# A Phase 1, Double-blind, Dose-ranging Study to Evaluate the Safety of MEDI7510, RSV Vaccine, in Elderly Adults

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'GMT'Z) |
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# A Phase 1a Study to Evaluate the Safety of the Respiratory Syncytial Virus Vaccine MEDI7510 in Older Adults

**Sponsor Protocol Number:** CD-VA-MEDI7510-1134

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# Protocol Synopsis

**TITLE**

A Phase 1a Study to Evaluate the Safety of the Respiratory Syncytial Virus Vaccine MEDI7510 in Older Adults

**HYPOTHESES**

**Primary Hypothesis**

The primary hypothesis of this study is that administration of single ascending intramuscular (IM) doses of the respiratory syncytial virus soluble F (RSV sF) antigen or MEDI7510 will be safe and well tolerated in adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions.

**Secondary Hypotheses**

The secondary hypotheses are that the administration of single ascending IM doses of RSV sF or MEDI7510 will result in dose-dependent humoral immune responses in adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions, and that MEDI7510 will induce cell-mediated immunity greater than that observed with RSV sF alone.

**OBJECTIVES**

**Primary Objective**

The primary objective of this study is to assess the safety and tolerability of a single ascending IM dose of RSV sF or MEDI7510 in adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions.

**Secondary Objectives**

The secondary objectives of this study are:

1. To assess the humoral immune responses to RSV F following immunization with RSV sF or MEDI7510
2. To assess the cell-mediated (T-cell) immune responses to RSV F following immunization with RSV sF or MEDI7510

**Exploratory Objective**

The exploratory objective of this study is to further assess immune responses to RSV sF and MEDI7510 using exploratory assays.

**STUDY ENDPOINTS**

**Primary Endpoint**

The primary endpoint is the safety and tolerability of single ascending doses of RSV sF and MEDI7510 as assessed by the occurrence of all solicited symptoms (whether or not treatment emergent) and treatment-emergent adverse events (AEs), serious adverse events (SAEs), new onset chronic diseases (NOCDs), and adverse events of special interest (AESIs) as follows:

- The proportion of subjects experiencing each solicited symptom from administration of investigational product (Day 1) through Day 7 post vaccination (7 days)
- The proportion of subjects experiencing each AE from administration of investigational product (Day 1) through Day 28 post vaccination (28 days)
- The proportion of subjects experiencing each SAE from administration of investigational product (Day 1) through Day 28 post vaccination (28 days)
- The proportion of subjects experiencing each SAE from administration of investigational product (Day 1) through Day 360 post vaccination (360 days)
- The proportion of subjects experiencing each NOCD from administration of investigational product (Day 1) through Day 360 post vaccination (360 days)
- The proportion of subjects experiencing each AESI from administration of investigational product (Day 1) through Day 360 post vaccination

**Secondary Endpoints**

The secondary endpoints relate to the immunogenicity of RSV sF and MEDI7510 as follows:

1. Humoral immunity endpoints

- Post-dose geometric mean titers (GMTs) and post-dose geometric mean fold rises (GMFRs) from baseline in RSV A neutralizing antibody on Days 29, 61, 91, 181, 271, and 361
- The proportion of subjects who experience a post-dose seroresponse to RSV on Days 29, 61, 91, 181, 271, and 361 as measured by neutralizing antibody to RSV A, with seroresponse defined as a ≥ 4-fold rise from baseline
- Post-dose GMTs and GMFRs from baseline of anti-F immunoglobulin G(IgG) antibodies as measured by an anti-F IgG assay derived from an RSV-specific 4-plex Meso Scale Discovery (MSD; Gaithersburg, MD) assay on Days 29, 61, 91, 181, 271, and 361
- The proportion of subjects who experience a post-dose seroresponse to RSV on Days 29, 61, 91, 181, 271, and 361 as measured by anti-F IgG assay, with seroresponse defined as ≥ 4-fold rise from baseline

2. Cellular immunity endpoints

- Post-dose geometric mean counts (GMCs) and GMFRs from baseline of RSV F peptide pool interferon gamma (IFNγ) ELISPOT responses on Days 8 and 29
- The proportion of all subjects in the immunogenicity population who experience a post-dose cell-mediated immune response to RSV F on Days 8 and 29 as measured by the RSV F peptide pool IFNγ ELISPOT assay

**Exploratory Endpoints**

Depending on assay availability and the availability of suitable samples, the following exploratory endpoints may be assessed to further evaluate immune responses to RSV:

- The proportion of subjects who experience a post-dose seroresponse to RSV on Days 29, 61, 91, 181, 271, and 361 as measured by palivizumab-competitive enzyme-linked immunosorbent assay (cELISA), with seroresponse defined as ≥ 4-fold rise from baseline
- Post-dose GMTs and GMFRs from baseline of palivizumab-competitive antibodies as measured by a palivizumab-cELISA on Days 29, 61, 91, 181, 271, and 361
- The proportion of subjects who experience a post-dose seroresponse to RSV on Days 29, 61, 91, 181, 271, and 361 as measured by neutralizing antibody to RSV B, with seroresponse defined as a ≥ 4-fold rise from baseline
- Post-dose GMTs and GMFRs from baseline of RSV B neutralizing antibodies on Days 29, 61, 91, 181, 271, and 361
- The number of RSV F-specific CD8+ and CD4+ T cells that secrete interleukin 2 (IL-2), IFNγ, tumor necrosis factor alpha (TNF-α), interleukin-4 (IL-4), interleukin 5 (IL-5), and/or other cytokines prior to and post dosing in subjects who received MEDI7510. An exploratory intracellular cytokine flow cytometry assay may be used for these analyses.
- The types of cytokines (Th1 vs Th2 vs inflammatory) secreted by RSV F-specific T cells prior to and post dosing in subjects who received MEDI7510. An exploratory Luminex assay for Th1/Th2 cytokines may be used for these analyses.

**STUDY DESIGN**

This is a Phase 1a, first time in human (FTIH), double-blind, randomized, placebo-controlled, cohort escalation study evaluating the safety and tolerability of a single ascending IM dose of RSV sF or MEDI7510 in adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions. Approximately 144 subjects will be enrolled at approximately 3 study centers in the United States and randomized in a 5:1 ratio by cohort to receive a single dose of either RSV sF or placebo or MEDI7510 or placebo on Day 1 in ascending doses as follows:

- Cohort 1: 20 µg RSV sF (n = 20) or placebo (n = 4) as a single IM injection
- Cohort 1a: 20 µg MEDI7510 (n = 20) or placebo (n = 4) as a single IM injection
- Cohort 2: 50 µg RSV sF (n = 20) or placebo (n = 4) as a single IM injection
- Cohort 2a: 50 µg MEDI7510 (n =20) or placebo (n = 4) as a single IM injection
- Cohort 3: 80 µg RSV sF (n = 20) or placebo (n = 4) as a single IM injection

- Cohort 3a: 80 µg MEDI7510 (n = 20) or placebo (n = 4) as a single IM injection

For Cohorts 1a, 2a, and 3a, the indicated dose for MEDI7510 represents the RSV sF dose, and the GLA-SE dose will be fixed at 2.5 µg GLA + 2% (w/v) SE.

Dosing within each cohort will be staggered for safety. Cohort escalation will occur after all subjects in the previous cohort(s) are followed for 7 days, with parallel cohort progression for Cohorts 1a and 2, and Cohorts 2a and 3. In addition, cohorts may be expanded to improve safety assessment.

One interim analysis is planned after all subjects have completed 90 days post-dose safety follow-up. This interim analysis will provide safety and immunogenicity data needed to select an antigen dose to include in the Phase 1b study, which will explore GLA-SE adjuvant doses in combination with the selected dose of RSV sF antigen.

Subjects will be in the study for a little more than a year (56 weeks), which includes a screening period of up to 30 days, a treatment period of 1 day, and a 360-day posttreatment safety follow-up period.

**TARGET SUBJECT POPULATION**

The subjects in this study will be adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions.

**INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION**

Subjects will be randomly assigned to receive a single dose of either RSV sF or placebo or MEDI7510 or placebo administered by IM injection on Day 1 in 1 of 6 fixed-dose cohorts: 20 µg, 50 µg, or 80 µg RSV sF, or 20 µg, 50 µg, or 80 µg MEDI7510.

**STATISTICAL ANALYSIS PLAN**

**General Considerations**

Tabular summaries will be presented by treatment arm within each dose cohort (Cohorts 1, 1a, 2, 2a, 3, and 3a) except that all placebo recipients will be grouped into a single placebo treatment arm, regardless of dose cohort. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan.

The As-treated Population (ATP) includes all subjects who receive any amount of investigational product. Subjects will be included in the ATP according to the investigational product received even if different from that to which the subject was randomized.

All analyses will be performed on the ATP unless otherwise specified.

**Sample Size**

Approximately 144 adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions will be enrolled and randomized in a 5:1 ratio by cohort to receive a single IM dose of either RSV sF or placebo (Cohorts 1, 2 and 3) or MEDI7510 or placebo (Cohorts 1a, 2a, and 3a). These cohorts may be expanded for safety, so the maximum number of subjects that can be dosed under this protocol is 216 (144 + [12 × 6]).

Because all analyses will be descriptive in nature, and no formal hypothesis is being tested, no formal sample size calculation was performed.

**Safety**

The primary endpoint is the safety and tolerability of RSV sF and MEDI7510 as assessed by the occurrence of all solicited symptoms (whether or not treatment emergent) and treatment-emergent AEs, SAEs, NOCDs, and AESIs.

Safety evaluations will be descriptive in nature, and observed differences will be evaluated for medical relevance.

Solicited symptoms, whether or not treatment emergent, will be summarized by day and overall, and by severity. They will not be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized regardless of whether or not they are treatment emergent. They will not be assessed by relationship to investigational product, because they are assumed to be possibly related. Treatment-emergent AEs, SAEs, NOCDs, and AESIs will be summarized by system organ class and preferred term using MedDRA. Adverse events, SAEs, and AESIs will also be summarized by severity and relationship to investigational product, and

NOCDs will be summarized by relationship.

Summaries of solicited symptoms through Day 7 post dose, AEs and SAEs through Day 28 post dose, and SAEs, NOCDs, and AESIs through Day 360 post dose will be provided.

**Efficacy**

This is a Phase 1 safety and immunogenicity study in healthy subjects, therefore disease evaluation is not planned. Immunogenicity will be assessed. Descriptive statistics will be the primary method used for the secondary immunogenicity endpoint analyses.

**External Safety Monitoring Committee**

A study-specific External Safety Monitoring Committee (ESMC) that is advisory to MedImmune will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety for cohort escalation decisions. This committee will also review data at other timepoints in response to events meeting enrollment and dosing stopping criteria or events assessed as medically relevant by the medical monitor or one of the site investigators. Details are provided in the ESMC charter.

**Interim Analysis**

One interim analysis is planned after all subjects have completed the 90 days post dose safety follow-up. This interim analysis will provide safety and immunogenicity data needed to select an antigen dose to include in the Phase 1b study, which will explore single ascending adjuvant doses in combination with the selected dose of RSV sF.

**Final Analysis**

A final, complete analysis will be conducted after all subjects have completed the Day 361 visit; data will be monitored, cleaned, and locked before final analysis.

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# List of Abbreviations

| Abbreviation or Specialized Term | Definition |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine transaminase |
| AST | aspartate transaminase |
| ATP | As-treated Population |
| BMI | body mass index |
| BP | blood pressure |
| CHO | Chinese hamster ovary |
| cELISA | competitive enzyme-linked immunosorbent assay |
| CRO | contract research organization |
| dRMP | developmental risk management plan |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ESMC | External Safety Monitoring Committee |
| FAAN | Food Allergy and Anaphylaxis Network |
| FTIH | first time in human |
| GCP | Good Clinical Practice |
| GLA | glucopyranosyl lipid A |
| GLA-SE | glucopyranosyl lipid A in 2% (w/v) stable emulsion |
| GLP | Good Laboratory Practice |
| GMC | geometric mean count |
| GMFR | geometric mean fold rise |
| GMP | Good Manufacturing Practice |
| GMT | geometric mean titer |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IFNγ | interferon gamma |
| IgG | immunoglobulin G |
| IL-2, IL-4, IL-5 | interleukin 2, interleukin 4, interleukin 5 |
| IM | intramuscular |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IWRS | interactive web response system |
| mAb | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MSD | Meso Scale Discovery |

| Abbreviation or Specialized Term | Definition |
|---|---|
| NIAID | National Institute of Allergy and Infectious Diseases |
| NOAEL | no observed adverse effect level |
| NOCD | new onset chronic disease |
| PBMC | peripheral blood mononuclear cells |
| PCR | polymerase chain reaction |
| PEF | peak expiratory flow |
| RBC | red blood cell |
| RSV | respiratory syncytial virus |
| RSV F | respiratory syncytial virus fusion protein |
| RSV sF | respiratory syncytial virus soluble fusion antigen |
| SAE | serious adverse event |
| SE | stable emulsion |
| SID | subject identification |
| SUSAR | suspected unexpected serious adverse reaction |
| sWFI | sterile water for injection |
| Th | T-helper (cells) |
| TLR4 | Toll-like receptor 4 |
| TNF-α | tumor necrosis factor alpha |
| ULN | upper limit of normal |
| US | United States |
| US FDA | United States Food and Drug Administration |
| USA | United States of America |
| WBDC | Web Based Data Capture |

# 1 INTRODUCTION

## 1.1 Disease Background

Respiratory syncytial virus (RSV) is a significant cause of respiratory disease, including pneumonia, in adults as well as children. Symptomatic RSV re-infection occurs commonly throughout life. RSV outbreaks occur in a seasonal pattern that is similar, but not identical, to that of influenza, generally spanning the months of November to April in the Northern Hemisphere; however, unlike influenza, RSV re-infection is not dependent on seasonal antigenic variation and is thought to occur because of a short duration of immunity after infection (Hall et al, 1991). Most RSV infections are unrecognized in adults because respiratory samples are not routinely tested for RSV in this population. Recent epidemiologic data highlight the importance of RSV as a cause of respiratory illness in adults, including illness resulting in hospitalization and death, particularly in older adults or in those with underlying cardiac or pulmonary disease (Falsey et al, 2005; Walsh et al, 2004; Widmer et al, 2012; Mullooly et al, 2007). Older adults are more likely than younger adults to have severe manifestations of RSV illness (Mullooly et al, 2007; Walsh et al, 2013; Zhou et al, 2012).

In a recently completed 4-season assessment of patients with polymerase chain reaction (PCR)-confirmed RSV-associated respiratory disease that resulted in medical provider contact, the estimated seasonal incidence of medically attended RSV disease was 1.6% per season in patients ≥ 50 years of age and 1.8% in patients ≥ 60 years of age (McClure et al, Marshfield Clinic, unpublished data). In another prospective study of healthy older adults ≥ 65 years of age followed for respiratory illness for 4 consecutive seasons, the incidence of RSV infection (not necessarily medically attended) diagnosed by culture, PCR, or serology was 3% to 7% annually (Falsey et al, 2005). Illness duration averaged 16 days, and one third sought medical care. In patients with high-risk conditions (chronic heart or lung disease), rates of RSV infection were 4% to 10% during the 4-year surveillance period; about half consulted a physician, 9% visited an emergency room, and 16% were hospitalized (Falsey et al, 2005).

In a prospective 3-year study of hospitalized patients ≥ 50 years of age, annual rates of hospitalization due to RSV and influenza were estimated to be 15.01 and 11.81 per 10,000 residents, respectively (Widmer et al, 2012). In another study, the rate of RSV hospitalization was even higher in patients ≥ 65 years of age, 25.4 per 10,000 residents (Mullooly et al, 2007). Estimated RSV circulatory and respiratory hospitalization rates (a component of all hospitalizations due to RSV) were 10.6 per 10,000 patients ≥ 65 years of age and 44.4 per 10,000 high-risk patients ≥ 65 years of age. The annual United States (US)

cost of RSV hospitalization in patients ≥ 65 years of age was estimated at between $150 and $680 million (Han et al, 1999). RSV is estimated to cause approximately 10,000 US deaths annually in persons > 65 years of age (Mullooly et al, 2007; Falsey et al, 2005; Kurzweil et al, 2013).

Overall, the medical burden from RSV in older adults may be only slightly lower than that of influenza, although estimates vary, and vaccination may have affected estimates of the influenza burden (Widmer et al, 2012; Zhou et al, 2012; Mullooly et al, 2007; Falsey et al, 2005; Thompson et al, 2003). Given the current absence of any preventive or therapeutic strategy for RSV in older adults, there is a significant unmet medical need in this population.

## 1.2 MEDI7510 Background

MEDI7510 is briefly described below. Refer to the current Investigator's Brochure for additional details.

The vaccine MEDI7510 comprises recombinant RSV soluble fusion (RSV sF) antigen and the adjuvant glucopyranosyl lipid A (GLA) in an oil-in-water emulsion (stable emulsion [SE]; GLA-SE). The antigen, RSV sF, which contains known neutralizing epitopes in the F1 subunit (McLellan et al, 2011), is expressed in a Chinese hamster ovary (CHO) cell line. Glucopyranosyl lipid A adjuvant is a synthetic analogue of monophosphoryl lipid A, a Toll-like receptor 4 (TLR4) agonist (Coler et al, 2010;Clegg et al, 2012). The SE is squalene based.

RSV sF was selected as the antigen because the RSV F protein is essential for productive infection, is highly conserved across RSV A and B subtype isolates, and contains multiple neutralizing epitopes as well as CD4 and CD8 T-cell epitopes. Immunity to RSV F has been shown to protect from RSV replication in preclinical animal models, and high titers to RSV F correlate with protection against challenge. It is also a clinically validated target, because antibodies to RSV F (palivizumab) have been demonstrated to protect young infants from RSV disease.

The adjuvant GLA-SE is included in the vaccine to boost RSV F-specific neutralizing antibodies as well as RSV F-specific CD4 T-helper (Th) cells and CD8 cytotoxic T-cells and to stimulate a Th1 cytokine profile. These elements of the immune response are thought to be important for preventing RSV infection and limiting RSV replication, thus diminishing RSV disease. Older adults respond to RSV antigens with a less effective Th2 profile and, although eliciting neutralizing antibodies is likely to be an important component of a vaccine, it is also

likely that a successful RSV vaccine in the older adult population must induce a significant cell-mediated immune response. Both GLA and SE are important contributors to the adjuvant effect in animal models, and GLA-SE has been shown to upregulate Th1 type chemokines and to induce stronger responses than alum, GLA, or SE alone (Coler et al, 2010; Lambert et al, 2012). MEDI7510 is designed to optimize the immune response to RSV F in the older adult population.

MedImmune is developing MEDI7510 for annual vaccination against RSV disease in individuals 60 years of age and older.

## 1.3 Summary of Nonclinical Experience

In animal models, MEDI7510 was highly immunogenic and elicited the desired immunogenicity profile, including cell-mediated and Th1-biased responses. Mouse studies confirmed that RSV sF was essential for the induction of F-specific immunity; GLA was needed to elicit cell-mediated responses and a Th1-biased response, and SE was needed to elicit optimal levels of RSV neutralizing antibodies. MEDI7510 protected mice and cotton rats from challenge with wild-type RSV.

Rat toxicology and rabbit local tolerability studies demonstrated that the primary effect was minimal to moderate injection site inflammation. Corresponding secondary changes in clinical chemistry parameters (mild to moderate increases in fibrinogen, C-reactive protein [rabbits], or alpha-2 macroglobulin and alpha-1 acid glycoprotein [rodent biomarkers of acute inflammation], mild increase in globulin, mild decrease in albumin) along with minimally enlarged lymph nodes, splenic extramedullary hematopoiesis and some minimally increased myeloid cellularity observed in the bone marrow were monitorable, fully reversible, and were not considered adverse. The systemic no observed adverse effect level (NOAEL) was the highest dose tested: 90 ± 12 µg RSV sF with 5 µg GLA in 2% weight per volume (w/v) SE. For the highest dose in the planned FTIH study, based on the rat toxicology study NOAEL for systemic effects, the safety margin for systemic toxicity or effects other than injection site inflammation is approximately 110-fold on a body weight (mg/kg) basis. These studies conservatively support single clinical doses of up to 80 µg RSV sF with 5 µg GLA in 2% (w/v) SE. GLA-SE has also been shown to be safe and to contribute to vaccine immunogenicity in nonhuman primate (cynomolgus macaques) dose-escalation studies of 1 to 50 µg of GLA-SE in combination with an influenza vaccine (Fluzone®) over 30 days (Coler et al, 2010).

## 1.4 Summary of Clinical Experience

No clinical studies have been conducted with MedImmune's RSV sF antigen or with MEDI7510. This is a first time in human (FTIH) study.

There are no approved RSV vaccines for either adults or children. Vaccines consisting of purified F protein alone and in combination with other antigens or with adjuvants have been studied in adults with antigen doses as high as 100 µg. These studies have demonstrated the immunogenicity of the F protein, with antibody responses most likely to be observed in those with low prevaccination titers. There have been no significant safety concerns with RSV F vaccines, although local site reactions have generally been higher in active than placebo arms (Falsey and Walsh, 1996; Falsey and Walsh, 1997; Langley et al, 2009; Glenn et al, 2013). Clinical efficacy has not been demonstrated for any of these vaccines. Although MEDI7510 is an RSV F subunit vaccine, none of these vaccines is similar to MEDI7510.

GLA-SE is a component of multiple investigational vaccines, but available safety data are limited. In a clinical trial of 1 µg GLA with 2% SE in combination with a recombinant pandemic H5N1 influenza antigen in healthy adults 18 to 49 years of age, higher geometric mean titers (GMTs) of antibody were achieved with lower doses of antigen in the presence of GLA-SE. The influenza antigen in combination with GLA-SE resulted in increased rates of injection site pain and/or tenderness, but most complaints were mild to moderate in intensity (Treanor et al, 2013).

## 1.5 Rationale for Conducting the Study

RSV causes significant morbidity in older adults, but there is no specific treatment or prevention strategy available for this population. Palivizumab, a monoclonal antibody (mAb) targeting the RSV F protein, is available only for specified groups of infants, and aerosolized ribavirin, a treatment with unclear efficacy, is not approved for adult use. MEDI7510 is designed to fill the unmet medical need by preventing symptomatic respiratory disease caused by RSV in older adults.

The goal of this FTIH study is to evaluate the safety and tolerability of single ascending intramuscular (IM) doses of RSV sF antigen and of MEDI7510 in adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions, and to determine if any of these doses result in both humoral and cellular immunity. A single fixed dose of GLA-SE is used in this study so that the immunogenicity of single ascending doses of RSV sF can be assessed in the presence of adjuvant and the contribution of GLA-SE to the immunogenicity of RSV sF can be assessed. Escalating doses of GLA-SE will be evaluated

in a subsequent Phase 1b study to maximize the extent and duration of neutralizing antibody and cellular immune responses to RSV in older adults. This selected dosage level will subsequently be assessed for efficacy against RSV-confirmed respiratory illness.

### 1.5.1 Risk-benefit Assessment

There are no data on the human safety profile of RSV sF or MEDI7510. Limited clinical data exist for GLA-SE in combination with an influenza antigen in a younger population, in which GLA-SE was associated with increased reactogenicity. Nonclinical toxicology studies of MEDI7510 did not identify any MEDI7510-related safety concerns other than self-limited local reactogenicity. The important potential risks outlined in the development risk management plan (dRMP; also see Section 5.4 of the Investigator's Brochure) are based primarily on the common safety risks observed with injectable vaccines. These potential risks include, but are not limited to, allergic reactions (including anaphylaxis) and severe injection site reactions. Autoimmune and autoinflammatory disorders were not observed in toxicology studies but are a theoretical risk of any adjuvanted vaccine. The risk of developing such conditions with RSV sF or MEDI7510 is unknown.

Subjects will be monitored for important potential risks in MEDI7510 clinical trials, and routine pharmacovigilance and risk minimization activities will be performed.

There are no current preventive or therapeutic strategies for RSV in older adults. The possibility of benefit from participating in this study is unknown, and benefit will not be assessed in this study. It is possible that some subjects in this study might receive a vaccine that has some level of efficacy against RSV disease. Efficacy of MEDI7510 has been demonstrated in experiments in which vaccinated animals have been protected from RSV disease.

## 1.6 Research Hypotheses

### 1.6.1 Primary Hypothesis

The primary hypothesis of this study is that administration of single ascending IM doses of the RSV sF antigen or MEDI7510 will be safe and well tolerated in adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions.

### 1.6.2 Secondary Hypotheses

The secondary hypotheses are that the administration of single ascending IM doses of RSV sF or MEDI7510 will result in dose-dependent humoral immune responses in adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions,

and that MEDI7510 will induce cell-mediated immunity greater than that observed with RSV sF alone.

# 2 OBJECTIVES

## 2.1 Objectives

### 2.1.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of a single ascending IM dose of RSV sF or MEDI7510 in adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions.

### 2.1.2 Secondary Objectives

The secondary objectives of this study are:

1. To assess the humoral immune responses to RSV F following immunization with RSV sF or MEDI7510
2. To assess the cell-mediated (T-cell) immune responses to RSV F following immunization with RSV sF or MEDI7510

### 2.1.3 Exploratory Objective

The exploratory objective of this study is to further assess immune responses to RSV sF and MEDI7510 using exploratory assays.

## 2.2 Study Endpoints

### 2.2.1 Primary Endpoint

The primary endpoint is the safety and tolerability of single ascending doses of RSV sF and MEDI7510 as assessed by the occurrence of all solicited symptoms (whether or not treatment emergent) and treatment-emergent adverse events (AEs), serious adverse events (SAEs), new onset chronic diseases (NOCDs), and adverse events of special interest (AESIs) as follows:

- The proportion of subjects experiencing each solicited symptom from administration of investigational product (Day 1) through Day 7 post vaccination (7 days)
- The proportion of subjects experiencing each AE from administration of investigational product (Day 1) through Day 28 post vaccination (28 days)
- The proportion of subjects experiencing each SAE from administration of investigational product (Day 1) through Day 28 post vaccination (28 days)

- The proportion of subjects experiencing each SAE from administration of investigational product (Day 1) through Day 360 post vaccination (360 days)
- The proportion of subjects experiencing each NOCD from administration of investigational product (Day 1) through Day 360 post vaccination (360 days)
- The proportion of subjects experiencing each AESI from administration of investigational product (Day 1) through Day 360 post vaccination (360 days)

### 2.2.2 Secondary Endpoints

The secondary endpoints relate to the immunogenicity of RSV sF and MEDI7510 as follows:

1. Humoral immunity endpoints

- Post-dose GMTs and post-dose geometric mean fold rises (GMFRs) from baseline in RSV A neutralizing antibody on Days 29, 61, 91, 181, 271, and 361
- The proportion of subjects who experience a post-dose seroresponse to RSV on Days 29, 61, 91, 181, 271, and 361 as measured by neutralizing antibody to RSV A, with seroresponse defined as a ≥ 4-fold rise from baseline
- Post-dose GMTs and GMFRs from baseline of anti-F immunoglobulin G (IgG) antibodies as measured by an anti-F IgG assay derived from an RSV-specific 4-plex Meso Scale Discovery (MSD; Gaithersburg, MD) assay on Days 29, 61, 91, 181, 271, and 361
- The proportion of subjects who experience a post-dose seroresponse to RSV on Days 29, 61, 91, 181, 271, and 361 as measured by anti-F IgG assay, with seroresponse defined as ≥ 4-fold rise from baseline

2. Cellular immunity endpoints

- Post-dose geometric mean counts (GMCs) and GMFRs from baseline of RSV F peptide pool interferon gamma (IFNγ) ELISPOT responses on Days 8 and 29
- The proportion of subjects who experience a post-dose cell-mediated immune response to RSV F on Days 8 and 29 as measured by the RSV F peptide pool IFNγ ELISPOT assay

### 2.2.3 Exploratory Endpoints

Depending on assay availability and the availability of suitable samples, the following exploratory endpoints may be assessed to further evaluate immune responses to RSV:

- The proportion of subjects who experience a post-dose seroresponse to RSV on Days 29, 61, 91, 181, 271, and 361 as measured by palivizumab-competitive enzyme-linked immunosorbent assay (cELISA), with seroresponse defined as ≥ 4-fold rise from baseline
- Post-dose GMTs and GMFRs from baseline of palivizumab-competitive antibodies as measured by a palivizumab-cELISA on Days 29, 61, 91, 181, 271, and 361

- The proportion of subjects who experience a post-dose seroresponse to RSV on Days 29, 61, 91, 181, 271, and 361 as measured by neutralizing antibody to RSV B, with seroresponse defined as a ≥ 4-fold rise from baseline
- Post-dose GMTs and GMFRs from baseline of RSV B neutralizing antibodies on Days 29, 61, 91, 181, 271, and 361
- The number of RSV F-specific CD8+ and CD4+ T cells that secrete interleukin 2 (IL-2), IFNγ, tumor necrosis factor alpha (TNF-α), interleukin 4 (IL-4), interleukin 5 (IL-5), and/or other cytokines prior to and post dosing in subjects who received MEDI7510. An exploratory intracellular cytokine flow cytometry assay may be used for these analyses
- The types of cytokines (Th1 vs Th2 vs inflammatory) secreted by RSV F-specific T cells prior to and post dosing in subjects who received MEDI7510. An exploratory Luminex assay for Th1/Th2 cytokines may be used for these analyses

# 3 STUDY DESIGN

## 3.1 Description of the Study

### 3.1.1 Overview

This is a Phase 1a, FTIH, double-blind, randomized, placebo-controlled, cohort escalation study evaluating the safety and tolerability of a single ascending IM dose of RSV sF or MEDI7510 in adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions. Approximately 144 subjects will be enrolled at approximately 3 study centers in the US and randomized in a 5:1 ratio by cohort to receive a dose of either RSV sF or placebo or MEDI7510 or placebo on Day 1 in ascending doses as follows:

- Cohort 1: 20 µg RSV sF (n = 20) or placebo (n = 4) as a single IM injection
- Cohort 1a: 20 µg MEDI7510 (n = 20) or placebo (n = 4) as a single IM injection
- Cohort 2: 50 µg RSV sF (n = 20) or placebo (n = 4) as a single IM injection
- Cohort 2a: 50 µg MEDI7510 (n =20) or placebo (n = 4) as a single IM injection
- Cohort 3: 80 µg RSV sF (n = 20) or placebo (n = 4) as a single IM injection
- Cohort 3a: 80 µg MEDI7510 (n = 20) or placebo (n = 4) as a single IM injection

For Cohorts 1a, 2a, and 3a, the indicated dose for MEDI7510 represents the RSV sF dose, and the GLA-SE dose will be fixed at 2.5 µg GLA + 2% (w/v) SE.

Dosing within each cohort will be staggered as described in Section 3.1.2. Cohort escalation will occur after all subjects in the previous cohort(s) are followed for 7 days as described in Section 3.1.3, with parallel cohort progression for Cohorts 1a and 2, and Cohorts 2a and 3 as

described in Section 3.1.3. In addition, cohorts may be expanded to improve safety assessment in accordance with Section 3.1.3.

One interim analysis is planned after all subjects have completed 90 days post dose safety follow-up (Section 4.8.6). This interim analysis will provide safety and immunogenicity data needed to select an antigen dose to include in the Phase 1b study, which will explore GLA-SE adjuvant doses in combination with the selected dose of RSV sF antigen.

Subjects will be in the study for a little more than a year (56 weeks), which includes a screening period of up to 30 days, a treatment period of 1 day, and a 360-day posttreatment safety follow-up period.

A study schematic is shown in Figure 3.1.1-1.

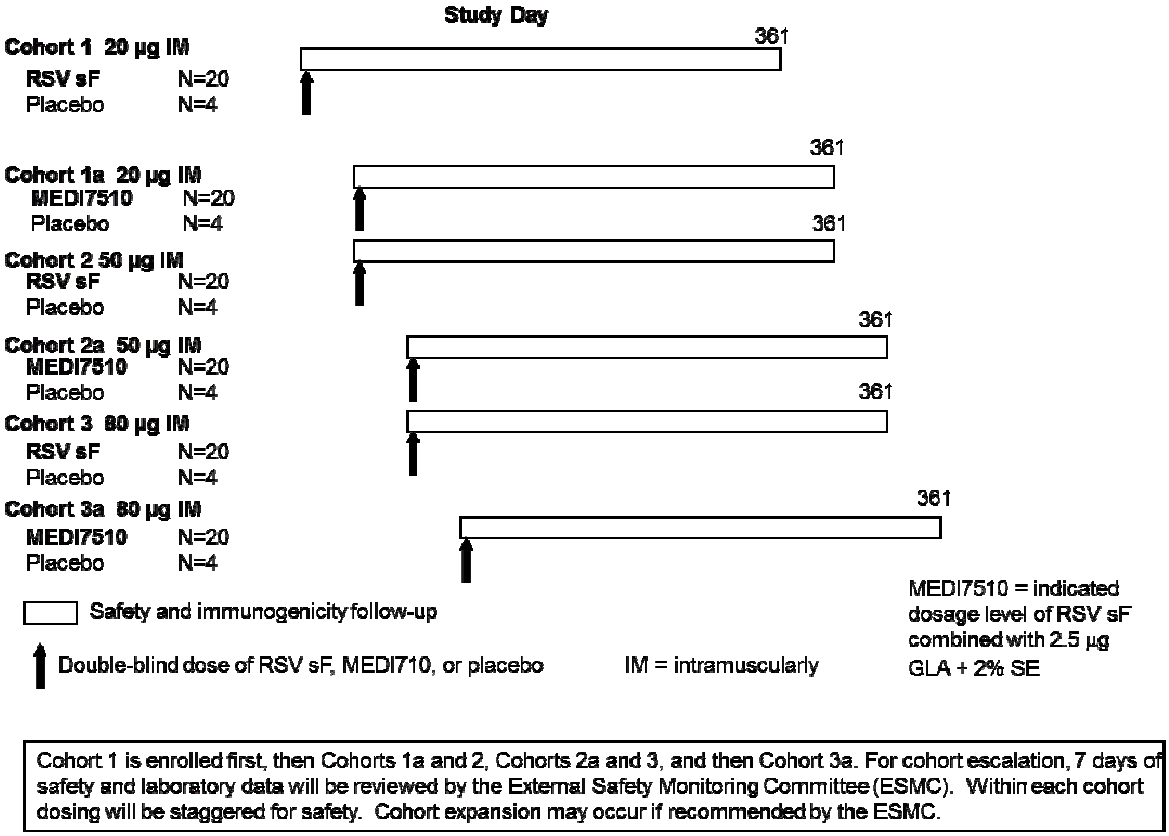


**Figure 3.1.1-1 Study Flow Diagram**

ESMC= external safety monitoring committee; GLA = glucopyranosyl lipid A; IM = intramuscularly; RSV sF = respiratory syncytial virus soluble fusion (protein); SE = squalene emulsion

The endpoints to be measured in this study are described in Section 2.2.

### 3.1.2 Treatment Regimen

A total of 144 subjects is planned to be randomized at a 5:1 ratio in 6 cohorts to receive a single dose of either RSV sF or placebo or MEDI7510 or placebo administered by IM injection on Day 1 as described in Table 3.1.2-1.

**Table 3.1.2-1 Treatment Regimen**

| Cohort | Number of Subjects | Treatment Regimen |
|---|---|---|
| 1 | 24 | 20 µg RSV sF (N = 20) or placebo (N = 4) as a single IM dose |
| 1a | 24 | 20 µg MEDI7510 (N = 20) or placebo (N = 4) as a single IM dose |
| 2 | 24 | 50 µg RSV sF (N = 20) or placebo (N = 4) as a single IM dose |
| 2a | 24 | 50 µg MEDI7510 (N = 20) or placebo (N = 4) as a single IM dose |
| 3 | 24 | 80 µg RSV sF (N = 20) or placebo (N = 4) as a single IM dose |
| 3a | 24 | 80 µg MEDI7510 (N = 20) or placebo (N = 4) as a single IM dose |

GLA = glucopyranosyl lipid A; IM = intramuscular; RSV sF = respiratory syncytial virus soluble fusion antigen; SE = squalene emulsion; w/v = weight per volume

Note: MEDI7510 comprises RSV sF with 2.5 µg GLA + 2% (w/v) SE; placebo = normal saline

**Staggering of Dosing**

Within individual cohorts, dosing will be staggered for safety. A minimum of 3 days is required between the initial (N = 5) and final (N = 19) dosing groups of subjects within each cohort.

### 3.1.3 Cohort Escalation

A partially parallel cohort progression design will be used for this study, with collection, compilation, and assessment by the External Safety Monitoring Committee (ESMC) of a total of 7 days of safety and laboratory data from the preceding single or concurrent cohorts required prior to enrolling in the subsequent cohort(s). In this schema, Cohort 1 will be enrolled first and all subjects in Cohort 1 will be followed for safety for 7 days prior to enrollment in any subsequent cohort(s). Cohort progression will occur after review of all cumulative safety data, including safety laboratory data (but not including immunogenicity data) by the MedImmune medical monitor, who will review only blinded data, and the ESMC, who will review blinded data and can choose to also review unblinded data. The principal investigators are invited to the open session for blinded review of data. External Safety Monitoring Committee review of cohort progression is described in Section 4.8.5. If there are no safety concerns, Cohorts 1a and 2 may enroll at the same time. After all subjects in those cohorts have been followed for 7 days, Cohorts 2a and 3 will be enrolled in the same

fashion. After all subjects in Cohorts 2a and 3 have been followed for 7 days, Cohort 3a will be completed.

Cohort expansion will occur at the recommendation of the ESMC as described in Section 4.4.1. If cohort expansion occurs, a total of 12 subjects will be added to the expanded cohort with the same randomization ratio (5:1) applied.

### 3.1.4 Management of Study Medication-related Toxicities

Toxicities related to vaccine administration will be treated in accordance with best medical practices for the observed event.

## 3.2 Study Design and Dose Rationale

The study will be randomized, placebo-controlled, and double-blind to ensure a robust design and minimize bias.

The sample size for this study is selected to support the assessment of the safety of MEDI7510.

Both antibody and cell-mediated immunity are considered to be important to the immune response in the target population of older adults, with the adjuvant expected to provide for the cell-mediated responses that would not be expected from RSV sF alone and also to contribute to the duration of antibody responses. Thus, after the initial safety of a dose of RSV sF has been assessed, that dose will be assessed in combination with a low dose of adjuvant. An antigen dosage that maximizes humoral and cell-mediated immune responses and that is safe and tolerable will be selected for further study.

Subjects will be followed for 360 days after dosing both to assess the long-term safety of the antigen and adjuvant combination and to permit assessment of the duration of the immune response.

### 3.2.1 Dose Rationale

Starting doses of 20 µg of RSV sF initially alone and then, as MEDI7510, with 2.5 µg GLA in 2% (w/v) SE are proposed for the Phase 1a single-dose study based on FTIH dosing considerations. The 2.5 µg dose of GLA in combination with 2% (w/v) SE was selected to be a low dose based on FTIH dosing considerations but to be high enough to permit assessment of adjuvant effect on immune responses and to support selection of a dose of antigen to be assessed with ascending doses of GLA-SE in a subsequent Phase 1b study. These proposed initial doses provide safety factors of > 130-fold for the antigen dose and > 60-fold for the

adjuvant dose compared to the NOAEL for systemic toxicities observed in the Good Laboratory Practice (GLP) toxicity studies in animals, based on a human equivalent dose comparison. The highest dose of MEDI7510 to be tested in this Phase 1a protocol will be 80 µg RSV sF with 2.5 µg GLA in 2% (w/v) SE. The GLP toxicity study found no significant safety issues at a dose of 90 ± 12 µg RSV sF with 5 µg GLA in 2% (w/v) SE, the highest dose tested; therefore, safety margins for humans, based on body weight comparisons, were approximately 110-fold in the rat. These studies conservatively support single clinical doses of up to 80 µg RSV sF with 5 µg GLA in 2% (w/v) SE.

### 3.2.2 Rationale for Study Population

The subject population selected for this FTIH study is that of older adults, a group that will be the target of efficacy studies of this vaccine because older adults are at greater risk of medically significant RSV disease than younger adults. Older adults also have been shown to have an immune response to RSV that differs from that of younger adults in that, while their antibody levels are similar to those of younger individuals, they have lower cell-mediated immune responses (Cherukuri et al, 2013).

A population of older adults that is generally healthy or that has stable, chronic underlying medical conditions was selected for this FTIH study, because enrolling adults ≥ 60 years of age who are completely healthy did not appear feasible and, in addition, would skew the enrollment population towards those closer to 60 years of age. Subjects with any history of autoimmune disorder will be excluded from this FTIH study because some subjects will receive adjuvant. Immunosuppressed subjects will also be excluded because they would be expected to have altered immune responses to vaccines. Finally, in the absence of any data on local site reactions, subjects with a history of thrombocytopenia or bleeding disorder will be excluded from this FTIH protocol. These older adults are an acceptable study population for this FTIH study from a safety perspective, and a preferred study population from an immunological perspective, because they represent the target population for the MEDI7510 vaccine. Younger adults do not have deficient cell-mediated immune responses and thus would not provide data for dose selection in older adults (Cherukuri et al, 2013). Older adults with more complicated medical problems, although ultimately planned for inclusion in future studies, will not be included in this FTIH study both to enhance the safety of the subjects and to provide a clearer assessment of vaccine safety.

### 3.2.3 Rationale for Endpoints

The primary endpoint for this study is intended to assess the safety and tolerability of single ascending IM doses of RSV sF antigen and MEDI7510 in adults ≥ 60 years of age who are

healthy or who have stable, chronic underlying medical conditions. Local and systemic solicited symptoms occurring during the week post dosing are important measures of tolerability. Adverse events and SAEs temporally associated with dosing will be collected to assess safety. Longer term evaluation will assess events, including SAEs, NOCDs, and AESIs, that may warrant increased follow-up in an adjuvanted vaccine.

The secondary endpoints are designed to assess both humoral and cell-mediated immunity. Humoral immunity will be assessed by a microneutralization assay for RSV A and an RSV F-specific IgG antibody assay. Cellular immunity will be measured by an RSV F peptide pool IFNγ ELISPOT assay, an assay selected for sensitivity and reproducibility.

# 4 MATERIALS AND METHODS

## 4.1 Subjects

### 4.1.1 Number of Subjects

Approximately 144 subjects will be enrolled at approximately 3 study centers in the US.

### 4.1.2 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1. Age ≥ 60 years at the time of screening
2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA]) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
3. Ambulatory or ambulatory with assistance (not institutionalized, bedridden, or homebound)
4. Weight ≥ 110 lbs (≥ 50 kg)
5. Hemoglobin within normal range for age and gender
6. Subject available by telephone
7. Subject able to understand and comply with the requirements of the protocol, as judged by the investigator
8. Subject able to complete follow-up period of 360 days after dosing as required by the protocol

### 4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. History of allergy to any component of the vaccine

2. Pregnancy or potential to become pregnant during the study. Females who (1) have had a menstrual period within the 12 months prior to study enrollment or (2) are undergoing any fertility treatment or who plan to undergo fertility treatments during the study period are excluded
3. Any unstable chronic medical condition, including one that has resulted in change in therapy (medication or other) in the 30 days prior to randomization or hospitalization in the previous year or might be predicted to result in hospitalization in the year after enrollment. Subjects with severe, untreated or uncontrolled underlying medical disease that might either compromise subject safety or affect the ability to assess safety of the investigational product are excluded
4. Clinically significant abnormalities in screening laboratory assessments or screening electrocardiogram (ECG), according to the judgment of the investigator
5. History of hepatitis B or hepatitis C infection
6. Cognitive disorder such that informed consent cannot be obtained directly from the subject
7. Previous vaccination against RSV
8. History of allergy to eggs in adulthood
9. History of or current autoimmune disorder (stable, treated hypothyroidism caused by Hashimoto's thyroiditis is acceptable)
10. Immunosuppression caused by disease, including human immunodeficiency virus (HIV) infection, or medications. Any oral prednisone dosing within 30 days of enrollment or planned dosing within the 360-day follow-up period would disqualify. Topical, intranasal, inhaled, or intra-articular corticosteroids do not disqualify. Expected need for immunosuppressive medications during the 360-day follow-up period would disqualify
11. History of splenectomy or of condition affecting splenic function (eg, hemoglobinopathy)
12. History of cancer within preceding 5 years other than treated non-melanoma skin cancer
13. Body mass index (BMI) $\geq 40$
14. Significant infection or other acute illness, including fever $\geq 100°F$ ($\geq 37.8°C$) on the day prior to or day of randomization
15. Receipt of any nonstudy vaccine within 30 days prior to study dosing or expected receipt of nonstudy vaccine within 30 days after study dosing
16. Receipt of any investigational product in the 90 days prior to randomization or expected receipt of investigational product during the period of study follow-up
17. Receipt of immunoglobulins or blood products within 4 months of study dosing (120 days) or expected receipt of investigational product during the period of study follow-up
18. History of thrombocytopenia or bleeding disorder or use of anticoagulants such as warfarin, heparin/low molecular weight heparin, thrombin inhibitors (dabigatran and others), or factor Xa inhibitors (rivaroxaban, apixaban, and others). Subjects receiving drugs with anti-platelet activity such as nonsteroidal antiinflammatory drugs, clopidogrel or aspirin are not excluded.

19. Expected receipt of antipyretic or analgesic medication on a daily or every other day basis from randomization through 72 hours after receipt of investigational product (Note: A daily dose of ≤ 163 mg of aspirin is not considered a contraindication to enrollment.)
20. Subjects who have significant scarring, tattoos, abrasions, cuts, or infections over the deltoid region of both arms that, in the opinion of the investigator, could interfere with evaluation of injection site local reactions.
21. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results
22. Concurrent enrollment in another clinical study that involves any invasive clinical procedure, including phlebotomy.
23. History of alcohol or drug abuse or psychiatric disorder that, in the opinion of the investigator, would affect the subject's safety or compliance with study
24. Employees of individuals directly involved with the conduct of the study, individuals who themselves are involved with the conduct of the study, or immediate family members of such individuals

### 4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by an interactive web response system (IWRS), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not be randomized or receive investigational product. These subjects may be reconsidered for enrollment if failure was due to a time-limited exclusion as long as the subject continues to meet all other eligibility criteria. Subjects who failed to meet laboratory or ECG criteria may not be enrolled based on repeated testing unless original testing resulted in laboratory error. Rescreening of the same subject is permitted if randomization did not occur within 30 days of screening, as described in Section 4.2.1.

### 4.1.5 Withdrawal from the Study

Subjects are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Subjects who

withdraw from the study will always be asked about the reason(s) for withdrawal and about the presence of any AEs. If possible, subjects who withdraw consent will be seen and assessed by the investigator. Adverse events will be followed up; diary cards should be completed and returned by the subject. If a subject withdraws consent from all further participation in the study, then no further study visits or data collection should take place. Subjects who withdraw consent for phlebotomy but not for safety follow-up should continue to be followed for safety events in accordance with the protocol. Telephone contacts may be substituted for face-to-face visits in these subjects.

### 4.1.6 Discontinuation of Investigational Product

Because this is a single dose vaccine study, discontinuation of investigational product does not apply.

### 4.1.7 Replacement of Subjects

Subjects who are randomized but not dosed may be replaced. At the discretion of the sponsor or at the recommendation of the ESMC, subjects who drop out of the study for reasons other than safety before Day 28 may also be replaced. The replacement subject will receive the same treatment assignment as the corresponding subject being replaced.

### 4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

**Biological Samples Obtained for the Main Study**

Study data are protected by the use of a SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any data or samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

**Samples Obtained for Future Research**

Samples obtained for future research will be labeled with a sample identification number but will not be labeled with personal identifiers such as the subject's name. A file linking this sample identification number with the SID number will be kept in a secure place at the sponsor with restricted access. If the subject withdraws consent for participating in the future research, this link will allow the sponsor to locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's sample(s) have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

## 4.2 Schedule of Study Procedures

All subjects who are assigned a SID number and receive any investigational product will be followed according to the protocol unless consent is withdrawn. The investigator must notify the sponsor or designee of deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule. Protocol deviations will be recorded on the source document with an explanation for the deviation and on logs designated for capturing protocol deviations. The investigator must comply with the applicable requirements related to the reporting of protocol deviations to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

### 4.2.1 Enrollment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at the screening visit. Assessments should be performed in the order shown in the table except that vital signs, height, and weight may be performed at any point in the history and physical examination. Urinalysis may be performed at any time after informed consent has been obtained.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, phlebotomy should occur after the vital signs and ECG have been completed.

A subject who is to be rescreened will be considered a screening failure and, after providing informed consent a second time, will be rescreened, including all Visit 1 (Day -30 to Day -1) assessments. Subjects who are screening failures based on abnormalities of laboratory values or ECG abnormality may not be rescreened.

### Table 4.2.1-1 Schedule of Screening Procedures

| Study Period | Screening |
|---|---|
| **Visit No.** | **V1** |
| **Procedure / Study Day** | **Day -30 to Day -1** |
| Written informed consent/assignment of SID number | X |
| Medical history including concomitant medications and assessment of AEs and SAEs | X |
| Physical examination, weight, height, vital signs | X |
| ECG | X |
| Blood for chemistry, hematology, and coagulation parameters | X |
| Urinalysis | X |
| Verify eligibility criteria | X |

AE = adverse event; ECG = electrocardiogram; SAE = serious adverse event; SID = subject identification; V = visit

## Description of Study Procedures, Screening, Visit 1

All screening procedures must be performed within 30 days before randomization (Day -30 to Day -1). The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations. However, if evaluations that have been performed for other purposes prior to informed consent are otherwise suitable for use as screening evaluations, they need not be repeated if the subjects allow use.

1. Obtain written informed consent and appropriate privacy act document authorization
2. Assign a SID number
3. Perform medical history
4. Perform physical examination, including height, weight, and vital signs
5. Perform an ECG (may be performed before or after physical examination)
6. Collect blood for screening samples, including serum chemistry, hematology and coagulation parameters
7. Collect urine for urinalysis
8. Assess AEs, SAEs

9. Record concomitant medications
10. Verify eligibility criteria

### 4.2.2 Randomized Treatment and Follow-up Periods

All randomized subjects will be followed for 360 days for safety and for vaccine immunogenicity. Subjects who plan to withdraw consent and who are willing to come to the study site should have study procedures for Day 361 performed unless blood for immunogenicity has been obtained within the previous 2 weeks. All subjects should have medical histories updated at the time of last contact to obtain the maximal duration of safety follow-up.

Subjects will be considered lost to follow-up only if no contact has been established by Day 361 + 10 days, such that there is insufficient information to ascertain the subject's status at that time. Subjects refusing to return to the site or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects until Day 361 + 10 days. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to the protocol.

Table 4.2.2-1 shows all procedures to be conducted during the randomized treatment and follow-up periods. Assessments on Day 1 should be performed in the order shown in the table, except that vital signs may be performed at any time prior to verification of eligibility criteria. For each phlebotomy, blood samples may be obtained in any order. Urinalysis may be performed at any time after randomization and before dosing.

## Table 4.2.2-1 Schedule of Treatment and Follow-up Periods Study Procedures

| **Study Period** | **Treat-ment Period** | **Follow-up Period** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit (V) /Telephone Contact (T) No.** | **V2** | **T3** | **V4** | **T5** | **V6** | **V7** | **V8** | **T9** | **T10** | **V11** | **T12** | **T13** | **V14** | **T15** | **T16** | **V17** |
| **Procedure/Study Day** | **D1** | **D3 +3** | **D8 +3** | **D14 +4** | **D 29 +4** | **D 61 ±5** | **D 91 ±5** | **D 121 ±12** | **D 151 ±12** | **D 181 ±12** | **D 211 ±12** | **D 241 ±12** | **D 271 ±12** | **D 301 ±12** | **D 331 ±12** | **D 361+10** |
| Medical history [a] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination (weight required D1 only) | X | | X [b] | | X [b] | X [b] | X [b] | | | X [b] | | | X [b] | | | X [b] |
| Vital signs | X [c] | | | | | | | | | | | | | | | |
| Verify eligibility criteria | X [d] | | | | | | | | | | | | | | | |
| Randomization | X | | | | | | | | | | | | | | | |
| Serum chemistry, hematology, and urinalysis [e] | X [d] | | X | | X | | | | | | | | | | | |
| Serum storage at baseline for potential later use for safety assessment | X [d] | | | | | | | | | | | | | | | |
| Humoral immunogenicity serum sample | X [d] | | | | X | X | X | | | X | | | X | | | X |
| Cell-mediated immunity PBMC (whole blood) sample | X [d] | | X | | X | | | | | | | | | | | |
| **Investigational product administration followed by 30 minutes of observation with vital signs prior to discharge** | **X** | | | | | | | | | | | | | | | |
| Provide thermometers, tape measures and diary cards [f] | X | | | | | | | | | | | | | | | |

## Table 4.2.2-1 Schedule of Treatment and Follow-up Periods Study Procedures

| Study Period | Treat-ment Period | Follow-up Period | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit (V) /Telephone Contact (T) No.** | **V2** | **T3** | **V4** | **T5** | **V6** | **V7** | **V8** | **T9** | **T10** | **V11** | **T12** | **T13** | **V14** | **T15** | **T16** | **V17** |
| **Procedure/Study Day** | **D1** | **D3 +3** | **D8 +3** | **D14 +4** | **D 29 +4** | **D 61 ±5** | **D 91 ±5** | **D 121 ±12** | **D 151 ±12** | **D 181 ±12** | **D 211 ±12** | **D 241 ±12** | **D 271 ±12** | **D 301 ±12** | **D 331 ±12** | **D 361+10** |
| Assessment of solicited symptoms | X | X | X | | | | | | | | | | | | | |
| Assessment of AEs | X | X | X | X | X | | | | | | | | | | | |
| Assessment of SAEs, NOCDs, AESIs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| All concomitant medications or prohibited concomitant medications only | X [g] | X [g] | X [g] | X [g] | X [g] | X [h] | X [h] | X [h] | X [h] | X [h] | X [h] | X [h] | X [h] | X [h] | X [h] | X [h] |

AE = adverse event; AESI = adverse event of special interest; D = Day; NOCD = new onset chronic disease; PBMC = peripheral blood mononuclear cells; SAE = serious adverse event; V = subject visit; T = telephone follow-up

[a] Update history for interim events or clarification or update (targeted) physical examination of areas suggested by medical history. Additional laboratory tests may be performed as clinically indicated, and abnormal laboratory values must be repeated for confirmation

[b] Targeted physical examination, if appropriate

[c] Prior to and 20 to 30 minutes after dosing

[d] Prior to dosing

[e] A baseline serum sample will be retained for all subjects to be used if an AESI occurs for which a baseline marker might help to clarify the temporal relationship to vaccination. Samples left over from the clinical laboratory testing at other timepoints will also be retained to assess safety events that might theoretically be related to an adjuvanted vaccine.

[f] After providing first set, only provide thermometers and tape measures if replacement needed

[g] All concomitant medications. On the dosing visit (V2), concomitant medications should be assessed prior to dosing to include in assessment of eligibility.

[h] Prohibited concomitant medications only (Section 4.7.2)

#### 4.2.2.1 Description of Study Procedures, Treatment Period

### Day 1: Dosing (Visit, V2)

1. Update medical history, including concomitant medications
2. Perform physical examination to update since screening, including weight
3. Collect vital signs
4. Verify eligibility criteria
5. Randomize and assign product kit number
6. Collect urine for urinalysis (may be collected after phlebotomy)
7. Collect blood samples (see Laboratory Manual for details):
   - for serum chemistry and hematology
   - for potential use in assessing treatment-emergent safety events
   - for humoral immunogenicity assays
   - for cell-mediated immunogenicity assays
8. Administer investigational product and observe for at least 30 minutes. Vital signs must be repeated between 20 and 30 minutes post dose.
9. Provide thermometers, diary cards, tape measures, and instructions for completing diary cards; ensure subject understands how to measure local reactions and take temperature
10. Assess for all solicited symptoms, and treatment-emergent AEs, SAEs, NOCDs, and AESIs
11. Record all concomitant medications

#### 4.2.2.2 Description of Study Procedures, Follow-up

A description of each follow-up study visit and telephone contact is provided below.

### Day 3 + 3 (Telephone Contact, T3)

1. Update medical history
2. Assess for all solicited symptoms, and treatment-emergent AEs, SAEs, NOCDs, and AESIs
3. Update all concomitant medications

### Day 8 + 3 (Visit, V4)

1. Update medical history, perform targeted physical examination if appropriate
2. Assess for all solicited symptoms, AEs, SAEs, and treatment-emergent NOCDs and AESIs
3. Update all concomitant medications
4. Collect urine for urinalysis (may be collected after phlebotomy)
5. Collect blood samples:

- for serum chemistry and hematology
- for cell-mediated immunogenicity assays

### Day 14 + 4 (Telephone Contact, T5)

1. Update medical history
2. Assess for all treatment-emergent AEs, SAEs, NOCDs, and AESIs
3. Update all concomitant medications

### Day 29 + 4 (Visit, V6)

1. Update medical history, perform targeted physical examination if appropriate
2. Assess for all treatment-emergent AEs, SAEs, NOCDs, and AESIs
3. Update all concomitant medications
4. Collect urine for urinalysis (may be collected after phlebotomy)
5. Collect blood samples:
   - for serum chemistry and hematology
   - for humoral immunogenicity assays
   - for cell-mediated immunogenicity assay

### Day 61 ± 5 (Visit, V7)

1. Update medical history, perform targeted physical examination if appropriate
2. Assess for all treatment-emergent SAEs, NOCDs, and AESIs
3. Assess prohibited concomitant medications
4. Collect serum sample for humoral immunogenicity assays

### Day 91 ± 5 (Visit, V8)

1. Update medical history, perform targeted physical examination if appropriate
2. Assess for all treatment-emergent SAEs, NOCDs, and AESIs
3. Assess prohibited concomitant medications
4. Collect serum sample for humoral immunogenicity assays

### Day 121 ± 12 (Telephone Contact, T9)

1. Update medical history
2. Assess for all treatment-emergent SAEs, NOCDs, and AESIs
3. Assess prohibited concomitant medications

### Day 151 ± 12 (Telephone Contact, T10)

1. Update medical history
2. Assess for all treatment-emergent SAEs, NOCDs, and AESIs
3. Assess prohibited concomitant medications

### Day 181 ± 12 (Visit, V11)

1. Update medical history, perform targeted physical examination if appropriate
2. Assess for all treatment-emergent SAEs, NOCDs, and AESIs
3. Assess prohibited concomitant medications
4. Collect serum sample for humoral immunogenicity assays

### Day 211 ± 12 (Telephone Contact, T12)

1. Update medical history
2. Assess for all treatment-emergent SAEs,NOCDs, and AESIs
3. Assess prohibited concomitant medications

### Day 241 ± 12 (Telephone Contact, T13)

1. Update medical history
2. Assess for all treatment-emergent SAEs, NOCDs, and AESIs
3. Assess prohibited concomitant medications

### Day 271 ± 12 (Visit, V14)

1. Update medical history, perform targeted physical examination if appropriate
2. Assess for all treatment-emergent SAEs, NOCDs, and AESIs
3. Assess prohibited concomitant medications
4. Collect serum sample for humoral immunogenicity assays

### Day 301 ± 12 (Telephone Contact, T15)

1. Update medical history
2. Assess for all treatment-emergent SAEs, NOCDs, and AESIs
3. Assess prohibited concomitant medications

### Day 331 ± 12 (Telephone Contact, T16)

1. Update medical history
2. Assess for all treatment-emergent SAEs, NOCDs, and AESIs
3. Assess prohibited concomitant medications

### Day 361 + 10 (Visit, V17)

1. Update medical history, perform targeted physical examination if appropriate
2. Assess for all treatment-emergent SAEs, NOCDs, and AESIs
3. Assess prohibited concomitant medications
4. Collect serum sample for humoral immunogenicity assays

## 4.3 Description of Study Procedures

### 4.3.1 Efficacy

This is a Phase 1a safety and immunogenicity study in healthy subjects, therefore disease evaluation is not planned.

### 4.3.2 Medical History and Physical Examination, Electrocardiogram, Weight, and Vital Signs

A complete medical history will be performed at screening and will be updated (targeted physical examination) at each subsequent subject visit to ensure adherence to inclusion/exclusion criteria, to identify safety events, and to identify events or medications that could affect study outcomes. A physical examination, including vital signs, will be conducted at screening (pelvic and rectal examinations are not required) and height and weight will be obtained. Physical examination, including weight and vital signs, will be updated on the day of dosing prior to administration of study vaccine.

At each study visit, targeted physical examinations will be performed if any AEs have occurred that would warrant an examination (for example, lung examination in the case of bronchitis; skin examination in the case of a rash, etc). Vital signs, height, and weight do not need to be performed except as needed for the assessment of an AE. A licensed, independent healthcare provider must perform the physical examinations in accordance with state licensing regulations. Height will be obtained at screening only.

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be obtained at screening and on the day of dosing prior to and at 20 to 30 minutes post dose. Temperature

may be collected by any route (Marcy et al, 2004). Abnormal vital signs must be repeated after the subject has been at rest for at least 5 minutes.

An ECG will be obtained at the screening visit with the subject supine.

### 4.3.3 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests will be performed in a licensed central clinical laboratory. Clinically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 72 hours).

The following clinical laboratory tests will be performed (see Table 4.2.1-1 and Table 4.2.2-1 for the schedules of tests):

**Serum Chemistry**

- Calcium
- Chloride
- Potassium
- Sodium
- Bicarbonate
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Alkaline phosphatase (ALP)
- Total and direct bilirubin
- Gamma glutamyl transferase (GGT)
- Creatinine
- Blood urea nitrogen (BUN)
- Glucose
- Albumin
- Total protein

**Note for serum chemistries:** Tests for AST, ALT, ALP, and total and direct bilirubin must be conducted concurrently and assessed concurrently.

**Hematology**

- White blood cell (WBC) count with differential
- Hematocrit
- Hemoglobin
- Platelet count

**Urinalysis**

- Color
- Appearance
- Microscopy including WBC/high power field (HPF), red blood cell (RBC)/HPF
- Specific gravity
- pH
- Dipstick assessment*

*Dipstick assessment must include at least glucose, blood, and protein; other parameters may be included depending on the characteristics of the dipstick being used

**Other Safety Tests**

- Coagulation tests: prothrombin time (PT), partial thromboplastin time (PTT) at screen only

A baseline serum sample will be retained for all subjects to be used if an AESI occurs for which a baseline marker might help to clarify the temporal relationship to vaccination. Samples left over from clinical laboratory testing at other timepoints will also be retained to assess safety events that might theoretically be related to an adjuvanted vaccine.

### 4.3.4 Immunogenicity Evaluation and Methods

Samples for immunogenicity testing will be obtained and handled in accordance with the Laboratory Manual provided separately.

#### 4.3.4.1 Humoral Immunity

Humoral immunity against RSV will be assessed by:

- RSV A microneutralization assay
- Anti-F IgG assay (derived from RSV-specific 4-plex MSD assay)

Humoral immunity to detect wild-type RSV infection will be assessed by RSV anti-Ga, anti-Gb or anti-N antibodies (derived from RSV-specific 4-plex MSD assay).

#### 4.3.4.2 Cell-mediated Immunity

Cell-mediated immunity will be assessed using an IFNγ ELISPOT assay to measure T-cell responses to the RSV F peptide pool using thawed, cryopreserved peripheral blood mononuclear cell (PBMC) samples (Patton et al, submitted).

### 4.3.5 Estimate of Volume of Blood to Be Collected

The amount of blood to be taken from an individual subject is estimated on a per-day basis across all tests combined and totaled for the study in Table 4.3.5-1. Additional samples may be obtained for assessment of safety; for example, clinically significant abnormal laboratory values are to be repeated, preferably within 24 to 72 hours, and certain AESIs for an adjuvanted vaccine may require serologic assessment such as antinuclear antibody, rheumatoid factor, etc. The baseline stored sample for safety will be used to assess such serologies if warranted by a clinical event. The maximum total volume of blood that will not be exceeded in the study for a given subject is approximately 224 mL per 6-week period (unless additional laboratory tests are performed for medical management).

**Table 4.3.5-1 Estimated Blood Volume to be Collected by Visit**

| Visit Day | Visit Number | Estimated Blood Volume (mL) |
|---|---|---|
| Day -30 to Day -1 | 1 | 8.2 |
| Day 1 | 2 | 67 |
| Day 8 | 4 | 55.5 |
| Day 29 | 6 | 65.5 |
| Day 61 | 7 | 10 |
| Day 91 | 8 | 10 |
| Day 181 | 11 | 10 |
| Day 271 | 14 | 10 |
| Day 361 | 17 | 10 |
| Total | | 246.20 |

## 4.4 Study Suspension or Termination

The Sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects. See Section 4.4.1 for specific study-stopping criteria
2. Subject enrollment is unsatisfactory
3. Noncompliance that might significantly jeopardize the validity or integrity of the study

If MedImmune determines that temporary suspension or termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advanced notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

### 4.4.1 Enrollment and Dosing Stopping Criteria

If any of the following events occur, administration of investigational product will be stopped and no additional subjects will be randomized into the study until review by the ESMC. Events that meet enrolling and dosing stopping criteria 1 through 4 must be reported within 24 hours of knowledge of the event to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 5.6 for contact information). The occurrence of these events does not automatically make an AE serious but, if the consequences of the event are serious, for example, death or hospitalization, the event is serious and must be reported as an SAE (see Section 5.2).These events may or may not be considered to be serious (ie, may or may

not meet criteria for SAEs as described in Section 5.2). Events that might meet enrollment and dosing stopping criteria 5 and 6, particularly investigational product-related Grade 3 or Grade 4 AEs, must first be conveyed to the site monitor and then be entered into the electronic case report form (eCRF) within 24 hours of awareness of the event to trigger reporting to the medical monitor.

1. Death in any subject in which the cause of death is assessed as related to investigational product
2. Anaphylactic reaction related to investigational product in any subject
3. Adverse event of special interest for an adjuvanted vaccine other than new onset or exacerbation of thyroid disorders occurring in any subject enrolled in a cohort dosing with MEDI7510 (RSV sF cohorts may continue dosing and enrolling if this stopping criterion is met)
4. Any SAE assessed as related to investigational product, or any SAE that is not clearly and obviously unrelated to investigational product
5. Any single Grade 4 AE assessed as related to investigational product occurring in any cohort or any two Grade 3 AEs of the same type assessed as related to investigational product occurring in more than one subject in any single cohort
6. Any other safety finding assessed as related to investigational product that, in the opinion of the investigators, the sponsor, or the ESMC might contraindicate further dosing of study subjects

If any of the above-listed events occurs, investigators will be notified immediately. The US Food and Drug Administration (FDA) will be promptly notified, and IRBs/IECs should be notified by investigators in accordance with their IRB/IEC's requirements. The ESMC will perform a prompt cumulative review of safety data and the circumstances of the event in question in order to make a recommendation to MedImmune regarding continued dosing. MedImmune will review the ESMC recommendation and the events to decide on a course of action. This review will be shared with the US FDA and investigators, who should submit to their IRB/IEC in accordance with its requirements. If the AE is considered potentially dose limiting but permits continued assessment, another 12 subjects may be enrolled in the same dose cohort. If the AE is considered dose limiting for the current dose cohort, another 12 subjects may be enrolled in the next lower MEDI7510 dosing cohort.

Any subjects who have already received investigational product and are currently in the study at the time dosing-stopping criteria are met will continue to be followed by the investigator for safety.

## 4.5 Investigational Products

### 4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational products (Table 4.5.1-1) and diluent using designated distribution centers. Sites will provide sterile 0.9% saline for injection to serve as a placebo and sterile water for injection (sWFI) to use to reconstitute the lyophilized RSV sF, as well as 0.3-mL and 1-mL syringes, and sterile 3-mL vials in which to mix the ingredients for each active vaccine dose in accordance with Section 4.5.1.1.

**Table 4.5.1-1 Identification of Investigational Products**

| Investigational Product | Manufacturer | Concentration and Formulation as Supplied |
|---|---|---|
| MEDI7510 (RSV sF plus GLA-SE) | | |
| RSV sF | MedImmune | [redacted] |
| GLA-SE | Althea Technologies, San Diego, CA. Supplied by IDC, Seattle, WA | [redacted] |
| SE | Althea Technologies, San Diego, CA. Supplied by IDC, Seattle, WA | [redacted] |
| Saline placebo | To be provided by study sites | 0.9% saline for injection |
| Diluent for reconstitution of lyophilized RSV sF | To be provided by study sites | Sterile water for injection |
| Diluent to prepare clinical doses of RSV sF | MedImmune | [redacted] |

GLA = glucopyranosyl lipid A; GLA-SE = glucopyranosyl lipid A in 2% (w/v) stable emulsion (SE); HCl = hydrochloride; IDC = Immune Design Corporation; KCl = potassium chloride; RSV sF = respiratory syncytial virus soluble fusion antigen; SE = stable emulsion; w/v = weight per volume

RSV sF, GLA-SE, SE, and diluent to prepare clinical doses of RSV sF or MEDI7510 (ie, all investigational product materials supplied by MedImmune) must be stored at 2°C to 8°C (36°F to 46°F) prior to mixing.

Saline placebo and sWFI must be stored in accordance with manufacturer's instructions.

All investigational product and diluent materials must be stored at 2℃ to 8℃ (36°F to 46°F).

Investigational product will be supplied to the site in unblinded kits that must be stored at 2℃ to 8℃ (36°F to 46°F). Kits for subjects randomized to receive RSV sF alone will contain 2 vials: 1) 1 vial of lyophilized RSV sF and 2) 1 vial of diluent. Kits for subjects randomized to receive MEDI7510 will contain 4 vials: 1) 1 vial of lyophilized RSV sF; 2) 1 vial of GLA-SE; 3) 1 vial of SE; and 4) 1 vial of diluent.

Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton is labeled with a unique number range that corresponds to the labeled number series of the containers within the carton. The identity of the unblinded kit assigned to any subject must not be revealed to subjects, site staff, or sponsor staff.

Subjects randomized to placebo will receive a kit with a label only to assist in the reconciliation of saline placebo vials.

Because the vaccines can be visually differentiated, the unblinded pharmacist will blind the dosing by wrapping the bore of the injection syringe prior to any observation of the syringe by blinded study personnel or subjects.

#### 4.5.1.1 Investigational Product Dose Preparation

No per-subject dose calculation is required.

Study vaccine must be drawn into the injection syringe within 3 hours of mixing the dose in the mixing vial and must be administered within 30 minutes of drawing the dose from the mixing vial into the injection syringe.

## Investigational Product Inspection

Each vial selected for dose preparation should be inspected by the unblinded pharmacist. RSV sF is supplied as a lyophilized powder at [redacted]. Once reconstituted with [redacted] of sWFI, it should be a clear to colorless, slightly yellow liquid, free from visible particles, at a concentration of [redacted]. GLA-SE is supplied as a milky white liquid [redacted]. SE is supplied as a milky white liquid [redacted]. Diluent to prepare clinical doses of RSV sF is provided as a sterile clear, colorless to slightly yellow liquid, free from visible particles. All product vial volumes are

3 mL; the contents of individual vials can easily be distinguished by the color of the over seals (before the dose preparation step).

If there are any defects noted with the investigational product by the unblinded pharmacist, the investigator and site monitor should be notified immediately. Refer to the Reporting Product Complaints section (Section 4.5.1.4) for further instructions.

**Dose Preparation Steps**

Dose preparation steps for subjects receiving RSV sF or MEDI7510 are described in Appendix 5, by dose cohort. Dose preparation steps for placebo are also provided.

**Investigational Product Stability**

Total in-use storage time from reconstitution of investigational product to drawing investigational product into the injection syringe should not exceed 3 hours at room temperature, and storage time from drawing the investigational product into the syringe until administration should not exceed 30 minutes. If storage times exceed these limits, a new dose must be prepared from new vials.

RSV sF, GLA-SE, SE, and diluent for this study do not contain preservatives, and any unused portion must be discarded after investigational product accountability has been performed. Dilution and mixing of RSV sF and MEDI7510 for administration of all investigational products must be performed aseptically. A new, unopened vial of sWFI or 0.9% saline for injection must be opened for each individual subject. The used vials of sWFI and the saline must be retained until unblinded accountability is performed.

#### 4.5.1.2 Treatment Administration

The day of dosing is considered Day 1.

All personnel who administer study vaccines must be trained and licensed in accordance with state laws.

All subjects must be safely positioned prior to immunization so that they cannot be hurt in the case of syncope. Topical analgesia may not be applied at the injection site. Investigational product should be administered IM into the deltoid muscle of the upper arm with needle selection according to Table 4.5.1.2-1.

**Table 4.5.1.2-1 Injection Site and Needle Size for Intramuscular Injection**

| Subject Gender/Body Weight | Needle Gauge & Length (Inches) |
|---|---|
| Male or female 110 to < 130 lbs | 22-25 Gauge, 5/8 a |
| Female 130-200 lbs | 22-25 Gauge, 1 - 1½ |
| Male 130-260 lbs | |
| Female 200+ lbs | 22-25 Gauge, 1½ |
| Male 260+ lbs | |

IM = intramuscular

[a] A 5/8-inch needle may be used for subjects weighing less than 130 lbs (< 60 kg) for IM injection in the deltoid muscle only if the subcutaneous tissue is not bunched and the injection is made at a 90° angle.

Adapted from: http://www.cdc.gov/vaccines/recs/vac-admin/default.htm

To administer investigational product (see instructions at http://www.cdc.gov/vaccines/recs/vac-admin/default.htm):

- Follow standard administration guidelines for site assessment/selection and site preparation
- To avoid injection into subcutaneous tissue, spread the skin of the selected vaccine administration site taut between the thumb and forefinger, isolating the muscle. Another technique, acceptable for geriatric patients, is to grasp the tissue and "bunch up" the muscle
- Insert the needle fully into the muscle at a 90° angle and inject the vaccine into the tissue
- Withdraw the needle and apply light pressure to the injection site for several seconds with a dry cotton ball or gauze

Additional information about administration of vaccines is available at http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/D/vacc_admin.pdf

### 4.5.1.3 Monitoring of Dose Administration

Subjects should be observed in the clinic for 30 minutes after vaccine administration. As with any vaccine, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis (Table 8, http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm#Tab7; Kroger et al, 2011). Management of anaphylaxis must be in accordance with current standard of care and clinical guidelines. Vital signs should be repeated between 20 to 30 minutes after dosing.

#### 4.5.1.4 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

Phone: 1-301-398-2105
1-877-MEDI-411 (1-877-633-4411)

Fax: 1-301-398-8800

Mail: MedImmune, LLC
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, Maryland, 20878, USA

### 4.5.2 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

### 4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

### 4.5.4 Storage

RSV sF, GLA-SE, SE and diluent to prepare clinical doses of RSV sF (eg, all investigational product materials supplied by MedImmune) must be stored at 2℃ to 8℃ prior to mixing.

Saline placebo and sWFI must be stored in accordance with manufacturer's instructions.

### 4.5.5 Treatment Compliance

Investigational product is administered by study site personnel, who will record either full, partial, or lack of administration.

### 4.5.6 Accountability

The investigator's or site's designated unblinded investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

## 4.6 Treatment Assignment and Blinding

### 4.6.1 Methods for Assigning Treatment Groups

Subject assignment to a cohort is not blinded. Subject assignment within a cohort is blinded.

An IWRS will be used for randomization to a treatment group and assignment of blinded investigational product.A subject is considered randomized into the study when the investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS provides the assignment of blinded investigational product to the subject.

Subjects will be randomized at a 5:1 ratio by cohort to receive a single dose of either RSV sF or placebo or MEDI7510 or placebo.

Investigational product (RSV sF, MEDI7510, or placebo) must be administered on the same day the investigational product is assigned. Total in-use storage time from reconstitution of investigational product to drawing investigational product into the injection syringe should not exceed 3 hours at room temperature, and time from drawing the investigational product into the syringe until administration should not exceed 30 minutes. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified *immediately*.

### 4.6.2 Methods for Ensuring Blinding

This is a double-blind study. Cohort allocation is not blinded, but treatment allocation within each cohort is blinded. Initially, subjects, investigators, blinded site staff, and MedImmune staff, including laboratory and site staff, are blinded. Subjects, investigators, and blinded site staff will remain blinded until the end of the study; however, MedImmune staff will be unblinded after Day 90 safety data have been cleaned and monitored and final immunogenicity data through Day 28 have been recorded as described in Section 4.8.6 (Interim Analysis).

In this double-blind study, RSV sF, MEDI7510, and placebo are not identical in appearance. Neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Conference on Harmonisation [ICH] E9; see Section 4.6.3.2 for unblinding related to interim analysis). Because RSV sF, MEDI7510, and placebo are not identical in appearance, investigational product will be handled by an unblinded investigational product manager at the site in accordance with the dosing cohorts of antigen alone and antigen plus adjuvant. An independent investigational product monitor, who may be the research pharmacist, will also be unblinded to perform investigational product accountability. Both investigational product and placebo will be drawn up by the unblinded pharmacist into a syringe that is subsequently blinded with a covered bore, such that vaccine contents are not visible, and provided to a blinded staff member for IM dosing. Thus, RSV sF and its placebo and MEDI7510 and its placebo will be identically labeled and indistinguishable in appearance when brought to the clinic. Refer to Appendix 5 (Mixing and Administration Instructions for RSV sF, MEDI7510, and Placebo) for blinding instructions.

The vendor for packaging and labeling of the clinical supplies, the on-site pharmacist, designated IWRS personnel, designated MedImmune Clinical Research Pharmacy Service personnel, designated persons in Clinical Operations, designated persons in MedImmune Quality Assurance, and personnel within MedImmune Patient Safety and Regulatory Affairs who are responsible for preparing reports to regulatory authorities are the only individuals who will have access to information that may identify a subject's treatment allocation prior to the interim analysis. These individuals must not reveal randomization or treatment information to anyone or participate in or be associated with the evaluation of study subjects. In addition to these personnel, members of the ESMC and employees of the vendor external to MedImmune that will provide unblinded data to the ESMC may be unblinded if necessary to assess safety events for decisions regarding cohort progression or continued enrollment into study as described in Section 3.1.3. If review of unblinded data by the sponsor is necessary for decisions about cohort progression or continued enrollment into the study, unblinded MedImmune employees must not directly interact with the site and must not reveal randomization or treatment information to anyone or participate in or be associated with the evaluation of study subjects. In the event that treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified *immediately*. If the treatment allocation for a subject needs to be known to treat an individual subject for an AE, the investigator must notify the sponsor *immediately* and, if possible, before unblinding the treatment allocation. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product administration used to maintain the blind.

### 4.6.3 Methods for Unblinding

#### 4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IWRS manual. The investigator should first discuss any unblinding with the medical monitor, if possible. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

MedImmune retains the right to unblind the treatment allocation for 1) SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities; and 2) AESIs for an adjuvanted vaccine, which potentially require expedited reporting to the US FDA in accordance with guidance provided at the pre-Investigational New Drug (IND) meeting.

#### 4.6.3.2 Unblinding for Interim Analysis Purposes

An interim analysis is planned for this study as described in Section 4.8.6. For this analysis and any ad hoc analysis that may occur between interim analysis and study completion MedImmune employees and the ESMC will be fully unblinded to all safety and immunogenicity data for data analysis purposes once all subjects complete the Day 91 visit. The subjects, the clinical research organizations that are responsible for site management and laboratory assay performance, and all site staff will remain blinded. Additional details will be documented in a separate unblinding plan.

#### 4.6.3.3 Unblinding at the Request of the External Safety Monitoring Committee

The ESMC, in accordance with its charter, may request unblinding to make decisions regarding cohort escalation, dosing stopping, cohort expansion, or other safety issues. Unblinding of the ESMC will be conducted by employees of the vendor external to MedImmune that will provide unblinded data to the ESMC or by the sponsor's personnel as specified in the ESMC charter, if requested by the sponsor. Such activities will be executed in accordance with the ESMC charter and recorded in the minutes.

## 4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed about any medication or vaccine taken from the time of dosing through Day 28. Any concomitant medication(s), including herbal preparations, taken during this period of the study will be recorded in the eCRF.

### 4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care. Subjects should, where possible, avoid drugs that might mask an injection site reaction (aspirin in doses higher than 163 mg/day, acetaminophen, nonsteroidal antiinflammatory agents) for the first 7 days after dosing; however, use of these drugs for treatment of discomfort is permitted but must be recorded.

In addition, in accordance with study exclusion criteria, chronic medications that have been well tolerated and were not initiated and/or did not have a dosage change within 30 days prior to randomization are permitted and must be recorded.

Concomitant medications used to treat SAEs or AESIs for an adjuvanted vaccine will be recorded on the **SAE/AESI form** that is faxed in to MedImmune Patient Safety (see Section 5.6). They will also be recorded on the eCRF if the administration of the medication occurred during Days 1 to 28.

### 4.7.2 Prohibited Concomitant Medications

Use of new concomitant medications including over-the-counter medications, herbal supplements, and new vitamins from Day 1 through Day 28 is discouraged; in particular, use of pain or anti-inflammatory agents is discouraged because of the possibility of masking reactions to the study vaccines.

The following medications or medical procedures are not permitted. The sponsor must be notified if a subject receives the following medications or undergoes any of the following medical procedures:

1. Any vaccine, whether licensed or investigational, between randomization and 30 days post dose
2. Any investigational product between randomization and collection of the Day 361 post dose blood sample
3. Glucocorticoids at a dose ≥ 20 mg/day of prednisone equivalent given daily or on alternate days for ≥ 14 consecutive days between randomization and collection of the Day 361 post dose blood sample

4. Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and collection of the Day 361 post dose blood sample
5. Systemic radiation therapy between randomization and collection of the Day 361 post dose blood sample
6. Immunoglobulin or blood products between randomization and collection of the Day 361 post dose blood sample

## 4.8 Statistical Evaluation

### 4.8.1 General Considerations

Tabular summaries will be presented by treatment arm within each dose cohort (Cohorts 1, 1a, 2, 2a, 3, and 3a) except that all placebo recipients will be grouped into a single placebo treatment arm, regardless of dose cohort. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan.

The As-treated Population (ATP) includes all subjects who receive any amount of investigational product. Subjects will be included in the ATP according to the investigational product received even if different from that to which the subject was randomized.

All analyses will be performed on the ATP unless otherwise specified.

### 4.8.2 Sample Size

Approximately 144 adults ≥ 60 years of age who are healthy or who have stable, chronic underlying medical conditions will be enrolled and randomized in a 5:1 ratio by cohort to receive a single IM dose of either RSV sF or placebo (Cohorts 1, 2 and 3) or MEDI7510 or placebo (Cohorts 1a, 2a, and 3a) as described in Section 3.1.3. These cohorts may be expanded for safety in accordance with Section 3.1.3, so the maximum number of subjects that can be dosed under this protocol is 216 (144 + [12 × 6]). Subjects may be replaced in accordance with Section 4.1.7.

Because all analyses will be descriptive in nature, and no formal hypothesis is being tested, no formal sample size calculation was performed.

### 4.8.3 Safety

The primary endpoint is the safety and tolerability of RSV sF and MEDI7510 as assessed by the occurrence of all solicited symptoms (whether or not treatment emergent) and treatment-emergent AEs, SAEs, NOCDs, and AESIs.

Safety evaluations will be descriptive in nature, and observed differences will be evaluated for medical relevance.

Solicited symptoms, whether or not treatment emergent, will be summarized by day and overall, and by severity. They will not be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized regardless of whether or not they are treatment emergent. They will not be assessed by relationship to investigational product, because they are assumed to be possibly related. Treatment-emergent AEs, SAEs, NOCDs, and AESIs will be summarized by system organ class and preferred term using MedDRA. Adverse events, SAEs, and AESIs will also be summarized by severity and relationship to investigational product, and NOCDs will be summarized by relationship.

Summaries of solicited symptoms through Day 7 post dose, AEs and SAEs through Day 28 post dose, and SAEs, NOCDs, and AESIs through Day 360 post dose will be provided.

### 4.8.4 Efficacy

This is a Phase 1 safety and immunogenicity study in healthy subjects, therefore disease evaluation is not planned. Immunogenicity will be assessed as described in Section 4.3.4.1 and Section 4.3.4.2. Descriptive statistics will be the primary methods used for the secondary immunogenicity endpoint analyses as described in Section 4.8.1.

### 4.8.5 External Safety Monitoring Committee

A study-specific ESMC that is advisory to MedImmune will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety for cohort escalation decisions. This committee will also review data at other timepoints in response to events meeting enrollment and dosing stopping criteria (Section 4.4.1) or events assessed as medically relevant by the medical monitor or one of the site investigators. Details are provided in the ESMC charter.

For cohort escalation decisions, the ESMC and the MedImmune medical monitor will review blinded data by cohort, including all AEs/SAEs, laboratory parameters, and AESIs observed between dosing of the initial subject in the cohort(s) and the time that the final subject enrolled in the cohort(s) has completed 7 days of safety follow-up. Cumulative safety data

for other cohorts will also be reviewed. In addition, the ESMC has the option of reviewing unblinded data but cannot reveal any grouped or unblinded data to blinded MedImmune or site staff. Dose escalation decisions and outcomes of reviews of safety and other relevant data will be communicated to MedImmune. The sponsor will notify sites when enrollment into each dose cohort has been completed and when enrollment into the next dose cohort is permitted. The US FDA and IRBs/IECs will be notified when the ESMC has recommended that study dosing be halted or that cohort escalation should not occur.

### 4.8.6 Interim Analysis

One interim analysis is planned after all subjects have completed the 90 days post dose safety follow-up. This interim analysis will provide safety and immunogenicity data needed to select an antigen dose to include in the Phase 1b study, which will explore single ascending adjuvant doses in combination with the selected dose of RSV sF. Interim safety and safety laboratory data will be monitored and cleaned but not locked to permit incorporation of any safety data that the sites become aware of subsequently into the Day 1 through 90 safety evaluations. Unblinding for this interim analysis is described in Section 4.6.3.2. Immunogenicity data that will be included in this interim analysis will be the results of the RSV A microneutralization assay; anti-F IgG assay derived from RSV-specific 4-plex MSD assay; and RSV F peptide pool IFNγ ELISPOT assay. In addition, wild-type RSV infection will be detected by anti-Ga, anti-Gb, or anti-N IgG assays derived from the RSV-specific 4-plex MSD assay to exclude subjects who have had wild-type RSV infections from the immunogenicity cohort.

### 4.8.7 Final Analysis

A final, complete analysis will be conducted after all subjects have completed the Day 361 visit; data will be monitored, cleaned, and locked before final analysis.

# 5 ASSESSMENT OF SAFETY

## 5.1 Definition of Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell [RBC] increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

## 5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, a blood dyscrasia, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

## 5.3 Definition of Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Hepatic function abnormality meeting the definition of Hy's law is considered an AESI and is considered immediately reportable. See Section 5.7.2 for the definition and reporting of AESIs of hepatic function abnormality.

Anaphylaxis is considered an AESI and is immediately reportable. See Section 5.7.3 for the definition and reporting of AESIs of anaphylaxis.

Certain AEs after receipt of an adjuvanted vaccine are considered AESIs and are immediately reportable. See Section 5.7.4 for the definition and reporting of AESIs for an adjuvanted vaccine.

## 5.4 Definition of New Onset Chronic Disease

A NOCD is a newly diagnosed medical condition that is of a chronic, ongoing nature. It is observed after receiving the investigational product and is assessed by the investigator as medically significant. Examples of NOCDs include but are not limited to diabetes, asthma, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy). Events that would not be considered an NOCD are mild eczema, diagnosis of a congenital anomaly present at study entry, or acute illness (eg, upper respiratory tract infection, otitis media, bronchitis).

## 5.5 Recording of Adverse Events, Serious Adverse Events, Adverse Events of Special Interest, and New Onset Chronic Diseases

Adverse events, including AESIs and NOCDs, will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. These events will be assessed by the investigator for severity, relationship to the investigational product, and whether the event meets criteria of an SAE and/or an immediately reportable AESI and therefore requires immediate notification of MedImmune Patient Safety. See Section 5.2 for the definition of SAEs, Section 5.7 for AESI events that require immediate reporting, Appendix 2 for guidelines for assessment of severity and relationship, and Appendix 4 for Tables for Clinical Abnormalities (Local Reactions, Vital Signs, Systemic [General]). If an

AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE/AESI report form.

The results of clinical laboratory tests obtained as part of this protocol (Section 4.3.3) will be transferred directly from the laboratory. Laboratory values flagged as abnormal need not be routinely entered as AEs; however, if the investigator considers that any laboratory result is clinically significant and cannot be considered to be part of an AE reported under another medical diagnosis (eg, elevated creatinine need not be reported if renal failure is reported), it should be reported as an AE.

Vital signs will not be collected on the eCRF. If the investigator considers it appropriate to report vital signs as AEs (ie, the result is clinically significant and is not included as part of an AE reported under a different medical diagnosis), the Tables for Clinical Abnormalities (Appendix 4) provide guidance for grading of these vital signs.

New onset chronic diseases will be recorded on the eCRF AE page using a recognized medical term or diagnosis that accurately reflects the event. A NOCD might also be an SAE (Section 5.2) and/or an AESI (Section 5.3); if so, it should also be reported as an SAE and/or AESI. See Section 5.6 for instructions on how to report SAEs and AESIs to MedImmune Patient Safety. A NOCD will be assessed by the investigator for relationship to the investigational product, treatments used or planned, and whether the event meets criteria of an AE, SAE, or an immediately reportable AESI.

### 5.5.1 Time Period for Collection of Adverse Events

Adverse events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period through Day 28 unless they meet criteria as an SAE or AESI.

All AESIs that do not meet criteria for anaphylaxis (see Section 5.7.3) will be collected from the time of dosing through Day 360.

All SAEs will be recorded from the time of informed consent through the day of last subject contact (Day 361+10, Visit 17).

All NOCDs will be recorded from the time of dosing through Day 360.

### 5.5.2 Follow-up of Unresolved Adverse Events

Adverse events/SAEs/AESIs should be followed until resolution or marked as ongoing at the subject's last visit (Day 361/Visit 17). MedImmune retains the right to request additional

information for any subject with ongoing AE(s)/SAE(s)/AESI(s) at the end of the study, if judged necessary.

## 5.6 Reporting of Serious Adverse Events

**Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE/AESI Report Form and fax it to MedImmune Patient Safety.**

MedImmune contact information:

Patient Safety
MedImmune
One MedImmune Way
Gaithersburg, Maryland, 20878, USA
Fax: 1-301-398-4205

The sponsor is responsible for reporting certain SAEs and/or AESIs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH guidelines and/or local regulatory requirements. The sponsor may be required to report certain SAEs and/or AESIs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

Investigators should provide all available information at the time of SAE/AESI Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE and/or AESI. When additional information becomes available, investigators should submit a follow-up SAE/AESI Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE and/or AESI also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

## 5.7 Other Events Requiring Immediate Reporting

### 5.7.1 Overdose

An overdose is one type of AESI and is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure. It should be recorded in the eCRF using the term "overdose."

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs/AESIs is required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 5.6 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE eCRF (see Section 5.5). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 5.5 and Section 5.6). MedImmune does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

### 5.7.2 Hepatic Function Abnormality

Adverse events of hepatic function abnormality of special interest to the sponsor are defined as any increase in ALT or AST to greater than 3 × upper limit of normal (ULN) **and concurrent** increase in bilirubin to greater than 2 × ULN (ie, Hy's law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

If the underlying diagnosis for the hepatic function abnormality is known, and it is not considered attributable to investigational product, the diagnosis should be recorded as an AE/SAE and is not reportable as an AESI.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE, and the event is an AESI.

Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the SAE/AESI Report Form, even if the event is considered to be nonserious (see Section 5.6 for contact information). The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor.

### 5.7.3 Anaphylaxis

Anaphylaxis is an acute onset, potentially fatal, systemic allergic reaction that is distinct from simple allergic reactions (illness of skin or mucosa or both, such as rash, pruritus) because of the simultaneous involvement of several organ systems.

Investigators should consider the guidance provided in Appendix 3 when evaluating a patient for a diagnosis of anaphylaxis. Events of anaphylaxis should be recorded as anaphylaxis. For analysis, all events that are MedDRA coded as the preferred term "anaphylaxis" will be analyzed as events of anaphylaxis.

### 5.7.4 Adverse Events of Special Interest for an Adjuvanted Vaccine

Adverse events of special interest for an adjuvanted vaccine include the following verbatim terms and, for analysis, will also include associated MedDRA terms. Events that are faxed in by investigators as potential AESIs for an adjuvanted vaccine that do not meet these criteria will not be analyzed as AESIs.

- Neuroinflammatory disorders:
  - Optic neuritis
  - Uveitis
  - Multiple sclerosis
  - Demyelinating disease
  - Transverse myelitis
  - Guillain-Barré syndrome
  - Myasthenia gravis
  - Encephalitis
  - ADEM (acute disseminated encephalomyelitis)
  - Neuritis
  - Bell's Palsy
- Musculoskeletal and connective tissue disorders:
  - Rheumatoid arthritis
  - Juvenile rheumatoid arthritis
  - Polymyalgia rheumatica
  - Psoriatic arthropathy
  - Ankylosing spondylitis
  - Spondyloarthropathy
  - Systemic lupus erythematosis
  - Cutaneous lupus

- Sjogren's syndrome
- Scleroderma
- Dermatomyositis
- Polymyositis
- Mixed connective tissue disease

- Vasculitides:
  - Vasculitis
  - Temporal arteritis
  - Wegener's granulomatosis
  - Behçet's syndrome
- Gastrointestinal disorders:
  - Crohn's disease
  - Ulcerative colitis
  - Inflammatory bowel disease (non-specific)
  - Celiac disease
  - Autoimmune hepatitis
  - Primary sclerosing cholangitis
  - Primary biliary cirrhosis
- Renal disorders:
  - Glomerulonephritis
  - Nephritis
- Cardiac disorders:
  - Carditis
  - Pericarditis
  - Myocarditis
- Skin disorders:
  - Psoriasis
  - Vitiligo
  - Raynaud's phenomenon
  - Erythema nodosum
  - Autoimmune bullous skin diseases
  - Stevens-Johnson syndrome
- Hematologic disorders:
  - Autoimmune hemolytic anemia
  - Idiopathic thrombocytopenic purpura
  - Antiphospholipid syndrome
- Metabolic disorders:

- Autoimmune thyroiditis
- Grave's disease (or its synonym, Basedow's disease)
- Hashimoto's thyroiditis
- Insulin-dependent diabetes mellitus
- Addison's disease

- Other disorders:
  - Sarcoidosis

### 5.7.5 Reporting and Recording of Adverse Events of Special Interest

Events of overdose, hepatic function abnormality, anaphylaxis, and AESIs for an adjuvanted vaccine (as defined in Section 5.3) are required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the SAE/AESI Report Form, even if the event is considered to be nonserious (see Section 5.6 for contact information).

Adverse events of special interest also should be recorded in the eCRF according to the definitions of AE and SAE (Section 5.1 and Section 5.2).

## 5.8 Solicited Symptoms

Solicited symptoms are events that are considered likely to occur post dosing. For this study, solicited symptoms include:

Local reaction to investigational product injection

- Pain at the site of injection
- Tenderness or soreness at the site of the injection
- Redness at the site of the injection
- Swelling at the site of the injection

Systemic symptoms that might be related to investigational product injection

- Fever ≥ 100.4°F (≥ 38°C) by any route
- Headache
- Generalized muscle aches
- Fatigue or tiredness

Solicited symptoms are recorded whether or not they are treatment emergent (ie, ongoing from prior to investigational product dosing). Solicited symptoms are not necessarily

considered to be AEs but should also be recorded as AEs when, according to the judgment of the investigator, they meet the definition of an AE. The definition of fever for this study is temperature measured by any route that is ≥ 38°C or ≥ 100.4°F (Marcy et al, 2004). Investigators who consider a temperature lower than this cut-off for fever or a "fever" reported by subjects without documentation by thermometer to represent an AE should record the event as "elevated body temperature." Because solicited symptoms are events that might be expected to occur after immunization, they will not be assessed for relationship to investigational product. They will not be MedDRA coded. They will be assessed for severity by the investigator consistent with the Tables for Clinical Abnormalities (Local Reactions, Vital Signs, Systemic [General]) provided in Appendix 4 and the diary card.

The reporting period for solicited symptoms for subjects receiving a single dose is 7 days after vaccination/investigational product administration.

Solicited symptoms will be reported using the terms as defined in this protocol. Diary cards will be provided for subjects to record solicited symptoms during Days 1 through 7. Thermometers and measuring tapes will also be provided for subject assessment of local reactions. The investigator must collect the diary cards to serve as source documentation. Solicited symptoms should be recorded in the eCRF. Investigators or their designees should question the subjects about solicited symptoms to confirm assessment of severity. If, upon questioning, a subject provides updated solicited symptom information that either changes or supplements that recorded on the diary card, the investigator or designee should record the updated data in the eCRF for the solicited symptom(s) and must note on the diary card that the data have been updated by the subject. This note must be signed and dated by site staff but subject signatures are not required. If, in the judgment of the investigator, a solicited symptom also warrants reporting as an AE or SAE, it should be recorded as stated in Section 5.5.

# 6 STUDY AND DATA MANAGEMENT

## 6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

## 6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contact with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being recorded in the eCRFs in an accurate and timely manner, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure that withdrawal of informed consent for the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

### 6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

### 6.2.2 Study Agreements

The principal investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the principal investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

### 6.2.3 Archiving of Study Documents

The investigator must follow the principles outlined in the Clinical Study Agreement.

## 6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through the last protocol-specified visit/assessment (including telephone contact).

Subjects who are not dosed will not be followed. All subjects who are dosed should be followed for 360 days unless consent was withdrawn. Subjects should not be declared lost to follow-up unless contact cannot be re-established by Day 361+10 days.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.1.5 and Section 4.2.2).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study. This date will be Day 361+10 days after the final subject is entered into the study.

## 6.4 Data Management

Data management will be performed by MedImmune Data Management according to the Data Management Plan.

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study sites.

## 6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the principal investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an

emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the principal investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

# 7 ETHICAL AND REGULATORY REQUIREMENTS

## 7.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

## 7.2 Subject Data Protection

The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

## 7.3 Ethics and Regulatory Review

An IRB/IEC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to MedImmune before enrollment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

MedImmune should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

MedImmune will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide regulatory authorities, IRB/IEC, and principal investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs) where relevant.

Each Principal Investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

## 7.4 Informed Consent

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed informed consent form(s) is/are stored in the investigator's study file
- Ensure a copy of the signed informed consent form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB/IEC
- Written informed consent will additionally be obtained for future use of blood samples obtained during this study using a separate consent form
- All subjects enrolled must be capable of providing informed consent

## 7.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigators and MedImmune.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRB/IEC see Section 7.3.

If a protocol amendment requires a change to a site's Informed Consent Form, MedImmune and the site's IRB/IEC are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

## 7.6 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to verify whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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# 9 CHANGES TO THE PROTOCOL

All changes described below have been incorporated into the current version of the protocol.

### Administrative Change 1

#### Rationale for Administrative Change

The purpose of this administrative change is to correct typographical errors; clarify parameters of long-term follow-up of missing subjects; clarify the order of procedures on Day 1; align descriptive text for a clinical laboratory safety parameter with the specifics of the test being performed; align text in 2 sections that describes unblinding for interim analysis purposes; align requirements for recording of concomitant medications with Table 4.2.2-1, footnote h; revise requirement to follow up on unresolved AEs post last visit and need for recording findings in the eCRF; and revise text in the dose preparation and administration instructions (Appendix 5), including reformatting of the tables that describe the procedures, ensuring the recording of the date, duration of the dose preparation, and the pharmacist identity; removing the Avery 5164 descriptor from Avery 5164 label, removing insulin descriptor from 1-ml insulin syringe, providing more specific instructions for labeling vials provided in the investigational product kits, and providing specific instructions for retaining the investigational product syringe label and disposing of the syringe itself.

#### Summary of Changes

The following changes were made:

- Section 3.1.1, Figure 3.1.1-1 - Changed Study Day 360 to Study Day 361

- Section 4.2.2 - Added text to specify that investigators document attempts to follow-up on any missing subject until Day 361 + 10 days

- Section 4.2.2 - Added text to state that on Day 1 subject vital signs may be assessed at any time prior to verifying eligibility criteria, that test blood samples may be obtained in any order, and that urinalysis may be performed at any time after randomization and before dosing

- Section 4.3.3 Urinalysis - Specified parameters required in dipstick assessment

- Section 4.6.2 - Revised text to confirm the unblinding of all MedImmune staff subsequent to the finalization of Day 90 safety and Day 28 immunogenicity data for the Day 90 interim analysis

- Section 4.7.1 - Removed the requirement that concomitant medications used to treat SAEs or AESIs need to be recorded on the eCRF, unless they occur during Days 1 to 28

- Section 5.5.2 - Removed text specifying investigator follow-up of AEs after Day 361/Visit 17 and without recording findings in the eCRF

- Appendix 5 - Reformatted the tables that describe the IP mixing and administration instructions for each cohort by adding columns for recording the date, time of start and completion of dose preparation, and pharmacist and verifier initials; removed “insulin” descriptor from “1-mL insulin syringe, ” removed “Avery 5164” descriptor from “Avery 5164 syringe,” added instructions for labeling vials in the kits (step 1); added instructions for retaining the label from the investigational product syringe and disposing of the syringe itself (step 6, cohorts 1, 2, 3; step 8, cohorts 1a, 2a, 3a).

# Appendix 1 Signatures

**Sponsor Signature(s)**

A Phase 1a Study to Evaluate the Safety of the Respiratory Syncytial Virus Vaccine MEDI7510 in Older Adults

I agree to the terms of this protocol.

Signature and date: _____

[redacted]

[redacted]

One MedImmune Way, Gaithersburg, Maryland, 20878, USA

[redacted]

## Signature of Coordinating Investigator

A Phase 1a Study to Evaluate the Safety of the Respiratory Syncytial Virus Vaccine MEDI7510 in Older Adults

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available) _____

# Appendix 2 Additional Safety Guidance

## Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grades 1 to 5 as defined below.

Grade 1 (mild) An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Grade 2 (moderate) An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 (severe) An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

Grade 4 (life threatening) An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).

Grade 5 (fatal) Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Tables for Clinical Abnormalities (Local Reactions, Vital Signs, Systemic [General]) are provided in Appendix 4 to guide investigators in their grading of severity.

## Assessment of Relationship

### Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

### Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE/AESI Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

# Appendix 3 National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

The National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al, 2006).

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
- Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

OR:

- Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
  - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
  - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
  - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

# Appendix 4 Toxicity Grading Scale for Healthy Adult Volunteers in Preventive Vaccine Clinical Trials

These toxicity grading scales are abridged from the US FDA Guidance dated September 2007. The full document is available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm

## Table 9-1 Tables for Clinical Abnormalities: Local Reactions to Injectable Product

| Local Reaction to Injectable Product | Reaction Grade | | | |
|---|---|---|---|---|
| | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)** |
| Pain | Does not interfere with activity | Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity | Any use of narcotic pain reliever or prevents daily activity | ER visit or hospitalization |
| Tenderness | Mild discomfort to touch | Discomfort with movement | Significant discomfort at rest | ER visit or hospitalization |
| Erythema/redness [a] | 1-2 inches | 2-4 inches | > 4 inches | Necrosis or exfoliative dermatitis |
| Induration/swelling [b] | 1-2 inches and does not interfere with activity | 2-4 inches or interferes with activity | > 4 inches or prevents daily activity | Necrosis |

ER = emergency room

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

[i] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement

## Table 9-2 Tables for Clinical Abnormalities: Vital Signs

| Vital Signs [a] | Vital Signs Grade | | | |
|---|---|---|---|---|
| | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)** |
| Fever (°C) [b]<br>(°F) [b] | 38-38.4<br>100.4-101.1 | 38.5-38.9<br>101.2-102.0 | 39.0-40<br>102.1-104 | > 40<br>> 104 |
| Tachycardia (beats/minute) | 101-115 | 116- 130 | > 130 | ER visit or hospitalization for arrhythmia |
| Bradycardia (beats/minute) [c] | 50-54 | 45-49 | < 45 | ER visit or hospitalization for arrhythmia |
| Hypertension; systolic (mm Hg) | 141-150 | 151-155 | > 155 | ER visit or hospitalization for malignant hypertension |
| Hypertension; diastolic (mm Hg) | 91-95 | 96-100 | > 100 | ER visit or hospitalization for malignant hypertension |
| Hypotension; systolic (mm Hg) | 85-89 | 80-84 | < 80 | ER visit or hospitalization for hypotensive shock |
| Respiratory rate (breaths/minute) | 17-20 | 21-25 | > 25 | Intubation |

ER = emergency room; Hg = mercury

Note: Record vital signs as adverse events only if clinically relevant and changed from baseline

[a] Subject should be at rest for vital signs measurements

[b] No recent hot or cold beverages or smoking

[c] When resting heart rate is between 60-100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes

## Table 9-3 Tables for Clinical Abnormalities: Systemic (General or Illness)

| Systemic (General) | Systemic Grade | | | |
|---|---|---|---|---|
| | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)** |
| Nausea/vomiting | No interference with activity or 1-2 episodes/24 hours | Some interference with activity or > 2 episodes/24 hours | Prevents daily activity, required outpatient IV hydration | ER visit or hospitalization for hypotensive shock |
| Diarrhea | 2-3 loose stools | 4-5 stools | ≥ 6 watery stools or requires outpatient IV hydration | ER visit or hospitalization |
| Headache | No interference with activity | Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity | Significant; any use of narcotic pain reliever or prevents daily activity | ER visit or hospitalization |
| Fatigue | No interference with activity | Some interference with activity | Significant; prevents daily activity | ER visit or hospitalization |
| Myalgia | No interference with activity | Some interference with activity | Significant; prevents daily activity | ER visit or hospitalization |
| **Systemic Illness** | | | | |
| Illness or clinical adverse event (as defined according to applicable regulations) | No interference with activity | Some interference with activity not requiring intervention | Prevents daily activity and required medical intervention | ER visit or hospitalization |

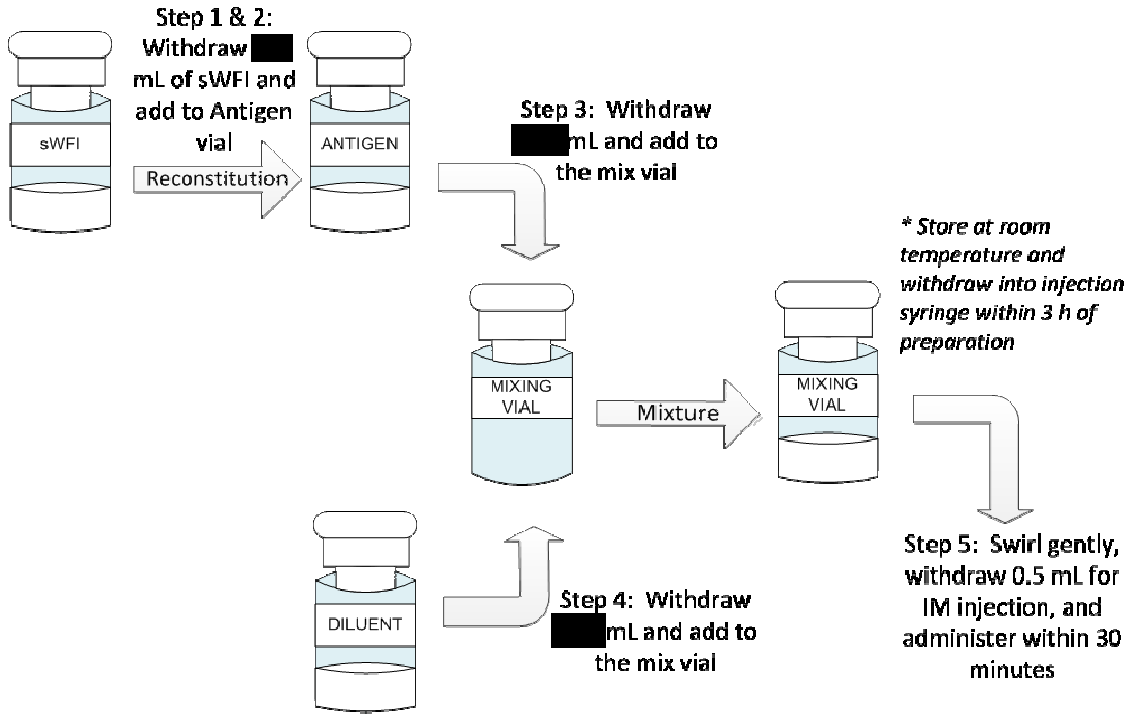
ER = emergency room; IV = intravenous

# Appendix 5 Mixing and Administration Instructions for RSV sF, MEDI7510, and Placebo

## Dose Preparation Instructions for Study CD-VA-MEDI7510-1134

# Cohort 1, RSV sF

| Description | Antigen (mL) | GLA-SE (mL) | SE (mL) | Diluent (mL) | Final Volume (mL) |
|---|---|---|---|---|---|
| Cohort 1, RSV sF (Antigen) | [redacted] | -- | -- | [redacted] | [redacted] |




Antigen = RSV sF; h = hours; IM = intramuscular; sWFI = sterile water for injection

| Date: ___/___/____ | Step | Dose Preparation Instructions for Cohort 1, RSV sF | Initials - Pharmacist | Initials - Verifier |
|---|---|---|---|---|
| Dose Prep Start Time: ____:____ | 1 | Unroll the label on each vial in kit, making note of the vial component (RSVsF, diluent, etc). Re-roll the label and write the component type on the label. Remove all flip-caps, wipe the septum of each vial with an alcohol swab, and allow the wiped surfaces to air dry. Pull a 3-mL mixing vial from your study-specific bulk supply for this study and attach the tear-off label from the kit onto the mixing vial. Handle all material aseptically. Using a 1-mL syringe, withdraw 0.6 mL of **sterile water for injection (sWFI).** | | |
| | 2 | Add [redacted] mL of **sWFI** to reconstitute the lyophilized **Antigen vial**. Swirl gently for 10 seconds followed by a pause for about 10 seconds. Repeat a total of 3 times. Allow solids to completely dissolve before proceeding. This solution is clear and colorless to slightly yellow. | | |

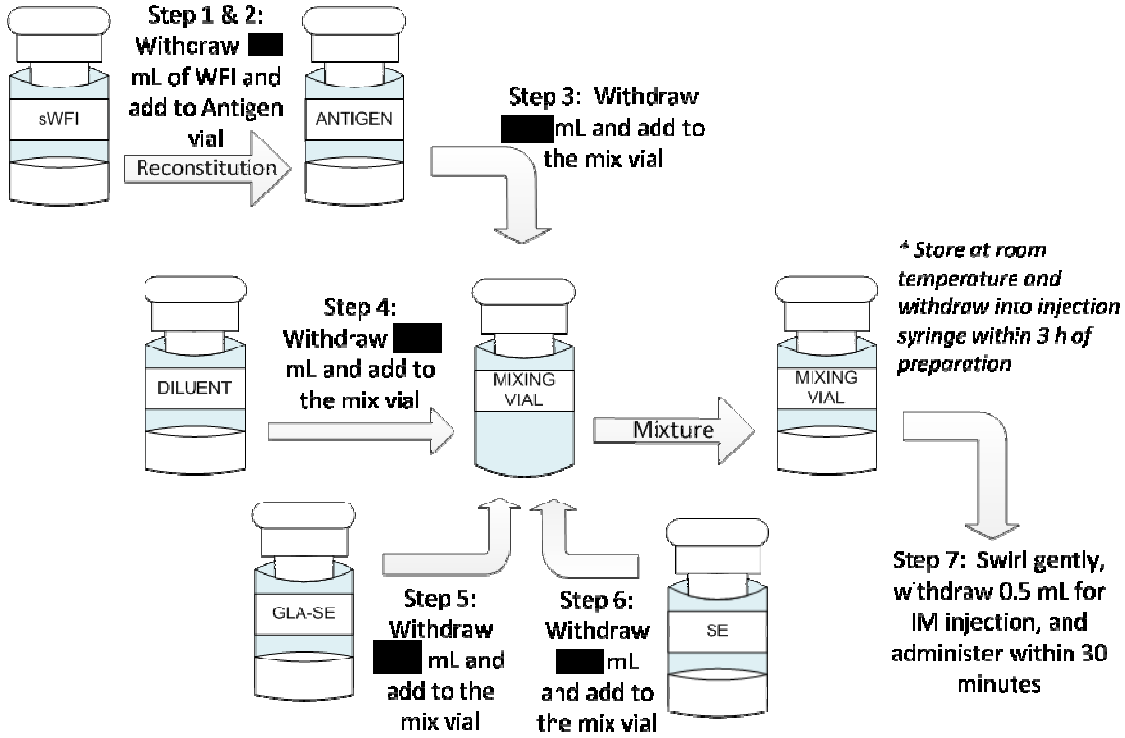
| | | | | |
|---|---|---|---|---|
| | 3 | Using a 0.3-mL syringe, withdraw [redacted] mL from the reconstituted **Antigen vial** and add the volume to the **Mixing vial**. | | |

# Cohort 1, RSV sF

| | | | | |
|---|---|---|---|---|
| | 4 | Using a 1-mL syringe, withdraw [redacted] mL from the **Diluent vial** and add the volume to the **Mixing vial** and swirl gently. This solution is colorless, appearing clear to slightly hazy. Store at room temperature and perform step 5 (vaccine administration) within **3 hours**. DO NOT FREEZE. | | |
| Completion Time of Dose Prep:<br><br>____:____ | 5 | Swirl gently and then withdraw 0.5 mL using a new, unused 1-mL syringe and a new appropriate size needle for IM injection (see protocol, Table 4.5.1.2-1). Blind the barrel of the syringe utilizing a blank label (provided) so that it completely covers the contents in the syringe. Using the label with project-specific text fields, complete the fields on the label, and then adhere the label to the barrel of the syringe, so that the text fields create a flag and are visible. Make sure the labels adhere firmly so that they cannot be removed from the syringe.<br>Administer within **30 minutes** of withdrawal. | | |
| | 6 | Return the empty **mixing vial** and all empty component vials to the kit and store appropriately for investigational product reconciliation. The label flag with completed text fields from the syringe should be cut from the syringe and stored with the kit for investigational product reconciliation. The empty syringe used to administer the investigational product should be discarded per site's SOPs. | | |

# Cohort 1a, MEDI7510 (RSV sF + GLA-SE)

| Description | Antigen (mL) | GLA-SE (mL) | SE (mL) | Diluent (mL) | Final Volume (mL) |
|---|---|---|---|---|---|
| Cohort 1a, MEDI7510 (RSV sF Antigen plus GLA-SE Adjuvant) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |




Antigen = RSV sF; h = hours; GLA-SE = glucopyranosyl lipid A; GLA-SE = glucopyranosyl lipid A in 2% (w/v) SE; SE = stable emulsion; sWFI = sterile water for injection

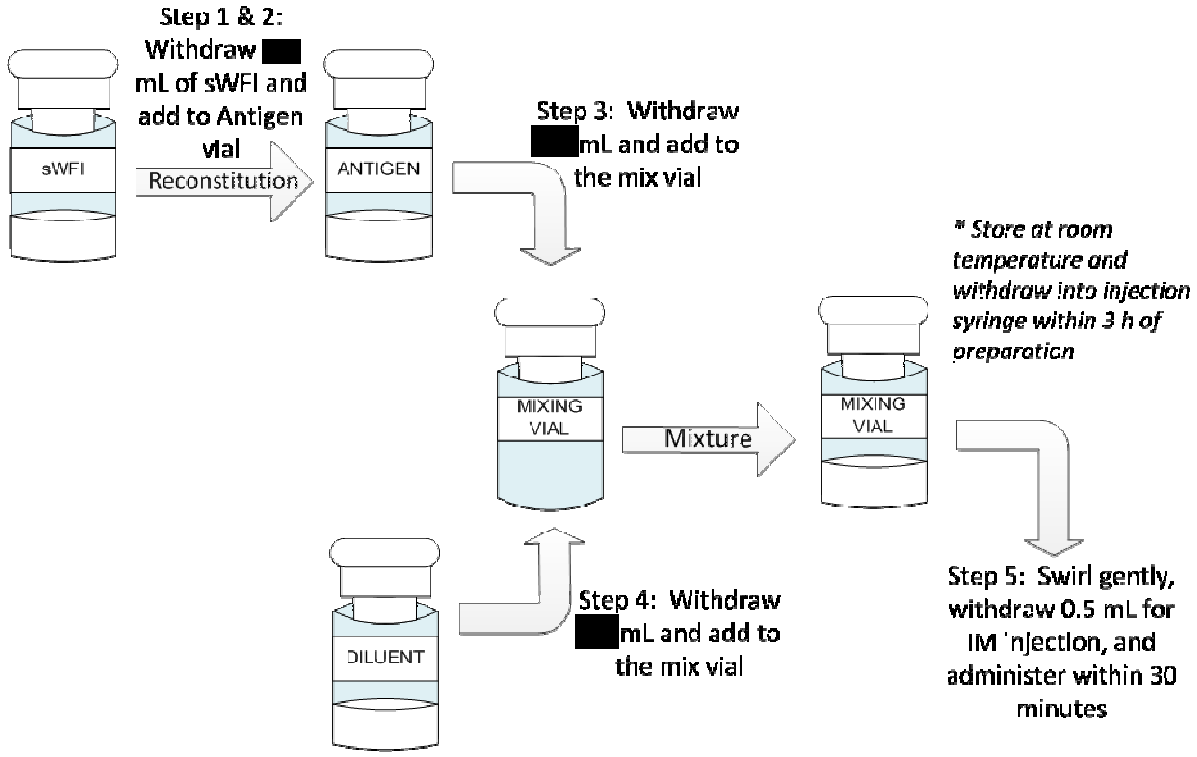
| Date: ___/___/___ | Step | Dose Preparation Instructions for Cohort 1a, MEDI7510 | Initials - Pharmacist | Initials - Verifier |
|---|---|---|---|---|
| Dose Prep Start Time: ____:____ | 1 | Unroll the label on each vial in kit, making note of the vial component (RSVsF, GLA-SE, GLA, etc). Re-roll the label and write the component type on the label. Remove all flip-caps, wipe the septum of each vial with an alcohol swab, and allow the wiped surfaces to air dry. Pull a 3-mL mixing vial from your study-specific bulk supply for this study and attach the tear-off label from the kit onto the mixing vial. Handle all material aseptically. Using a 1-mL syringe, withdraw [redacted] mL of **sterile water for injection (sWFI).** | | |
| | 2 | Add [redacted] mL of **sWFI** to reconstitute the lyophilized **Antigen vial**. Swirl gently for 10 seconds followed by a pause for about 10 seconds. Repeat a total of 3 times. Allow solids to completely dissolve before proceeding. This solution is clear and colorless to slightly yellow. | | |

# Cohort 1a, MEDI7510 (RSV sF + GLA-SE)

| | | | | |
|---|---|---|---|---|
| | 3 | Using a 0.3-mL syringe, withdraw [redacted] mL from the reconstituted **Antigen vial** and add the volume to the **Mixing vial**. | | |
| | 4 | Using a 1-mL syringe, withdraw [redacted] mL from the **Diluent vial** and add the volume to the **Mixing vial**. | | |
| | 5 | Using a 0.3-mL syringe, withdraw [redacted] mL from the **GLA-SE vial** and add the volume to the **Mixing vial**. This solution appears milky white. | | |
| | 6 | Using a 0.3-mL syringe, withdraw [redacted] mL from the **SE vial** and add the volume to the **Mixing vial** and swirl gently. This solution appears milky white. Store at room temperature and perform step 7 (vaccine administration) within **3 hours**. DO NOT FREEZE. | | |
| Completion Time of Dose Prep:<br><br>____:____ | 7 | Swirl gently and then withdraw 0.5 mL using a new, unused 1-mL syringe and a new appropriate size needle for IM injection (see protocol, Table 4.5.1.2-1). Blind the barrel of the syringe utilizing a blank label (provided) so that it completely covers the contents in the syringe. Using the label with project specific text fields, complete the fields on the label, and then adhere the label to the barrel of the syringe, so that the text fields create a flag and are visible. Make sure the labels adhere firmly so that they cannot be removed from the syringe.<br>Administer within **30 minutes** of withdrawal. | | |
| | 8 | Return the empty **mixing vial** and all empty component vials to the kit and store appropriately for investigational product reconciliation. The label flag with completed text fields from the syringe should be cut from the syringe and stored with the kit for investigational product reconciliation. The empty syringe used to administer the investigational product should be discarded per site's SOPs. | | |

# Cohort 2, RSV sF

| Description | Antigen (mL) | GLA-SE (mL) | SE (mL) | Diluent (mL) | Final Volume (mL) |
|---|---|---|---|---|---|
| Cohort 2, RSV sF (Antigen) | [redacted] | -- | -- | [redacted] | [redacted] |




Antigen = RSV sF; h = hours; IM = intramuscular; sWFI = sterile water for injection

| Date: ___/___/___ | Step | Dose Preparation Instructions for Cohort 2, RSV sF | Initials - Pharmacist | Initials - Verifier |
|---|---|---|---|---|
| Dose Prep Start Time: ____:____ | 1 | Unroll the label on each vial in kit, making note of the vial component (RSVsF, diluent, etc). Re-roll the label and write the component type on the label. Remove all flip-caps, wipe the septum of each vial with an alcohol swab, and allow the wiped surfaces to air dry. Pull a 3-mL mixing vial from your study-specific bulk supply for this study and attach the tear-off label from the kit onto the mixing vial. Handle all material aseptically. Using a 1-mL syringe, withdraw 0.6 mL of **sterile water for injection (sWFI)**. | | |
| | 2 | Add [redacted] mL of **sWFI** to reconstitute the lyophilized **Antigen vial**. Swirl gently for 10 seconds followed by a pause for about 10 seconds. Repeat a total of 3 times. | | |

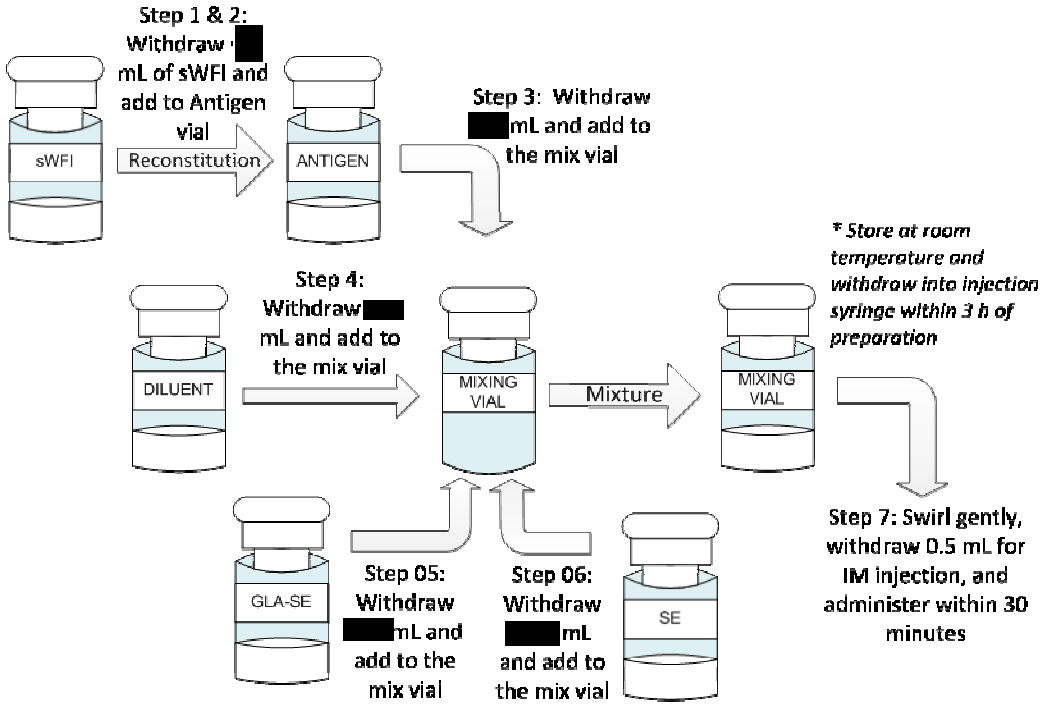
| | | | | |
|---|---|---|---|---|
| | | Allow solids to completely dissolve before proceeding. This solution is clear and colorless to slightly yellow. | | |

## Cohort 2, RSV sF

| | | | | |
|---|---|---|---|---|
| | 3 | Using a 1-mL syringe, withdraw [redacted] mL from the reconstituted Antigen vial and add the volume to **the Mixing vial**. | | |
| | 4 | Using a 1-mL syringe, withdraw [redacted] mL from the **Diluent vial** and add the volume to the Mixing vial and swirl gently. This solution appears clear to slightly hazy. Store at room temperature and perform step 5 (vaccine administration) within **3 hours**. DO NOT FREEZE. | | |
| Completion Time of Dose Prep:<br><br>____:____ | 5 | Swirl gently and then withdraw 0.5 mL using a new, unused, 1-mL syringe and a new appropriate size needle for IM injection (see protocol, Table 4.5.1.2-1). Blind the barrel of the syringe utilizing a blank label (provided) so that it completely covers the contents in the syringe. Using the label with project-specific text fields, complete the fields on the label, and then adhere the label to the barrel of the syringe, so that the text fields create a flag and are visible. Make sure the labels adhere firmly so that they cannot be removed from the syringe. Administer within **30 minutes** of withdrawal. | | |
| | 6 | Return the empty **mixing vial** and all empty component vials to the kit and store appropriately for investigational product reconciliation. The label flag with completed text fields from the syringe should be cut from the syringe and stored with the kit for investigational product reconciliation. The empty syringe used to administer the investigational product should be discarded per site's SOPs. | | |

# Cohort 2a, MEDI7510 (RSV sF + GLA-SE)

| Description | Antigen (mL) | GLA-SE (mL) | SE (mL) | Diluent (mL) | Final Volume (mL) |
|---|---|---|---|---|---|
| Cohort 2a, MEDI7510 (RSV sF Antigen plus GLA-SE Adjuvant) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |




Antigen = RSV sF; h = hours; GLA-SE = glucopyranosyl lipid A; GLA-SE = glucopyranosyl lipid A in 2% (w/v) SE; SE = stable emulsion; sWFI = sterile water for injection

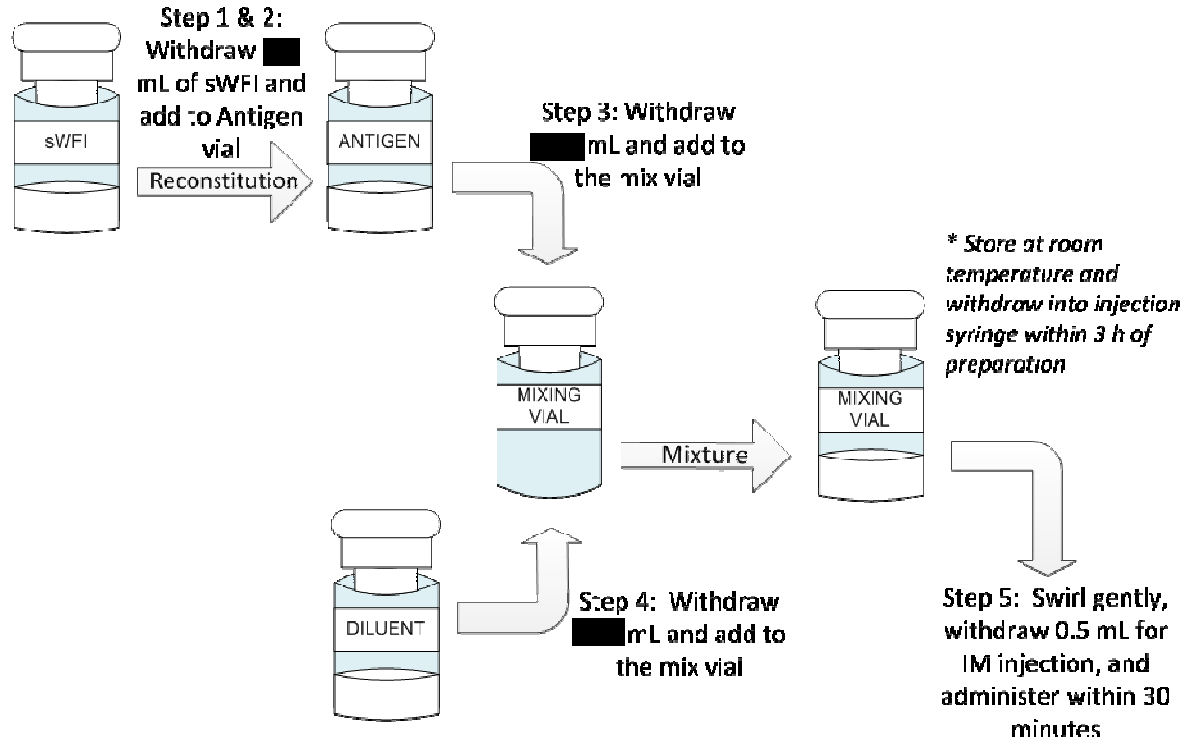
| Date: ___/___/___ | Step | Dose Preparation Instructions for Cohort 2a, MEDI7510 | Initials - Pharmacist | Initials - Verifier |
|---|---|---|---|---|
| Dose Prep Start Time: ____:____ | 1 | Unroll the label on each vial in kit, making note of the vial component (RSVsF, GLA-SE, GLA, etc). Re-roll the label and write the component type on the label. Remove all flip-caps, wipe the septum of each vial with an alcohol swab, and allow the wiped surfaces to air dry. Pull a 3-mL mixing vial from your study-specific bulk supply for this study and attach the tear-off label from the kit onto the mixing vial. Handle all material aseptically. Using a 1-mL syringe, withdraw 0.6 mL of **sterile water for injection (sWFI).** | | |
| | 2 | Add [redacted] mL of **sWFI** to reconstitute the lyophilized **Antigen vial**. Swirl gently for 10 seconds followed by a pause for about 10 seconds. Repeat a total of 3 times. Allow solids to completely dissolve before proceeding. This solution is clear and colorless to slightly yellow. | | |

# Cohort 2a, MEDI7510 (RSV sF + GLA-SE)

| | | | | |
|---|---|---|---|---|
| | 3 | Using a 1-mL syringe, withdraw [redacted] mL from the reconstituted **Antigen vial** and add the volume to the **Mixing vial.** | | |
| | 4 | Using a 1-mL syringe, withdraw [redacted] mL from the **Diluent vial** and add the volume to the **Mixing vial.** | | |
| | 5 | Using a 0.3-mL syringe, withdraw [redacted] mL from the **GLA-SE vial** and add the volume to the **Mixing vial**. This solution appears milky white. | | |
| | 6 | Using a 0.3-mL syringe, withdraw [redacted] mL from the **SE vial** and add the volume to the **Mixing vial** and swirl gently. This solution appears milky white. Store at room temperature and perform step 7 (vaccine administration) within **3 hours**. DO NOT FREEZE. | | |
| Completion Time of Dose Prep:<br><br>____:____ | 7 | Swirl gently and then withdraw 0.5 mL using a new, unused 1-mL syringe and a new appropriate size needle for IM injection (see protocol, Table 4.5.1.2-1). Blind the barrel of the syringe utilizing a blank label (provided) so that it completely covers the contents in the syringe. Using the label with project-specific text fields, complete the fields on the label, then adhere the label to the barrel of the syringe, so that the text fields create a flag and are visible. Make sure the labels adhere firmly so that they cannot be removed from the syringe.<br>Administer within **30 minutes** of withdrawal. | | |
| | 8 | Return the empty **mixing vial** and all empty component vials to the kit and store appropriately for investigational product reconciliation. The label flag with completed text fields from the syringe should be cut from the syringe and stored with the kit for investigational product reconciliation. The empty syringe used to administer the investigational product should be discarded per site's SOPs. | | |

# Cohort 3, RSV sF

| Description | Antigen (mL) | GLA-SE (mL) | SE (mL) | Diluent (mL) | Final Volume (mL) |
|---|---|---|---|---|---|
| Cohort 3, RSV sF (Antigen) | [redacted] | -- | -- | [redacted] | [redacted] |




Antigen = RSV sF; h = hours; IM = intramuscular; sWFI = sterile water for injection

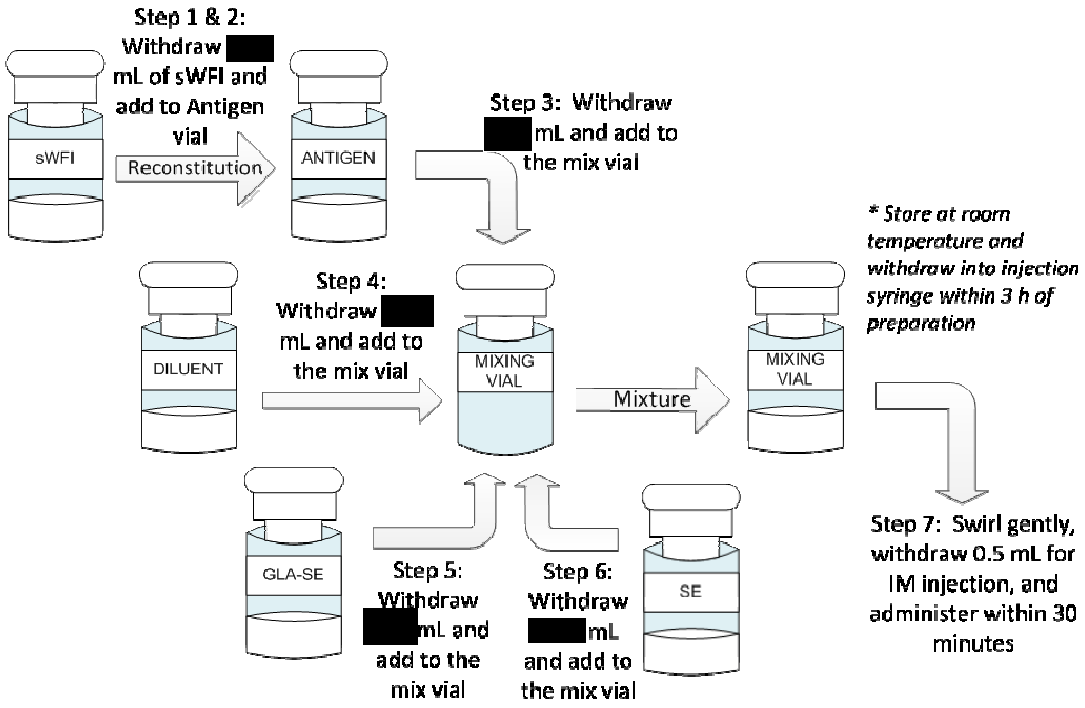
| Date: __/__/__ | Step | Dose Preparation Instructions for Cohort 3, RSV sF | Initials - Pharmacist | Initials-Verifier |
|---|---|---|---|---|
| Dose Prep Start Time: ____:____ | 1 | Unroll the label on each vial in kit, making note of the vial component (RSVsF, diluent, etc). Re-roll the label and write the component type on the label. Remove all flip-caps, wipe the septum of the vials with an alcohol swab, and allow the wiped surfaces to air dry. Pull a 3-mL mixing vial from your study specific bulk supply for this study and attach the tear-off label from the kit onto the mixing vial. Handle all material aseptically. Using a 1-mL syringe, withdraw 0.6 mL of sterile water for injection (sWFI). | | |
| | 2 | Add [redacted] mL of **sWFI** to reconstitute the lyophilized **Antigen vial**. Swirl gently for 10 seconds followed by a pause for about 10 seconds. Repeat a total of 3 times. Allow solids to completely dissolve before proceeding. This solution is clear and colorless to slightly yellow. | | |

# Cohort 3, RSV sF

| | | | | |
|---|---|---|---|---|
| | 3 | Using a 1-mL syringe, withdraw [redacted] mL from the reconstituted **Antigen** vial and add the volume to the **Mixing vial.** | | |
| | 4 | Using a 1-mL syringe, withdraw [redacted] mL from the **Diluent vial** and add the volume to the **Mixing vial** and swirl gently. This solution appears clear to slightly hazy. Store at room temperature and perform step 5 (vaccine administration) within 3 hours. DO NOT FREEZE. | | |
| Completion Time of Dose Prep:<br><br>____:____ | 5 | Swirl gently and then withdraw 0.5 mL using a new, unused 1-mL syringe and a new appropriate size needle for IM injection (protocol, Table 4.5.1.2-1). Blind the barrel of the syringe utilizing a blank label (provided) so that it completely covers the contents in the syringe. Using the label with project-specific text fields, complete the fields on the label, and then adhere the label to the barrel of the syringe, so that the text fields create a flag and are visible. Make sure the labels adhere firmly so that they cannot be removed from the syringe.<br>Administer within 30 minutes of withdrawal. | | |
| | 6 | Return the empty mixing vial and all empty component vials to the kit and store appropriately for investigational product reconciliation. The label flag with completed text fields from the syringe should be cut from the syringe and stored with the kit for investigational product reconciliation. The empty syringe used to administer the investigational product should be discarded per site's SOPs. | | |

# Cohort 3a, MEDI7510 (RSV sF + GLA-SE)

| Description | Antigen (mL) | GLA-SE (mL) | SE (mL) | Diluent (mL) | Final Volume (mL) |
|---|---|---|---|---|---|
| Cohort 3a, MEDI7510 (RSV sF Antigen plus GLA-SE Adjuvant) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |




Antigen = RSV sF; h = hours; GLA-SE = glucopyranosyl lipid A; GLA-SE = glucopyranosyl lipid A in 2% (w/v) SE; SE = stable emulsion; sWFI = sterile water for injection

| Date: ___/___/___ | Step | Dose Preparation Instructions for Cohort 3a, MEDI7510 | Initials - Pharmacist | Initials - Verifier |
|---|---|---|---|---|
| Dose Prep Start Time: ____:____ | 1 | Unroll the label on each vial in kit, making note of the vial component (RSVsF, GLA-SE, GLA, etc). Re-roll the label and write the component type on the label. Remove all flip-caps, wipe the septum of the vials with an alcohol swab, and allow the wiped surfaces to air dry. Pull a 3-mL mixing vial from your study-specific bulk supply for this study and attach the tear-off label from the kit onto the mixing vial. Handle all material aseptically. Using a 1-mL syringe, withdraw 0.6 mL of sterile water for injection (**sWFI**). | | |
| | 2 | Add [redacted] mL of **sWFI** to reconstitute the lyophilized **Antigen vial.** Swirl gently for 10 seconds followed by a pause for about 10 seconds. Repeat a total of 3 times. Allow solids to completely dissolve before proceeding. This solution is clear and colorless to slightly yellow. | | |

## Cohort 3a, MEDI7510 (RSV sF + GLA-SE)

| | | | | |
|---|---|---|---|---|
| | 3 | Using a 1-mL syringe, withdraw [redacted] mL from the reconstituted **Antigen vial** and add the volume to the **Mixing vial**. | | |
| | 4 | Using a 0.3-mL syringe, withdraw [redacted] mL from the **Diluent vial** and add the volume to the Mixing vial. | | |
| | 5 | Using a 0.3-mL syringe, withdraw [redacted] mL from the **GLA-SE vial** and add the volume to the **Mixing vial**. This solution appears milky white. | | |
| | 6 | Using a 0.3-mL syringe, withdraw [redacted] mL from the **SE vial** and add the volume to the **Mixing vial** and swirl gently. This solution appears milky white. Store at room temperature and perform step 7 (vaccine administration) within 3 hours. DO NOT FREEZE. | | |
| Completion Time of Dose Prep:<br><br>____:____ | 7 | Swirl gently and then withdraw 0.5 mL using a new, unused 1-mL syringe and a new appropriate size needle for IM injection (see protocol, Table 4.5.1.2-1). Blind the barrel of the syringe utilizing a blank label (provided) so that it completely covers the contents in the syringe. Using the label with project-specific text fields, complete the fields on the label, and then adhere the label to the barrel of the syringe, so that the text fields create a flag and are visible. Make sure the labels adhere firmly so that they cannot be removed from the syringe.<br>Administer within 30 minutes of withdrawal. | | |
| | 8 | Return the empty **mixing vial** and all empty component vials to the kit and store appropriately for investigational product reconciliation. The label flag with completed text fields from the syringe should be cut from the syringe and stored with the kit for investigational product reconciliation. The empty syringe used to administer the investigational product should be discarded per site's SOPs. | | |

# Placebo (All Cohorts)

| Description | 0.9% Sterile Saline (mL) | Final Volume (mL) |
|---|---|---|
| Placebo | 0.5 | 0.5 |

| Date: ___/___/___ | Step | Dose Preparation Instructions for Placebo (All Cohorts) | Initials - Pharmacist | Initials - Verifier |
|---|---|---|---|---|
| Dose Prep Start Time: ____:____ | 1 | Remove flip-cap, wipe the septum of the vial with an alcohol swab, and allow the wiped surface to air dry. Pull a 3-mL sterile saline vial from your study-specific bulk supply for this study and attach label provided by sponsor. Handle material aseptically. Placebo requires no mixing. | | |
| Completion Time of Dose Prep: ____:____ | 2 | Using a new, unused 1-mL syringe and a new, appropriate size needle for IM injection (see protocol, Table 4.5.1.2-1), withdraw 0.5 mL of **sterile 0.9% saline**. Blind the barrel of the syringe utilizing a blank label (provided) so that it completely covers the contents in the syringe. Using the label with project-specific text fields, complete the fields on the label, and then adhere the label to the barrel of the syringe, so that the text fields create a flag and are visible. Make sure the labels adhere firmly so that they cannot be removed from the syringe. | | |
| | 3 | Administer within **30 minutes** of withdrawal. | | |
| | 4 | Return the empty saline vial to the kit and store appropriately for investigational product reconciliation. The label flag with completed text fields from the syringe should be cut from the syringe and stored with the kit for investigational product reconciliation. The empty syringe used to administer placebo should be discarded per site's SOPs. | | |