responsible for regulation and surveillance of the development, manufacturing and sale of medicinal products.
LFF	Läkemedelsförsäkringen
LÖF	Landstingens Ömsesidiga Försäkringsbolag
LRTD	Lower Respiratory Tract Disease
mAb/Ab	Monoclonal antibody/Antibody
MGI	Mean geometric increase

Member State	European Union (EU) Member state where an application for authorisation of a clinical trial or of a substantial modification has been submitted.
MPL	3-O-desacyl-4'-monophosphoryl lipid A
mRNA/RNA	Messenger ribonucleic acid/ribonucleic acid
N/A	Not applicable
PBMC	Peripheral blood mononuclear cell
PI	Principal Investigator
pIMD	Potential immune-mediated disease = autoimmune diseases and other inflammatory and/or neurologic disorders which may or may not have an autoimmune etiology
postF	Postfusion
PP	Per Protocol analysis = including only data from participants who have completed the trial in accordance with the protocol, with no deviations from the protocol
preF	Prefusion
RSI	Reference safety information = A list of all known serious adverse reactions for the investigational medicinal product, including severity and frequency of the adverse reaction. The RSI is contained in the Summary of Product Characteristics or IB and is used to determine which adverse reactions should be reported as suspected unexpected serious adverse reactions (SUSARs).
RSV	Respiratory syncytial virus
RSVPreF3	Vaccine antigen; recombinant RSV glycoprotein F stabilized in pre-fusion conformation
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SPC or SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction = This is an event that is likely related to the investigational medicinal product but with unexpected occurrence. An adverse reaction is

	unexpected if its nature or seriousness is not consistent with the information on the product in the RSI.
Tfh	T follicular helper cell
TMB	3,3 ,5,5 -Tetramethylbenzidine
TNF	Tumor necrosis factor
US	United States
USM	Urgent Safety Measures
VE	Vaccine efficacy

1. Synopsis

EU Trial number:	2024-520141-23-01
Title:	Immunogenicity after a prime dose and revaccination with adjuvanted RSVPreF3 vaccine in the most elderly and frail population – an open-labeled phase IIIb trial RSV Immunogenicity Study in the Elderly (RISE)
Trial ID:	RISE
Short background/ Rationale/Aim:	Respiratory syncytial virus (RSV) is a common cause of respiratory tract infections leading to hospitalizations in infants and in elderly. Arexvy is an approved vaccine indicated for the prevention of RSV infections in older adults, however, there is yet limited information on the vaccine's efficacy in individuals ≥80 years old. This study aims to investigate potential differences in the immune responses induced upon vaccination with Arexvy between individuals above 80 years of age and adults 60-65 years old.
Primary objective:	To describe the induction of neutralizing antibodies against RSV A and B following the first dose of Arexvy in older adults aged 80 years and older and those aged 60 to 65 years.
Secondary objectives:	To evaluate the reactogenicity of Arexvy by recording the occurrence of solicited adverse events (AEs) in the study participants. To evaluate the safety of Arexvy in terms of the incidence of unsolicited AEs, SAEs/pIMDs and fatal SAEs.
Primary endpoint:	To assess the neutralizing antibody geometric mean titers (GMTs) against RSV A and B one month after the prime dose (day 31) of Arexvy in study participants aged 60-65 years and ≥80 years old, measured by a neutralization assay. Mean geometric increase (MGI), geometric increase (MGI) between day 0 and day 31 after prime will be calculated (equal to the geometric mean of the individual ratio). A more detailed description can be found in section 10.2.1.

Secondary endpoints:	Occurrence, intensity and duration of solicited AEs in the study participants at the administration site and solicited systemic AEs with an onset during the 4-day follow-up period after each vaccination. Incidence of unsolicited AEs in the study participants with an onset during the 30-day follow-up period after each vaccination. Incidence of SAEs or pIMDs in the study participants from the day of vaccination until 6 months. Occurrence of any fatal SAEs from day 1 up to study end.

Trial design:	Open-label phase IIIb trial where study participants will be vaccinated at study start and revaccinated 12 months after the first dose. The study period is 18 months.
Trial population:	Adults 60-65 years old and ≥80 years old.
Number of participants:	30 adults in the 60-65 years age group and 35-40 adults in the ≥80 years age group.
Inclusion criteria:	Male or female individuals who were born between 1965 and 1960 or 1945 and before, who live in the community or in a long-term care facility. Individuals who can understand and read Swedish. Individuals who can provide written consent and agree (by written consent) to receive the Arexvy vaccine. Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol. Participants who are medically stable in the opinion of the investigator at the time of first vaccination. Participants with chronic stable medical conditions with or without specific treatment, such as diabetes, hypertension or cardiac disease, are allowed to participate if considered by the investigator as medically stable.
Exclusion criteria:	Individuals who are medically immunocompromised, less than 2 years since hematopoietic stem cell transplantation (HSCT) or graft-versus-host disease (GVHD), solid-organ transplanted, using immunosuppressive drugs for treatment of cancer and who have inflammatory mediated or autoimmune conditions, as judged by the Investigator. Individuals who have already received an RSV vaccine dose at any time in the past. Any known or suspected reaction, hypersensitivity or allergies to be exacerbated by any product or component included in the vaccine and trial. Mental inability, reluctance or language difficulties that result in difficulty understanding the meaning of participation in the trial. Treatment or disease which, according to the

	investigator, can affect treatment or trial results. Any of the following medical conditions: - Unstable chronic illness - Recurrent or un-controlled neurological disorders or seizures - Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study - Any other medical condition that in the judgment of the investigator would make intramuscular injection unsafe - Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study - Any history of dementia or any medical condition that moderately or severely impairs cognition and understanding of the informed consent form and/or study procedures - History of chronic alcohol consumption and/or drug abuse as deemed by the investigator to render the potential participant unable/unlikely to provide accurate safety reports or comply with study procedures. [redacted] Planned move during the study period that will prohibit participating in the study until study end. Participation of any study personnel or their immediate dependents, family or household members as well as any family relations to Sponsor or PI. Co-administration of other vaccines less than 14 days before or after study vaccination. A period of less than 30 days before or after study vaccination applies in the case of Shingrix.
Intervention:	Study participants will be vaccinated at study start and revaccinated 12 months after. The study period is approximately 18 months per study participant, during which 10 blood draws are planned.
Investigational medicinal product(s),	Adjuvanted RSVPreF3 vaccine (trade name Arexvy, manufactured by GSK). Arexvy is a sterile injectable suspension for intramuscular use (0.5 mL) containing

dosage, administration:	120 µg of recombinant RSVPreF3 adjuvanted with AS01$_E$.
Ethical considerations, benefit/risk:	All study participants (60-65 years old and ≥80 years old) will be given Arexvy, an approved vaccine specifically indicated for preventing severe respiratory tract disease in this population. Arexvy has demonstrated a high protective efficacy, and an acceptable reactogenicity and safety profile. The overall benefit/risk balance is positive.
Planned duration of the trial:	Q3 2025 – Q2 2027

2. Background and rationale

Respiratory syncytial virus (RSV) is the primary cause of respiratory tract infections leading to hospitalizations in infants and in elderly (1,2). The two viral surface glycoproteins F and G are crucial for fusion and attachment to the respiratory cells. The F protein is the main target of neutralizing antibodies and hence pivotal for vaccine development (3). The infection spreads from contaminated nasal secretions via large droplets transferred via close human contact and contaminated surfaces. There is no lasting immunity after an RSV infection and the substantial burden of disease caused by RSV, in both infants as well as older adults, especially over the age of 75 or with certain underlying diseases, is well established and pose a large burden on the health care system (4).

Progress towards RSV vaccines has been slow despite more than half a century of efforts and an enormous global need. One major challenge in vaccine development is the specificity, breadth, and longevity of antibody (Ab) responses needed for protection. Two vaccines were approved in 2023 and one in 2024 for use in both Europe and the United States (US) for the prevention of lower respiratory tract disease (LRTD) in individuals 60 years of age and older, as well as adults aged 50 to 59 years of age who are at increased risk for RSV disease (5–8).

Arexvy (developed and manufactured by GSK) is an adjuvanted RSV vaccine based on RSV's F protein stabilized in its prefusion conformation (8). The AS01$_E$-adjuvanted vaccine formulation was selected for Arexvy based on data from prior clinical studies (9). One dose of Arexvy was recently shown to be efficacious against LRTD over three RSV seasons in ≥60-year-olds. Revaccination one year after the first dose did not however appear to provide additional efficacy benefit (10,11). The vaccine has an acceptable reactogenicity and safety profile. So far, in the still ongoing large clinical trials there has been a limited number of individuals in the age group 80 years and older, as well as frail individuals, to conclude on the vaccine efficacy (VE) in this subgroup. Although there is some data available (12), we still lack substantial knowledge about the vaccine's immunogenicity in a population that is markedly affected by severe RSV infections.

For several years, our group has studied in detail the responses to immunization with the prototype RSV vaccine antigen preF (DS-Cav1) in non-human primates. We have established methods to dissect antibody specificities and affinity, including neutralization to live RSV [redacted] (13,14). Additionally, we have a long-standing interest in studying mechanisms of action of vaccine adjuvants, since innate immune responses early after vaccination are critical for the subsequent adaptive responses. We therefore have developed expertise in methods to explore the immune activation induced by the AS01$_E$ adjuvant included in Arexvy. [redacted] (15–17). [redacted]

3. Benefit-risk evaluation

Expected therapeutic benefits to the individuals participating in the study

Arexvy is a vaccine already approved by the regulatory authorities in the US (Food and Drug Administration [FDA]) and Europe (European Medicines Agency [EMA]). Arexvy is indicated for adults ≥60 years of age, and recently also for adults 50-59 years old with underlying conditions increasing the risk for severe disease upon RSV infection (8). In Sweden, RSV vaccination is recommended by the Public Health Agency (Folkhälsomyndigheten) since September 2023 to individuals ≥75 years of age and to the younger age group >60 years with increased risk of severe RSV-infection. The vaccination coverage is assumed to be overall low in these high-risk groups, although there is no vaccination registration done to confirm this. All participants in this study (grouped in 60-65 years or ≥80 years age groups) will be offered Arexvy. In previous clinical studies the vaccine showed high protective efficacy. RSV vaccination is especially relevant for the older age group, given that the vaccine is recommended for them by national authorities and since additional knowledge about vaccine immunogenicity in the older group would be beneficial for future recommendations to this population.

Expected risks and inconvenience to the individuals participating in the study

The most commonly reported adverse reactions (ARs) with Arexvy (≥10%) in individuals 60 years of age and older are injection site pain (60.9%), fatigue (33.6%), myalgia (28.9%), headache (27.2%) and arthralgia (18.1%) (8). The local adverse reactions reported with Arexvy had a median duration of 2 days, while the systemic adverse reactions had a median duration ranging between 1 and 2 days. Based on currently available information, Arexvy shows an acceptable reactogenicity and safety profile (8).

Concerning the interventions of the study, they consist of blood-sampling at 10 different time points during a period of 13 months. Blood-sampling can cause a short-lived pain but is a standardized procedure of the routine healthcare, with no significant risks to the study participants given appropriate handling performed by adequately educated staff.

To summarize, the expected risk-benefit balance for the study-participants, who will be offered an already approved and recommended vaccine, is positive. To mitigate potential risks for adverse events, the participating sites have experienced PI and study staff, as well as Standard Operating Procedures (SOP) to ensure safe study procedures. Details about how adverse events will be reported and registered throughout the study are described in section 9.3.

4. Trial objectives

4.1. Primary objective

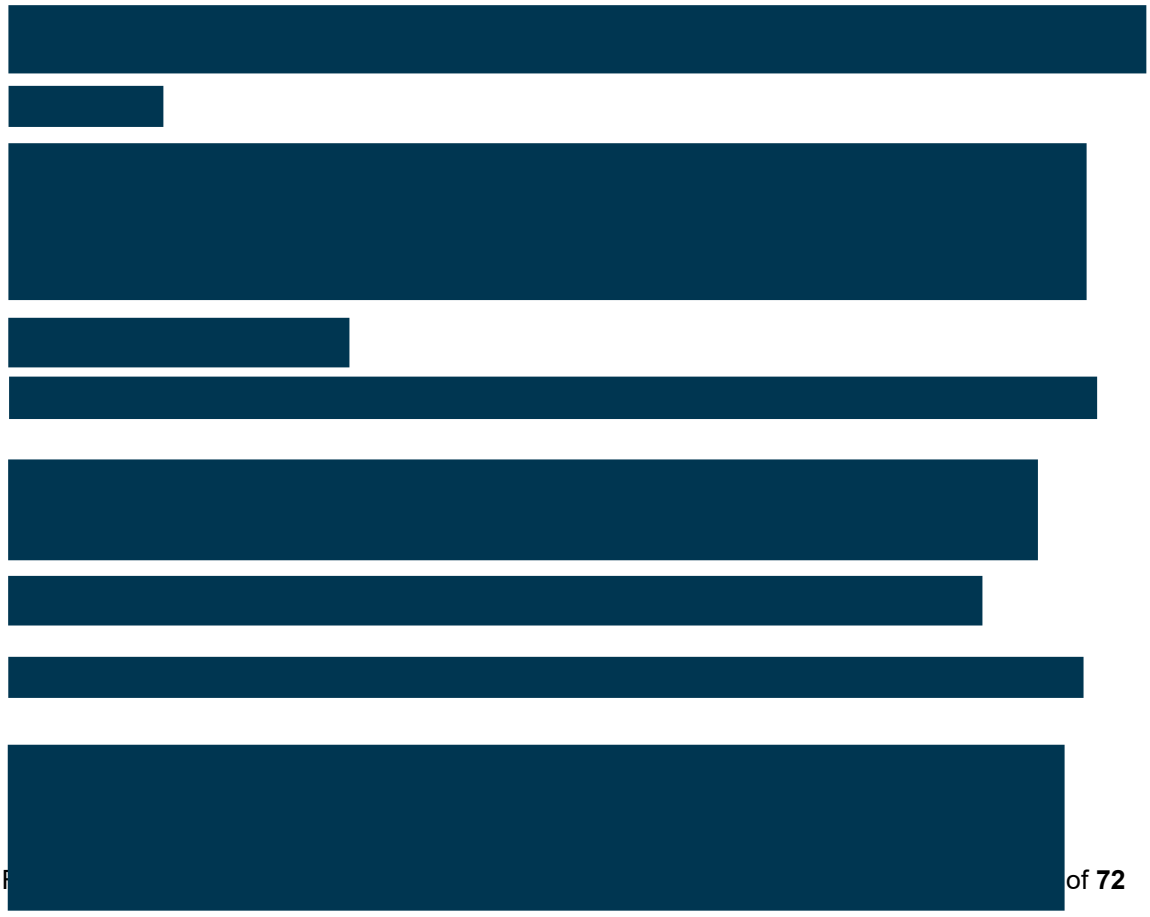
The primary objective of this study is to describe the induction of neutralizing antibodies following a first dose of Arexvy in older adults aged 80 years and older and those aged 60 to 65 years. We will descriptively compare the neutralizing antibody titers against RSV A and B one month (day 31) after a first dose in both groups.

4.2. Secondary objective(s)

The secondary objectives of this trial are to:

- evaluate the reactogenicity of Arexvy by recording the occurrence of solicited adverse events (AEs) in the study participants during the 4-day follow-up period after each vaccination. Exact endpoints are described in section 4.5, while detailed information on recording AEs is described in section 9.2.
- To evaluate the safety of Arexvy in terms of the incidence of unsolicited AEs, SAEs/pIMDs and fatal SAEs. Exact endpoints are described in section 4.5, while detailed methods to record any unsolicited AEs, SAE/pIMDs are described in section 9.2. The definition of SAEs and pIMDs are included in this study protocol in section 9.2.

4.3. Exploratory objective(s)



[redacted]

4.4. Primary endpoint

To assess the neutralizing antibody geometric mean titers (GMTs) against RSV A and B one month after the prime dose (day 31) of Arexvy in study participants aged 60-65 years and ≥80 years old, measured by a neutralization assay. Mean geometric increase (MGI), geometric increase (MGI) between day 0 and day 31 after prime will be calculated (equal to the geometric mean of the individual ratio). A more detailed description can be found in section 10.2.1.

4.5. Secondary endpoint(s)

The secondary endpoints are:

- Occurrence, intensity and duration of solicited AEs in the study participants at the administration site and solicited systemic AEs with an onset during the 4-day follow-up period after each vaccination (i.e., the day of vaccination and 3 subsequent days).

- Occurrence of unsolicited AEs in the study participants with an onset during the 30-day follow-up period after each vaccination (i.e., the day of vaccination and 29 subsequent days).
- Occurrence of SAEs in the study participants from the day of vaccination until 6 months. However, certain conditions will be excluded from this monitoring, to ensure that reporting is focused on relevant safety issues. The decision for this is based on the overall higher prevalence of certain conditions in the older age group. This includes but is not limited to falls, fractures, and the onset of tumors. A list of events that can be excluded is explicitly defined in the study protocol (see section 9.3.2). Such events are considered expected in an older patient population (>80 years). These do not need to be reported as SAEs unless there is an indication of a relationship with the investigational drug.
- Occurrence of pIMDs in the study participants from the day of vaccination until 6 months. A list of possible conditions that could qualify as pIMDs is added in section 18.
- Occurrence of any fatal SAEs in the study participants from Day 1 up to study end.

4.6. Exploratory endpoint(s)

[redacted]

[redacted]

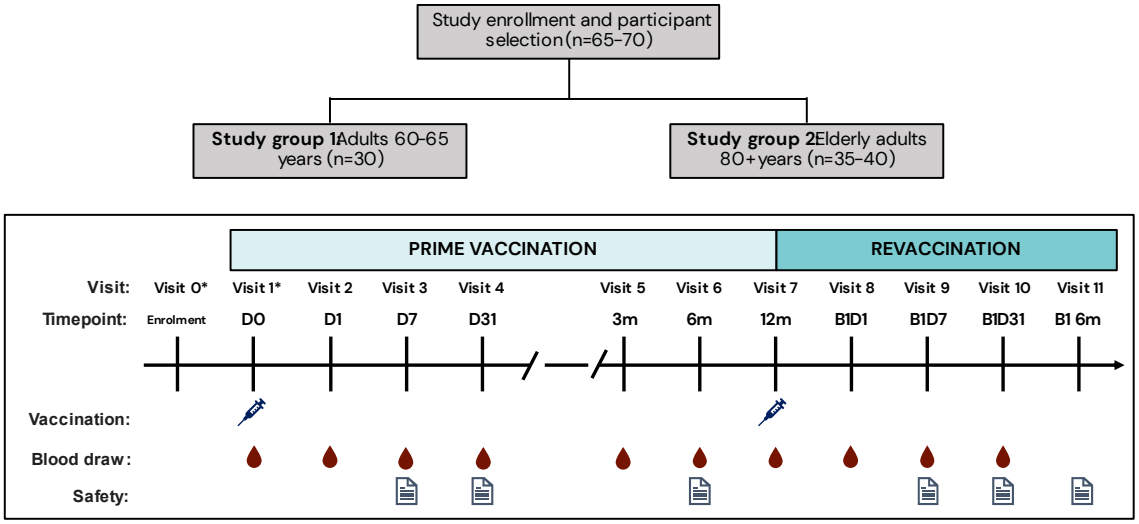
5. Trial design and procedure

5.1. Overall trial design

This is a phase IIIb open-label post-marketing clinical trial using an already approved vaccine in the targeted population group. The design will generate immu[redacted] and maintenance of RSV vaccine-induced immunity in the oldest vaccine recipients. The study includes a prime vaccination and revaccination after one year. [redacted] The study period is approximately 18 months per study participant. After screening and Informed Consent procedure, 10 visits are planned where one prime dose of vaccine Arexvy (GSK) 0.5 mL i.m is given at the first visit (V1) and a revaccination at the 12-month timepoint (V7). The design and scheduled activities are shown in Figure

1 and Table 1.

Figure 1 Trial design



D = day; m = month; w = weeks; B1 = revaccination

5.2. Procedures and flow chart

Table 1 summarizes the general procedures and visits at which they will be carried out.

Table 1 Visit schedule and planned activities

Procedure	*Inclusion/ exclusion criteria*	*Informed consent*	*Medical history/ concomitant medications*	*Targeted physical examination°*	*Vital signs‡*	*Blood draw*	*Adverse Events*	*Vaccine*
V0*	√	√	√	√				
V1(D0) (up to +10 days to V0)					√	√	√ (D0 of diary)§	√
V2 (D1)						√		
V3 (D7) (+/- 1 day)						√	√ (collect diary)§	
V4 (D31) (+/- 3 days)						√	√	
V5 (3m)						√		

(+/- 14 days)								
V6 (6m) (+/- 14 days)						√	√	
V7† (12m) (B1) (+/- 14 days)			√	√	√	√	√ (D0 of diary) §	√
V8 (B1D1)						√		
V9 (B1D7) (+/- 1 day)						√	√ (collect diary) §	
V10 (B1D31) (+/- 3 days)						√	√	
V11 (B1 6 m) (+/- 14 days)							√	

V = Visit; D = day; m = month; w = weeks; B1 = revaccination

**V0 is the baseline visit: can be done at the same time as Visit 1(V1). Visit 1 will be the date of prime vaccination and start of the safety monitoring activity. V1 can be delayed to V0 for up to 10 days.*

°Targeted physical examination includes determination of frailty status of the patient, body weight and body height.

†*Visit 7 will be the date of the revaccination (B1) with sampling prior to vaccination (12-month prime vaccination timepoint).*

‡*Vital signs that will be obtained include blood pressure, pulse and body temperature.*

§*Diaries will be given to the study participants upon vaccination (V1 and V7) to note down any solicited AEs (local and systemic) for the 4-day follow-up period and will be recollected at the next study visit (V2 and V8)*

For the trial, different medical parameters and vital signs will be measured at V0/V1 and V7. Medical history and concomitant medications will be noted to get an overview of the prevalence for certain co-morbidities. Targeted physical examination will include determination of a frailty index (using the Clinical Frailty Scale [CFS]), measurement of the body weight and the body height. Vital signs include blood pressure, pulse and body temperature.

Table 2 Immunological read-outs at the different study visits

Type of contact and time point	Sampling time point	No. of samples (Total)	Component	Priority rank
Prime vaccination				
Visit 1 (D0)	Pre-Dose 1	~65-70	RSV A neutralizing titers	1
			RSV B neutralizing titers	2
			RSVPreF3-specific IgG antibody	3
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]

			[redacted]	[redacted]
Visit 2 (D1)	Post Dose 1	~65-70	[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
Visit 3 (D7)	Post Dose 1	~65-70	[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			RSV A neutralizing titers	4
			RSV B neutralizing titers	5
			RSVPreF3-specific IgG antibody	6
			[redacted]	[redacted]
Visit 4 (D31)	Post Dose 1	~65-70	[redacted]ntibodies	1
			RSV B neutralizing antibodies	2
			RSVPreF3-specific IgG antibody	3
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	
Visit 5 (3m)	Post Dose 1	~65-70	RSV A neutralizing antibodies	1
			RSV B neutralizing antibodies	2
			RSVPreF3-specific IgG antibody	3
Visit 6 (6m)	Post Dose 1	~65-70	RSV A neutralizing antibodies	1
			RSV B neutralizing antibodies	2
			RSVPreF3-specific IgG antibody	3

Revaccination				
Visit 7 (12m)	Pre-Dose 2	~65-70	RSV A neutralizing antibodies	1
			RSV B neutralizing antibodies	2
			RSVPreF3-specific IgG antibody	3
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
Visit 8 (B1D1)	Post Dose 2	~65-70	[redacted]	[redacted]
			[redacted]	[redacted]

			[redacted]	[redacted]
Visit 9 (B1D7)	Post Dose 2	~65-70	[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			RSV A neutralizing antibodies	4
			RSV B neutralizing antibodies	5
			RSVPreF3-specific IgG antibody	6
			[redacted]	[redacted]
Visit 10 (B1D31)	Post Dose 2	~65-70	RSV A neutralizing antibodies	1
			RSV B neutralizing antibodies	2
			RSVPreF3-specific IgG antibody	3
			[redacted]	[redacted]
			[redacted]	[redacted]

*Baseline measurement

In case of insufficient blood sample volume to perform all assays, the samples will be analyzed according to the priority ranking provided in Table 2.

5.3. Biological sampling procedures

5.3.1. Handling, storage, and destruction of biological samples

Detailed sampling and handling procedures are described in a separate document. Collected biological samples will be used for protocol-mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. Future findings may make it desirable to use the samples acquired in this study for future research not described in this protocol. Therefore, all participants will be asked to give a specific consent to allow the sponsor or a contracted partner to use the samples for future research. Sample testing will be done in accordance with the recorded consent of the individual participant.

Throughout the trial 10 blood draws per participant are planned. Blood samples

(15-40 mL) will be collected at each time point (day 0, day 1, day 7, day 31, month 3, month 6, and month 12 after prime as well as day 1, day 7, and day 31 after revaccination) by venipuncture at the authorized clinical trial site. For PBMC isolation up to 4 EDTA tubes (or similar) of 8 mL will be drawn at each timepoint. In addition, one serum tube with a volume of 5 ml will be drawn.

[redacted] A full overview of all samplings including volumes, types of samples and planned assays will be made available as an annex to this study protocol.

The sampling will be carried out by trained and experienced personnel and in a specific sampling order. Samples will be labelled accordingly and transported to the principal investigator. SOPs for sampling and handling are in place and clearly communicated prior to study start. SOPs for sample processing and storage will be prepared and used throughout the trial.

Serum and plasma samples will be used for enzyme-linked immunosorbent assay (ELISA)-based measurements of antibody titers against different pathogens. Appropriate methods are in place at the laboratory of the principal investigator. Approved and accredited methods from external laboratories might be used for validation.

Measurements of neutralizing titers against RSV A and RSV B as well as serum levels of RSV preF3-specific IgG will be performed by GSK using validated methods. In addition, neutralization assays established in the laboratory of the principal investigator can be used for measurements of neutralizing antibody titers against other respiratory viruses.

[redacted]

[redacted]

[redacted]

[redacted]

5.3.2. Total volume of blood per participant

A total of 10 blood draws per participant is planned for this clinical trial over the course of 13 months. Per timepoint a maximum volume of 40 mL blood will be taken. A blood sample will be taken from all participants at each visit. The overall volume of blood that will be collected during the entire study period is ~308 mL (4x ~40 mL, 2x ~37 mL, 2x 21 mL, 2x ~16 mL).

Table 3 Overview of blood draws and planned volumes

	Prime						Revaccination			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Time	**D0**	**D1**	**D7**	**D31**	**3m**	**6m**	**12m**	**B1D1**	**B1D7**	**B1D31**
Blood	32 mL	8 mL	32 mL	32 mL	16 mL	16 mL	32 mL	8 mL	32 mL	32 mL
Serum	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**40 mL**	**16 mL**	**40 mL**	**37 mL**	**21 mL**	**21 mL**	**40 mL**	**16 mL**	**40 mL**	**37 mL**

5.3.3. Laboratory assays

Laboratory assays are summarized in Table 4. Please refer to section 8.1. for a brief description of the laboratory assays summarized here and performed in this study.

Table 4 Laboratory assays planned in this study

Test Classification	System	Component	Challenge	Method	Laboratory[1]
Humoral immunity	Serum	RSV-A and RSV-B	N/A	Neutralization assay	GSK*
	Serum	Total IgG	PreF3	ELISA	GSK*
[redacted]					

CMI = Cell-mediated immunity; GSK = GlaxoSmithKline Biologicals S.A.; ICS = Intracellular cytokine staining; N/A = Not applicable; PBMC = Peripheral blood mononuclear cell; PreF = prefusion protein; RSV = Respiratory syncytial virus.
*Certain analyses will be carried out by subcontractors employed by GSK.
A list of (clinical) laboratories used for sample analysis are provided in a separate document accompanying this study protocol, including address and information on analyses carried out by them.

Additional exploratory testing on collected samples might be done to gain a better understanding of the vaccine, of the clinical study data and/or of the disease or other diseases, to inform the development of other investigational products or to support development of vaccine-related assays, should such assay(s) become available at Karolinska Institute's laboratory, or a laboratory designated by Karolinska Institute. These assay(s) may not be represented in the objectives/endpoints of the protocol and will be described in ancillary study protocol(s), as needed. 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 but laboratory-independent Quality Department. Certain assays will be carried out by subcontractors outside of the European Union that have been selected by GSK. The Informed Consent Form states that samples will be sent to collaboration partners outside the EU or EEC.

GSK will be responsible for providing certain assay components including proteins such as RSVPreF3 for different assays including but not limited to antigen-specific cell probing and ELISA.

5.3.4. Biobank

All samples taken in this trial, covered by the Biobank Act, are registered in a biobank and handled according to the current national laws and regulations. The samples are coded to protect the participant´s identity. All samples and the identification/code list are stored securely and separately to prevent access by unauthorized persons.

5.4. Start, end, temporary halt and early termination

5.4.1. Start of the clinical trial

The start of the trial is defined as the start of screening activities. Sponsor will report the start of the trial in Sweden through notification in the Clinical Trial Information System (CTIS) within 15 days.

5.4.2. Temporary halt or early termination

The trial may be prematurely terminated for safety reasons affecting the risk-benefit balance or if the recruitment of participants cannot be completed within reasonable time. Decisions on premature termination are taken by the sponsor. The Competent Authorities (CA) should be informed as soon as possible via

CTIS, but no later than 15 days after trial suspension.
If the trial is prematurely terminated or suspended, the investigator should immediately inform the participants and ensure appropriate treatment and follow-up.

5.4.3. End of the clinical trial

The trial ends when the last participant has completed the last follow-up including the safety follow-up visit six months after revaccination.

6. Participant selection

Participants in the study will be enrolled as part of one of two age categories (60-65 years, and equal or older than 80 years). The goal is to have a similar ratio between male and female participants in both subgroups. Participants from both community dwelling and long-term care facilities will be enrolled in the study. Study participants will be enrolled at two different sites. The younger age group (60-65 years) representing community dwelling individuals will be enrolled at Studieenheten Akademiskt Specialistcentrum, Region Stockholm. Participants in the older age group (80 years and above) will be enrolled from long-term care facilities at Familjeläkarnas Särskilda boenden (SÄBO).

Adherence to the inclusion criteria as specified in the protocol is essential. Inclusion criteria deviations are not allowed because they can jeopardize the scientific integrity or regulatory acceptability of the study or participant safety. All participants must satisfy all of the following criteria at study entry:

- Male or female individuals who were born between 1965 and 1960 or 1945 and before, who live in the community or in a long-term care facility.
- Individuals who can understand and read Swedish.

- Individuals who can provide written consent and agree (by written consent) to receive the RSV vaccine.
- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol.
- Participants who are medically stable in the opinion of the investigator at the time of first vaccination. Participants with chronic stable medical conditions with or without specific treatment, such as diabetes, hypertension or cardiac disease, are allowed to participate in this study if considered by the investigator as medically stable.

6.1. Exclusion criteria

Adherence to criteria specified in the protocol is essential. Exclusion criteria deviations are not allowed because they can potentially jeopardize the scientific integrity or regulatory acceptability of the study or safety of the participant. The following criteria should be checked at the time of study entry.

Potential participants must not be included in this trial if any of the following exclusion criteria applies:

- Individuals who are medically immunocompromised (definition of medications as separate list), less than 2 years since hematopoietic stem cell transplantation (HSCT) or graft-versus-host disease (GVHD), solid-organ transplanted, other immunosuppressive drugs for treatment of cancer and inflammatory mediated or autoimmune conditions e.g. TNF-inhibitors, anti-CD20 drugs, IL-inhibitors, methotrexate, cytostatics etc., as judged by the investigator.
- Individuals who have already received an RSV vaccine dose at any time in the past.
- Any known or suspected reaction, hypersensitivity or allergies to be exacerbated by any product or component included in the vaccine and

trial.

- Mental inability, reluctance or language difficulties that result in difficulty understanding the meaning of participation in the trial.
- Treatment or disease which, according to the investigator, can affect treatment or trial results. However, if a participant begins a treatment during the study that could affect the immune system, they will not be discontinued from the study. In such cases, the details of the treatment will be documented appropriately. The participant will be followed for safety until the end of the safety follow-up period. If the participants continue the study, they will also receive the revaccination at one year.
- Any of the following medical conditions:
    - Unstable chronic illness
    - Recurrent or un-controlled neurological disorders or seizures.
    - Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study.
    - Any other medical condition that in the judgment of the investigator would make intramuscular injection unsafe
    - Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.
    - Any history of dementia or any medical condition that moderately or severely impairs cognition and understanding of the informed consent form and/or study procedures.
    - History of chronic alcohol consumption and/or drug abuse as deemed by the investigator to render the potential participant unable/unlikely to provide accurate safety reports or comply with study procedures.
- [redacted]
- Planned move during the study period that will prohibit participating in the

study until study end.

- Participation of any study personnel or their immediate dependents, family or household members as well as any family relations to sponsor or PI.
- Co-administration of other vaccines less than 14 days before or after study vaccination. A period of less than 30 days before or after study vaccination applies in the case of Shingrix.

6.2. Screening and inclusion

Participant eligibility (that participants fulfil all inclusion criteria and do not meet any exclusion criteria) is established at baseline visit before visit 1, or if these two visits are at the same time, before deciding to give the first dose of the study vaccine.

Study vaccine administration may be postponed within the permitted timeframe for each study vaccination if a possible candidate cannot receive the vaccine at the baseline visit. Vaccination can be delayed for 10 days in case of:

- Acute disease and/or fever at the time of vaccination. Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route. The route for measuring temperature can be oral, axillary or tympanic.

Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be vaccinated at the discretion of the investigator.

6.3. Withdrawal criteria

Participants can discontinue their participation in the trial at any time without any consequence to his/her continued treatment. The investigator/sponsor can at any time terminate the trial for a participant due to, e.g., unacceptable AEs/ARs or because the participant does not follow the procedures in the clinical trial protocol.

If a participant prematurely discontinues the trial, a safety follow-up visit will be performed (at 6 months following prime vaccination or revaccination). If the participant does not want to attend the follow-up visit or if it is not possible to establish contact, this will be recorded.

No replacement of discontinued participants will be done. Data from participants who discontinue the trial prematurely can be included in the analysis, provided the participant has given consent for such use.

7. Trial treatments

7.1. Description of investigational medicinal product(s)

Arexvy (manufactured by GSK) is a sterile injectable suspension for intramuscular use (8). The vaccine comes as a vial of lyophilized recombinant RSV glycoprotein F stabilized in pre-fusion conformation (RSVPreF3) as the antigen component, which must be reconstituted at the time of use with the accompanying vial of $AS01_E$ as the adjuvant suspension component. $AS01_E$ is composed of 3-*O*-desacyl-4'-monophosphoryl lipid A [MPL] from *Salmonella minnesota* and QS-21, a saponin purified from plant extract *Quillaja saponaria* Molina, combined in a liposomal formulation. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol in a phosphate-buffered saline solution containing disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride and water for injection. Each dose also contains trehalose, dipotassium phosphate and polysorbate 80 as formulation excipients.

7.1.1. Dose and administration

Two doses of the EMA-approved study vaccine (Arexvy, 0.5mL, intramuscular) will be administered 12 months apart. Vaccine preparation and administration will be done by authorized medical personnel who will not participate in any of the study clinical evaluation assays. Vaccination will be performed under medical

supervision.

7.1.2. Packaging, labelling, and handling of investigational medicinal product(s)

Arexvy is procured via a medicinal product vendor and therefore labelled and packaged as commercially available. The integrity of the cold chain for vaccine storage will be maintained through temperature logs during transportation and continuous monitoring of refrigerators used for vaccine storage. Site staff will be trained in proper procedures for vaccine handling, including the safe disposal of vaccines when necessary.

7.1.3. Drug Accountability and treatment compliance

The clinical sites will maintain an inventory log to track the receipt, storage and use of the vaccines. The lot number, expiration date and condition of the vials upon arrival will be documented.

7.1.4. Randomisation

This is an open label study, and no randomisation will be performed. Participants are included, and allocated to the respective age group, consecutively as they are found to be eligible for inclusion in the trial. If a participant discontinues their participation, the participant's trial-specific code will not be reused, and the participant will not be allowed to re-enter the trial again. In this trial, no replacement will be recruited for any participant that discontinues their participation in the trial.

7.1.5. Blinding

This is an open trial, however each participant who consents to participate in the study will be assigned a unique identification number. This number will be used

to label all study-related data and biological samples to ensure confidentiality. Laboratory testing in this trial will be partially blinded. For laboratory tests carried out by GSK laboratories, data will be collected in an observer-blind manner, only the sample ID and date of the sampling will be made available. The laboratory in charge of the sample testing will be blinded to the intervention assignment. Codes will be used to link the participant and study (without any link to the intervention attributed to the participant) to each sample.

The sponsor's lab personnel will be aware of the specific site in which a sample was obtained and thereby also have knowledge about the respective allocation in an age group.

7.1.6. Code breaking

Not applicable.

7.1.7. Destruction

If needed, destruction of vaccine doses will follow standard practice at each trial site. The number of vials and their lot numbers will be documented.

7.2. Auxiliary medicinal products

Not applicable.

7.2.1. Dose and administration

Not applicable.

7.2.2. Drug accountability and treatment compliance

Not applicable.

7.3. Concomitant use of other medicinal products and treatments

Medications considered necessary for the safety and well-being of the participant may be provided at the discretion of the investigators, unless otherwise specified in the exclusion criteria. Concomitant medication should be recorded in the Case Report Form (CRF).

7.4. Treatment after trial end

Not applicable.

8. Methods for measurement of endpoints for clinical efficacy and safety

8.1. Methods for measurement of endpoints for clinical efficacy

An overview of all planned laboratory assays can be found in section 5.3.3. (Table 4).

8.1.1. Methods for the primary endpoint

The primary endpoint of this trial is defined as the descriptive analysis of the differences in RSV A and B neutralizing antibodies at D31 after prime vaccination in the two age groups enrolled in this study. The primary endpoint will be measured in serum by an established neutralization assay. The assays will be performed at accredited laboratories of GSK. The analysis will be performed after the collection of all D31 samples. A short description of the method can be found in section 16.

8.1.2. Methods for the exploratory endpoints

[redacted]

8.2. Methods for measurement of endpoints for clinical safety

To assess reactogenicity of the vaccine, all solicited AEs will be recorded over the 4-day follow-up period after each vaccination. The AEs will be reported by the study participants on standardized diary cards and information will be collected by the respective study personnel. Solicited AEs include:

- Injection site pain
- Injection site erythema
- Injection site swelling
- Fever (similar definition as described in section 6.2.)
- Headache
- Fatigue
- Myalgia
- Arthralgia

Grading of intensity of solicited AEs will follow the description in section 18.2.

To assess safety, all unsolicited AEs with an onset during the 30-day follow-up period after each vaccination (i.e., the day of vaccination and 29 subsequent days) will be recorded.

To assess safety, any SAEs or pIMD will be recorded from the day of vaccination until up to 6 months after vaccination.

Fatalities will be recorded throughout the whole study period.

9. Handling Adverse Events

9.1. Definitions

9.1.1. Adverse Event (AE)

Any untoward medical occurrence in a participant to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

9.1.2. Adverse Reaction (AR)

The phrase “reaction” to a medicinal product means that the causal relationship between the medical product and an adverse event is at least a reasonable possibility, that is the relationship cannot be ruled out.

9.1.3. Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

Medical and scientific assessment will be made to determine if an event is serious. A list of SAEs that have been excluded from reporting in this study are registered in section 9.3.

9.1.4. Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction/event that is unexpected, serious, and suspected to be caused by the treatment, i.e. adverse reactions/events that are not included in the RSI section of the Investigator’s Brochure (IB) or SmPC.

9.1.5. Potential immune-mediated diseases (pIMD)

Adverse events of special interest (AESIs) collected during this study include potential immune-mediated diseases (pIMDs). No other AESIs will be collected. 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 5 (see section 18).

9.2. Assessment of Adverse Events (AE)

9.2.1. Assessment of causal relationship

The investigator is responsible for determining whether there is a causal relationship between the AE/SAE and use of the investigational medicinal product.

Consideration should be given to whether there is a reasonable possibility of establishing a causal relationship between the adverse event and the investigational medicinal product based on the analysis of the available evidence. All AEs can be categorized as either related (yes) or not related (no).

Those AEs which are suspected of having a causal relationship to the investigational medicinal product will be followed up until the participant has recovered or is stabilized and on the way to good recovery (see also section 9.3.).

If the reporting investigator does not provide any information on causality, the sponsor should consult with the reporting investigator and encourage the expression of a position on this issue. The sponsor must take into account the assessment of causality provided by the investigator. If the sponsor disagrees with the investigator's assessment of causality, both the investigator's and the sponsor's views should be included in the report.

9.2.2. Assessment of intensity

Each adverse event shall be classified by an investigator as mild, moderate or severe. Assessment of intensity of solicited AEs is described further in section 18.2.

Mild: The adverse event is relatively tolerable and transient in its nature but does not affect the participant's normal life.

Moderate: The adverse event causes deterioration of function but does not affect health. The event can be sufficiently unpleasant and interferes with normal activities but does not completely obstruct them.

Severe: The adverse event causes deterioration of function or work ability or poses a health risk to the participant.

9.2.3. Assessment of seriousness

The investigator is responsible for assessing the seriousness (serious or non-serious). If the adverse event is considered serious, this should be reported as a serious adverse event (SAE) by the investigator to the sponsor.

9.3. Reporting and registration of Adverse Events

Reporting of AEs will follow standard procedures, including follow-up on reactogenicity for 4 days after each vaccination for systemic and local solicited adverse events. Unsolicited AEs are reported for 30 days following each vaccination while SAEs are reported for 6 months following each vaccination. Follow-up of fatalities is carried out throughout the whole study period.
AEs that occur during the trial and not excluded from follow-up, which are observed by the investigator/trial nurse or reported by the participant will be registered in the CRF regardless of whether they are assessed as related to the investigational medicinal product or not. Assessment of causal relationship,

severity, and whether the AE is considered to be an SAE will be made by the investigator directly in the CRF (RedCap) or on a trial-specific worksheet. At minimum, for each AE/SAE, a description of the event is recorded (diagnosis/symptom if diagnosis is missing), start and stop dates, causal relationship, severity, if the AE is considered to be an SAE, measures and outcome.

9.3.1. Reporting of Adverse Events (AE)

All AEs shall be registered in the CRF within 3 days as indicated above (section 9.3, Reporting and registration of Adverse Events).

9.3.2. Reporting of Serious Adverse Events (SAE)

Serious Adverse Events (SAE) are reported to the sponsor on a special SAE form within 24 hours of the investigator being informed of the SAE.

Follow-up information describing the outcome and handling of the SAE is reported as soon as this information is available. The original SAE form should be kept in the Investigator Site File.

Duplicate reporting will be avoided by reporting to one of the entities. This process will be conducted according to the standard clinical routine.

Reporting of the following list of conditions will not be recorded as these conditions are commonly occurring in the studied age group:

- Falls and fractures even if they would, by definition, qualify as SAE (i.e. if they would lead to hospitalization, prolonged hospitalization or disability)
- Onset of cancers and tumors
- Dementia and dementia related delirium or confusion unless they are related to AEs following vaccination (e.g. in case of fever-induced delirium) and would qualify as SAE

- Bacterial or fungal infections

To assess safety, any fatal SAEs will be recorded from the day of vaccination until the end of the study period.

9.3.3. Reporting of Suspected Unexpected Serious Adverse Reactions

Those SAE which are assessed by sponsor to be SUSAR are to be reported to the EudraVigilance database. The completed CIOMS form will be the basis for the reporting, by the Swedish Medical Products Agency in the EudraVigilance database according to the specified time frames.

Any SAE/pIMD must be reported to the sponsor as soon as possible and not later than 24 h after the site has become aware of the SAE. SUSAR that are fatal or life-threatening are reported as soon as possible and no later than 7 days after the SAE/pIMD has become known to the sponsor. Relevant follow-up information is sent thereafter within an additional 8 days. Other SUSAR are reported as soon as possible and no later than 15 days after they have come to the sponsor's knowledge.

9.4. Follow-up of Adverse Events

Study participants who have been reported with AE/SAE/SUSAR or AESI will be followed up until the condition has resolved or remains stable/persistent and even if the study period has ended.

9.5. Independent Data Monitoring Committee

Not applicable.

9.6. Annual Safety Report (ASR)

Since the sponsor is non-commercial and the marketing authorization holder of the investigational medicinal product is within the EU/EEA the SPC is used as RSI. The simplified template of Annual Safety Report will be used for the ASR reporting.

9.7. Procedures in case of emergencies

Medication errors and use of other medicinal products than those specified in the protocol, including misuse and abuse of the investigational medicinal product, shall be subject to the same reporting obligations as adverse events, as described more detailed in section 9.3. Any failure to produce the expected benefits would also lead to reporting. This would include RSV infection or RSV-related disease. Since no active follow-up for infections is carried out, this aspect is only relevant if any study participant reports such an incident.

If an unforeseen event is likely to have a serious impact on the benefit/risk relationship of the trial, the sponsor and investigator should take appropriate Urgent Safety Measures (USM) necessary to protect the participants. Examples of such measures are to temporarily halt the clinical trial or to introduce supplementary monitoring measures. The sponsor should, via CTIS, inform the concerned Member States about the event and the measures taken. Notification must be made as soon as possible, but no later than seven days after the measures have been taken.

10. Statistics

10.1. Analysis population

The trial intends to include all participants into the analysis for the primary endpoint. A primary per-protocol analysis will be performed and can be complemented by a secondary analysis including all enrolled participants that have received at least one dose of Arexvy.

10.2. Statistical analyses

10.2.1. Statistical methods

Descriptive statistics for the primary endpoint will include reporting the geometric mean neutralizing titers (GMTs) against RSV A and B one month (D31) after the prime dose with Arexvy with their corresponding standard deviations for both study groups. In addition, the sero-response rate, defined as the percentage of participants with at least a 4-fold increase from baseline to D31, and the mean geometric increase (MGI) between D31 and D0 after prime will be calculated (equal to the geometric mean of the individual ratio).

The same analysis will be applied to the neutralizing titers for RSV A and B following revaccination, which includes calculation of the sero-response rate following revaccination after one year as well as MGI between D31 after revaccination compared to m12 and the MGI between D31 after revaccination over D31 after prime. Statistical analysis will also include the width of the confidence interval around the GMT.

Safety measurements, such as occurrence of solicited AEs, unsolicited AEs, SAEs or any pIMDs will be reported as frequency counts and percentages in both age groups. Analysis of the intensity, relationship and duration will be performed.

Any analysis of other parameters and experimental outcomes will be outlined in a separate statistical analysis plan (SAP).

The results of this study will be interpreted in the context of its exploratory nature and aligned with the descriptive study objectives.

10.2.2. Drop-outs

A 10-20% of dropouts in the older adult cohort (80+ years) is expected during the study based on previous experience. Enrollment of participants will therefore intend to account for this, including 65-70 participants in total, with 30 participants in the 60-65 years age group and 35-40 participants in the 80+ older adult cohort. The extent of missing data will be reported.

10.3. Adjustments of significance and confidence interval

Not applicable

10.4. Sample size calculations

This study is primarily designed to gather descriptive immunogenicity data in older adults upon vaccination with Arexvy, including adults of 80 years of age and older for which data is currently limited. As the study objective is purely descriptive rather than to demonstrate efficacy or test a hypothesis, no formal power-based sample size calculation has been made.

A sample size of 30 individuals in the 60-65 years group and of 35-40 individuals in the 80+ years group was chosen based on feasibility of recruitment, clinical judgement and a 10-20% drop-out expected in the older age group. This sample size of approximately 30 individuals per age group is expected to generate valuable immunogenicity data in an otherwise understudied population and to allow for exploratory comparisons between age groups. Given the descriptive nature of the study, its findings will be interpreted as preliminary.

10.5. Interim analysis (if relevant)

Given the exploratory nature of the study objectives and that this study employs a licensed vaccine under already approved conditions, no formal interim analysis will be performed. Analysis of the different endpoints and study outcomes will be conducted as the samples are collected and following the priority list given in Table 2 (see section 5.2.).

The primary endpoint will be analysed once all study participants have completed their D31 follow-up visit after prime vaccination. Secondary endpoints regarding safety after prime vaccination can be completed once the 6-month follow-up data has been collected.

For the revaccination timepoints a similar approach will be applied, including a final analysis after reaching the end of the trial.

11. Quality Control and Quality Assurance

11.1. Quality Assurance and Sponsor oversight

The sponsor's quality-related work is based on a risk analysis of the trial as a whole: design, conduct, data collection, evaluation, reporting and archiving. The sponsor will perform quality assurance and quality control activities for the trial; however, responsibility for the accuracy, completeness, and reliability of the trial data presented to the sponsor lies with the PI (and delegate(s)) generating the data.

11.2. Monitoring

The trial will be monitored by an independent monitor before the trial begins, during the conduct of the trial, and after the trial has been completed. This is to ensure that the trial is carried out according to the protocol, that data are reliable and collected, documented, and reported according to ICH-GCP and applicable

ethical and regulatory requirements. Monitoring will be risk-based, which means that the extent of the monitoring is based on the sponsor`s risk-assessment and is performed as per the trial's monitoring plan. The monitoring is intended to ensure that the participant's rights, safety, and well-being are met and that data in the CRF are complete, correct, and consistent with the source data.

11.3. Source data

The investigator must keep source documents for each participant in the trial. A document describing what has been classified as source data in the trial (source data reference document) should be included in the Investigator Site File (ISF). The investigator must ensure that all source documents are accessible for monitoring and other quality control activities.

Source data is defined before trial start at each individual site and can, in cases where source data is not registered in another document, consist of the CRF. This should be decided in consultation with the monitor and clearly stated in the source data reference document.

Access to trial-related documentation, such as participants' medical records, CRFs, other source data and other trial documentation will be provided for monitoring and auditing purposes. Access to participants' medical records will require a confidentiality agreement to be signed by the person in charge of the medical records at the trial site and by the monitor and auditor, if applicable. Access will also be granted in the context of regulatory inspections.

11.4. Deviations, serious breaches and other reporting obligations

The responsible investigator and/or any involved service provider shall, without delay, report to the sponsor any suspected serious breaches from the trial

protocol, the CTR, ICH-GCP and other regulations that are likely to affect the safety, rights of the participants and/or the data reliability and robustness to a significant degree. The sponsor should assess the suspected serious breach, the consequences of the deviations and without undue delay, but no later than 7 days (from knowledge), report these to the CAs via CTIS.

Other unexpected events that may affect the benefit/risk relationship for the clinical trial must be reported via CTIS without undue delay, but no later than 15 days after the sponsor becomes aware of the event.

Minor deviations that do not affect participants' integrity or safety, nor significantly affect the trial's scientific value, are documented in the trial documentation of the principal investigator and the sponsor and appropriate measures shall be taken. The deviations, including minor deviations, must be recorded in the clinical trial report.

11.5. Audits and inspections

The purpose of an audit or inspection is to review trial-related activities and documents systematically and independently, to determine whether these activities were performed, registered, analyzed and reported correctly according to the protocol, ICH-GCP and applicable regulations.
Authorized representatives for the sponsor and CAs may carry out audits or inspections at the trial site, including source data verification. The investigator must ensure that all source documents are available for audits and inspections.

12. Ethics

12.1. Compliance to the protocol, ICH-GCP and regulations

The trial will be performed in compliance with this clinical trial protocol, the EU regulation on clinical trials on medicinal products for human use (536/2014), the

Declaration of Helsinki, ICH-GCP, and current national regulations governing this clinical trial. This is to ensure the safety and integrity of the trial participants as well as the quality of the data collected.

12.2. Ethical review of the trial

The final protocol for clinical trials on medicinal products must be approved, as a part of the application for a permit for clinical trials via CTIS, by the CAs, before the trial can be conducted. The authorities must be informed via CTIS of any changes in the trial protocol in accordance with current requirements. See also section 13.

12.3. Procedures for obtaining informed consent

The principal investigator at each site shall ensure that the participant is given full and adequate oral and written information about the trial, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Participants must also be informed that they are free to discontinue their participation in the trial at any time without having to provide a reason. Participants should be given the opportunity to ask questions and be allowed time to consider the provided information. If the participant chooses to participate, both the participant and the investigator shall sign the informed consent form. A copy of the participant information as well as the informed consent form shall be provided to the participant. The participant's signed and dated informed consent must be obtained before any trial-specific activity is performed. Each participant who participates in the trial will be identified by a participant number on a participant identification list. The participant agrees that monitors, auditors, and inspectors may have access to the participants' medical records and other source data. If new information is added to the trial, the participant has the right to reconsider whether he/she will continue their

participation.

12.4. Data protection

Data protection takes into account the General Data Protection Regulation (GDPR) (EU) 2016/679. In case data will be handled, stored or transferred outside the EU, a level of data protection similar to the GDPR is taken into account. When study data is compiled for transfer to the sponsor and other authorized parties, participant names, address, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by the sponsor in order to de-identify the study participant. The study site will maintain a confidential list of participants linking their numerical code to the participant's actual identity. In case of data transfer, the sponsor will maintain high standards of confidentiality and protection of participant personal data consistent with applicable privacy laws.

In the information provided to the participants, they will be fully informed about how their trial data will be collected, used and disclosed. The content of the informed consent form complies with relevant integrity and data protection legislation. The participant information and the informed consent form will explain how trial data are stored to maintain confidentiality in accordance with national data legislation.
The informed consent form will also explain that for verification of the data, representatives delegated by the sponsor, as well as relevant authorities, may require access to parts of medical records or trial records that are relevant to the trial, including the participant's medical history.

12.5. Insurances

All participants taking part in the trial are covered by the Swedish Patient Insurance (patientförsäkringen) through Regionernas Ömsesidiga

Försäkringsbolag, LÖF, and by the Swedish Pharmaceutical Insurance (Läkemedelsförsäkringen) through LFF.

13. Substantial changes to the trial

Substantial changes to the signed clinical trial protocol are only possible through approved protocol amendments.

In the event that substantial changes to the protocol need to be implemented during the course of the trial which may affect the safety, rights of participants or the reliability and robustness of data generated, permission from the relevant authority via application in CTIS should be obtained before implementing the change. This includes the addition of a new trial site or a change of the principal investigator at the trial site.

Non-substantial amendments are entered into the CTIS in the next substantial amendment application concerning the same part. If the non-substantial change is relevant to the Authority's oversight (e.g. contact details), the CTIS should be updated on an ongoing basis.

14. Collection, handling and archiving of data

Participants who participate in the trial are coded with a trial-specific identification number. All participants are registered in a participant identification list (participant enrolment and identification list) that connects the participant’s name and personal number with a participant number/trial identification number.
All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification. The complete Trial Master File with essential documents will be archived for at least 25 years. The content of the Clinical Trial Master file will be archived in a way that ensures that it is readily available and accessible upon reasonable request. Source data in the medical

records system are stored and archived in accordance with national regulations.

14.1. Case report form

An electronic Case Report Form (eCRF) is used for data collection (RedCap). The investigator must ensure that data are registered and any corrections in the eCRF are made as stated in the clinical trial protocol and in accordance with the instructions. The investigator must ensure that the registered data is consistent with the source documents, and that reporting takes place according to the timelines that have been predefined and agreed. In the event of discrepancies, these must be explained. The principal investigator signs the completed eCRF. A copy of the completed eCRF will be archived at the site.

15. Notification of trial completion, reporting, and publication

End of recruitment of participants and end of the trial is reported in CTIS, within 15 days from occurrence in the Member state. Within one year of trial completion in all Member states a summary of the clinical trial results must be reported in CTIS, including a summary for lay people. In addition, a full clinical trial report with individual data is to be completed and archived in the trial master file by sponsor and in the ISFs at each site.

16. Appendix

16.1. Laboratory Assay Description (refers to assays in 5.3.3)

RSVPreF3 ELISA

The principle of these assays has been previously described by Papi et. al. (2023) (19). Shortly, the method works as follows: RSVPreF3 protein antigen will be adsorbed onto a 96-well polystyrene microplate. After washing and blocking steps, dilutions of serum samples, controls and standards will be added to the

coated microplate. A reference standard curve will be prepared using a pool of commercial human serum containing anti-RSV antibodies. After incubation, the microplate will be washed to remove unbound primary antibodies. Bound IgG will be detected by the addition of a secondary anti-human antibody (total IgG specific), conjugated to HRP. Bound antibodies are quantified by the addition of the HRP substrate, tetramethylbenzidine (TMB) and hydrogen peroxide, whereby a colored product develops proportionally to the amount of anti-RSVPreF3 protein total IgG antibodies present in the serum sample. The optical density of each sample dilution is then interpolated on the reference standard. The corresponding antibody concentration, corrected for the dilution factor, is expressed in arbitrary ELISA Laboratory Units per milliliter (ELU/mL).

RSV A/B neutralization assay

The serum neutralization assay is a functional assay that measures the ability of serum antibodies to neutralize RSV entry and replication in a host cell line. The method has been previously described in the study protocol published by Papi et. al. (2023) (19). Virus neutralization is performed by incubating a fixed amount of RSV A strain (Long, ATCC No. VR-26) with serial dilutions of the test serum. The serum-virus mixture is then transferred onto a layer of Vero cells (African Green Monkey, kidney, *Cercopitheus aethiops*, ATCC CCL 81) and incubated for 2 days to allow infection of the Vero cells by non-neutralized virus and the formation of plaques in the cell layer. Following a fixation step, RSV-infected cells are detected using a primary antibody directed against RSV (polyclonal anti-RSV A IgG) and a secondary antibody conjugated to horse-radish peroxidase (HRP), allowing the visualization of plaques after coloration with *TrueBlue* peroxidase substrate. Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with a Reading software). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at each serum dilution and the number of plaques in the virus control wells (no serum added). The serum neutralizing titre is expressed in ED60 (Estimated Dilution 60) and corresponds to the inverse of the interpolated serum

dilution that yields a 60% reduction in the number of plaques compared to the virus control wells, as described by others (20,21). Titres will also be expressed in International Units per millilitre (IU/mL). Secondary standard calibrated against the international reference (NIBSC 16/284) will be included in the runs.

17. References

1. Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. The Lancet. 2022 May 28;399(10340):2047–64.

2. Shi T, Vennard S, Jasiewicz F, Brogden R, Nair H, RESCEU Investigators. Disease Burden Estimates of Respiratory Syncytial Virus related Acute Respiratory Infections in Adults With Comorbidity: A Systematic Review and Meta-Analysis. The Journal of Infectious Diseases. 2022 Aug 1;226(Supplement_1):S17–21.

3. Langedijk AC, Bont LJ. Respiratory syncytial virus infection and novel interventions. Nature Reviews Microbiology. 2023 Nov;21(11):734–49.

4. Carrico J, Hicks KA, Wilson E, Panozzo CA, Ghaswalla P. The Annual Economic Burden of Respiratory Syncytial Virus in Adults in the United States. The Journal of Infectious Diseases. 2024 Aug 15;230(2):e342–52.

5. Ruckwardt TJ. The road to approved vaccines for respiratory syncytial virus. npj Vaccines. 2023 Sep 25;8(1):1–8.

6. Topalidou X, Kalergis AM, Papazisis G. Respiratory Syncytial Virus Vaccines: A Review of the Candidates and the Approved Vaccines. Pathogens. 2023 Oct;12(10):1259.

7. Mullard A. FDA approves mRNA-based RSV vaccine. Nature Reviews Drug Discovery. 2024 Jun 7;23(7):487–487.

8. GSK. Full Prescribing Information AREXVY. GlaxoSmithKline; 2024.

9. Leroux-Roels I, Davis MG, Steenackers K, Essink B, Vandermeulen C, Fogarty C, et al. Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F (RSVPreF3) Candidate Vaccine in Older Adults: Phase 1/2 Randomized Clinical Trial. The Journal of Infectious Diseases. 2023 Mar 15;227(6):761–72.

10. Ison MG, Papi A, Athan E, Feldman RG, Langley JM, Lee DG, et al. Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over 2 RSV Seasons. Clinical Infectious Diseases. 2024 Jun 15;78(6):1732–44.

11. Ison MG, Papi A, Athan E, Feldman RG, Langley JM, Lee DG, et al. Efficacy, Safety, and Immunogenicity of the AS01E-Adjuvanted Respiratory Syncytial

Virus Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over Three RSV Seasons: A Randomized Trial [Internet]. Rochester, NY: Social Science Research Network; 2024 [cited 2025 Jan 8]. Available from: https://papers.ssrn.com/abstract=5011569

12. GSK. RSVPreF3 Vaccine for Respiratory Syncytial Virus (RSV) in Older Adults [Internet]. FDA Vaccines and Related Biological Products Advisory Committee; 2023 Mar 1 [cited 2024 Oct 16]. Available from: https://www.fda.gov/media/165649/download

13. Marcandalli J, Fiala B, Ols S, Perotti M, Schueren W de van der, Snijder J, et al. Induction of potent neutralizing antibody responses by a designed protein nanoparticle vaccine for respiratory syncytial virus. Cell. 2019 Mar 7;176(6):1420-1431.e17.

14. Ols S, Lenart K, Arcoverde Cerveira R, Miranda MC, Brunette N, Kochmann J, et al. Multivalent antigen display on nanoparticle immunogens increases B cell clonotype diversity and neutralization breadth to pneumoviruses. Immunity. 2023 Oct 10;56(10):2425-2441.e14.

15. Hellgren F, Cagigi A, Arcoverde Cerveira R, Ols S, Kern T, Lin A, et al. Unmodified rabies mRNA vaccine elicits high cross-neutralizing antibody titers and diverse B cell memory responses. Nature Communications. 2023 Jun 22;14(1):3713.

16. Lenart K, Arcoverde Cerveira R, Hellgren F, Ols S, Sheward DJ, Kim C, et al. Three immunizations with Novavax's protein vaccines increase antibody breadth and provide durable protection from SARS-CoV-2. npj Vaccines. 2024 Jan 20;9(1):1–17.

17. Hellgren F, Rosdahl A, Cerveira RA, Lenart K, Ols S, Gwon YD, et al. Modulation of innate immune response to mRNA vaccination after SARS-CoV-2 infection or sequential vaccination in humans. JCI Insight. 2024 May 8;9(9).

18. Phung E, Chang LA, Mukhamedova M, Yang L, Nair D, Rush SA, et al. Elicitation of pneumovirus-specific B cell responses by a prefusion-stabilized respiratory syncytial virus F subunit vaccine. Science Translational Medicine. 2022 Jun 22;14(650):eabo5032.

19. Papi A, Ison MG, Langley JM, Lee DG, Leroux-Roels I, Martinon-Torres F, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. New England Journal of Medicine. 2023 Feb 15;388(7):595–608.

20. Barbas CF, Crowe JE, Cababa D, Jones TM, Zebedee SL, Murphy BR, et al. Human monoclonal Fab fragments derived from a combinatorial library bind

to respiratory syncytial virus F glycoprotein and neutralize infectivity. Proceedings of the National Academy of Sciences. 1992 Nov;89(21):10164–8.

21. Bates JT, Keefer CJ, Slaughter JC, Kulp DW, Schief WR, Crowe JE. Escape from neutralization by the respiratory syncytial virus-specific neutralizing monoclonal antibody palivizumab is driven by changes in on-rate of binding to the fusion protein. Virology. 2014 Apr 1;454–455:139–44.

18. Attachments
18.1. List of pIMDs considered for the study

Table 5 List of pIMDs considered in this study (according to MedDRA version 28.0)

Blood disorders and coagulopathies	**Cardio-pulmonary inflammatory disorders**	**Endocrine disorders**

- Antiphospholipid syndrome
- Autoimmune aplastic anemia
- Autoimmune hemolytic anemia, including:
  - Warm antibody hemolytic anemia
  - 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"
	- Idiopathic Myocarditis/Pericarditis, including:
	  - Autoimmune / Immune-mediated myocarditis
	  - Autoimmune / Immune-mediated pericarditis
	  - Giant cell myocarditis
	- Idiopathic pulmonary fibrosis, including:
	  - Idiopathic interstitial pneumonia (Interstitial lung disease, Pulmonary fibrosis, Immune-mediated pneumonitis)
	  - Pleuroparenchymal fibroelastosis (PPFE)
	- Pulmonary alveolar proteinosis (PAP)
	  - Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"
		- Addison's disease
		- Autoimmune / Immune-mediated thyroiditis, including:
		  • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)
		  - Atrophic thyroiditis
		  - Silent thyroiditis
		  - Thyrotoxicosis
		- Autoimmune diseases of the testis and ovary, including:
		  - Autoimmune oophoritis
		  - Autoimmune ovarian failure
		  - Autoimmune orchitis
		- Autoimmune hyperlipidemia
		- Autoimmune hypophysitis
		- Diabetes mellitus type I
		- Graves' or Basedow's disease, including:
		  - Marine Lenhart syndrome
		  - Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
		- Insulin autoimmune syndrome
		- Polyglandular autoimmune syndrome, including:
		  - Polyglandular autoimmune syndrome type I, II and III

Eye disorders	**Gastrointestinal disorders**	**Hepatobiliary disorders**

- Ocular Autoimmune / Immune-mediated disorders, including:
  - Acute macular neuroretinopathy (also
	- Autoimmune / Immune-mediated pancreatitis
	- Celiac disease
	- Inflammatory Bowel disease, including:
	  - Crohn's disease
		- Autoimmune cholangitis
		- Autoimmune hepatitis
		- Primary biliary cirrhosis
		- Primary sclerosing cholangitis

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	- Microscopic colitis - Terminal ileitis - Ulcerative colitis - Ulcerative proctitis	
Musculoskeletal and connective tissue disorders	**Neuroinflammatory/neuromuscular disorders**	**Renal disorders**

- Gout, including:
  - Gouty arthritis
- Idiopathic inflammatory myopathies, including:
  - Dermatomyositis
  - Inclusion body myositis
  - Immune-mediated necrotizing myopathy
  - Polymyositis
- Mixed connective tissue disorder
- Polymyalgia rheumatica (PMR)
- Psoriatic arthritis (PsA)
- Relapsing polychondritis
- Rheumatoid arthritis, including:
  - Rheumatoid arthritis associated conditions
  - Juvenile idiopathic arthritis
  - Palindromic rheumatism
  - Still's disease
  - Felty's syndrome
- Sjogren's syndrome
- Spondyloarthritis, including:
  - Ankylosing spondylitis
  - Juvenile spondyloarthritis
  - Keratoderma blenorrhagica
  - Psoriatic spondylitis
  - Reactive Arthritis
  - Undifferentiated spondyloarthritis
- Systemic Lupus Erythematosus, including:
  - Lupus associated conditions (e.g., Cutaneous lupus erythematosus, Lupus nephritis, etc.)
	- Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants, including:
	  - 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), including:
	  - Variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
	- Idiopathic cranial nerve palsies/paresis and inflammations (neuritis), including:
	  - Cranial nerve neuritis (e.g., Optic neuritis)
	  - Idiopathic nerve palsies/paresis (e.g., Bell's palsy)
	  - Melkersson-Rosenthal syndrome
		- Autoimmune/Immune-mediated glomerulonephritis, including:
		  - IgA nephropathy
		  - IgM nephropathy
		  - C1q nephropathy
		  - Fibrillary glomerulonephritis
		  - Glomerulonephritis rapidly progressive
		  - Membranoproliferative glomerulonephritis
		  - Membranous glomerulonephritis
		  - Mesangioproliferative glomerulonephritis
		  - Tubulointerstitial nephritis and uveitis syndrome

- Complications such as shrinking lung syndrome (SLS)
- Systemic Scleroderma (Systemic Sclerosis), including:
  - Raynaud's syndrome
  - Systemic sclerosis with diffuse scleroderma
  - Systemic sclerosis with limited scleroderma (also known as CREST syndrome)
	- Multiple cranial nerve palsies/paresis
	- Multiple Sclerosis (MS), including:
	  - 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, including:
	  - Ocular myasthenia
	  - Lambert-Eaton myasthenic syndrome
	- Narcolepsy (with or without presence of unambiguous cataplexy)
	- Peripheral inflammatory demyelinating neuropathies and plexopathies, including
	  - 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), including:
	  - Acute partial transverse myelitis (APTM)
	  - Acute complete transverse myelitis (ACTM)	

Skin and subcutaneous tissue disorders	**Vasculitis**	**Other (including multisystemic)**

- Alopecia areata
- Autoimmune / Immune-mediated blistering dermatoses, including:
  - Bullous Dermatitis
  - Bullous Pemphigoid
  - Dermatitis herpetiformis
	- Large vessels vasculitis, including:
	  - Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)
	  - Giant cell arteritis (also called temporal arteritis)
	  - Takayasu's arteritis
		- Anti-synthetase syndrome
		- Capillary leak syndrome
		  - Frequently used related terms include: "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"

- Epidermolysis bullosa acquisita (EBA) - Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease - Pemphigus - Erythema multiforme - Erythema nodosum - Lichen planus, including: - Lichen planopilaris - Localised Scleroderma (Morphoea) - Eosinophilic fasciitis (also called Shulman syndrome) - Psoriasis - Pyoderma gangrenosum - Reactive granulomatous dermatitis, including: - Interstitial granulomatous dermatitis - Palisaded neutrophilic granulomatous dermatitis - Stevens-Johnson Syndrome (SJS), including: - Toxic Epidermal Necrolysis (TEN) - SJS-TEN overlap - Sweet's syndrome, including: - Acute febrile neutrophilic dermatosis - Vitiligo	- Medium sized and/or small vessels vasculitis, including: - 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 - Necrotizing vasculitis - Polyarteritis nodosa - Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) - Granulomatosis with polyangiitis	- Goodpasture syndrome - Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)" - Immune-mediated enhancement of disease, including: - 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 (ADE) - Immunoglobulin G4 related disease - Langerhans' cell histiocytosis - Multisystem inflammatory syndromes, including: - Kawasaki's disease - Multisystem inflammatory syndrome in adults (MIS-A) - Multisystem inflammatory syndrome in children (MIS-C) - Overlap syndrome - Raynaud's phenomenon - Sarcoidosis, including: - Loefgren syndrome - Susac's syndrome

18.2. Grading of solicited AEs

Table 6 Grading of solicited AEs as applied in this study

Event	Intensity grade	Parameter
Pain at the injection 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 every day activities
	3	Severe: Significant pain at rest. Prevents normal everyday activities
Headache	0	None
	1	Mild: Headache that is easily tolerable
	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 that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia
Arthralgia	0	None
	1	Mild: Arthralgia that is easily tolerated
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity
Erythema the injection site		Record greatest surface diameter in mm
Swelling at the injection site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C/°F

* Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route. The route for measuring temperature can be oral, axillary or tympanic.

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 maximum intensity of local injection site erythema/swelling and fever will be scored as follows:

Table 7 Grading of Erythema/Swelling and Fever

Intensity grade	Erythema/Swelling	Fever

0	≤ 20 mm	<38.0°C (100.4°F)
1	>20 - ≤50 mm	≥ 38.0°C (100.4°F) - ≤38.5°C (101.3°F)
2	>50 - ≤100 mm	> 38.5°C (101.3°F) - ≤39.0°C (102.2°F)
3	>100 mm	> 39.0°C (102.2°F)