A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

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PROTOCOL SYNOPSIS

TITLE

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

HYPOTHESES

Primary Hypothesis:

Compared to placebo, a single [redacted] mg intramuscular (IM) dose of MEDI8897 will be efficacious in reducing medically attended lower respiratory tract infection (LRTI) caused by real-time reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed respiratory syncytial virus (RSV) in healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age (GA) and entering their first RSV season, and the safety profile will be acceptable.

Secondary Hypotheses:

1. There will be a reduction in the incidence of hospitalizations attributable to RSV
2. The predicted extended terminal half-life ($t_{1/2}$) will be adequate for the duration of the RSV season
3. Anti-drug antibody (ADA) to MEDI8897 will not significantly impact the serum concentrations or safety of MEDI8897 over the 5-month RSV season

OBJECTIVES

Primary Objective:

To assess the efficacy of MEDI8897 when administered as a single [redacted] mg IM dose to healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and entering their first RSV season for the reduction of medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo

Secondary Objectives:

1. To assess the efficacy of MEDI8897 for the reduction of hospitalizations due to RT-PCR-confirmed RSV, compared to placebo
2. To evaluate the safety and tolerability of MEDI8897 when administered as a single fixed IM dose, compared to placebo
3. To evaluate single-dose serum concentrations of MEDI8897
4. To evaluate ADA responses to MEDI8897 in serum

Exploratory Objective:

To assess healthcare resource utilization (HRU) and caregiver burden for MEDI8897 recipients compared to placebo recipients

STUDY ENDPOINTS

Primary Endpoint:

Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season

Secondary Endpoints:

1. Incidence of hospitalizations due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season
2. Safety and tolerability of MEDI8897 as assessed by the occurrence of all treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and new onset chronic diseases (NOCDs)
3. Single-dose MEDI8897 serum concentrations
4. Incidence of ADA to MEDI8897 in serum

Exploratory Endpoints:

1. Magnitude of HRU (eg, number of admissions to hospitals and intensive care units [ICUs] and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of

use; number and type of outpatient visits, eg, emergency room [ER], urgent care, outpatient clinic; and number of prescription and over-the-counter [OTC] medications and duration of use) for MEDI8897 recipients compared to placebo recipients.

2. Caregiver burden (eg, caregiver missed work days, subject absence from day care) for subjects with medically attended LRTI caused by RT-PCR-confirmed RSV

STUDY DESIGN

This pivotal Phase 2b study is a randomized, double-blind, placebo-controlled, single-dose study to determine if MEDI8897 will be efficacious in reducing medically attended RSV-confirmed LRTI in healthy preterm infants entering their first RSV season. The population to be enrolled is healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA who would not receive RSV prophylaxis based on the American Academy of Pediatrics (AAP) or other local or national guidelines. These infants will not be receiving palivizumab, allowing for a placebo comparator group for the determination of efficacy and the safety profile. A total of 1,500 infants will be randomized 2:1 to receive a [redacted] mg IM dose of MEDI8897 (N = 1000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age at the time of randomization (ie, ≤ 3 months, > 3 – ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500. All infants will be followed for approximately 360 days after dosing.

Subjects will be monitored throughout the study for LRTI. All subjects seeking medical attention for a respiratory illness (inpatient or outpatient setting) will be evaluated for the occurrence of LRTI. Subjects who have a primary hospitalization for a respiratory illness, a respiratory deterioration during a hospitalization, or who seek outpatient medical attention, including ER visits for a respiratory illness, will be assessed for RSV by diagnostic testing of respiratory secretions and clinical assessment for the presence of LRTI. Testing for RSV will be performed centrally using the United States Food and Drug Administration (US FDA)-approved and *Conformité Européenne* or European Conformity (CE) - marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + human metapneumovirus [hMPV] Assay, Quidel, San Diego, CA www.quidel.com). A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by RT-PCR.

Subjects with signs of LRTI must have documented physical exam findings of rhonchi, rales, crackles, or wheeze AND any of the following:

- Increased respiratory rate at rest (age < 2 months, ≥ 60 breaths/min; age 2–6 months, ≥ 50 breaths/min; age > 6 months – 2 years, ≥ 40 breaths/min) OR
- Hypoxemia (in room air: oxygen saturation < 95% at altitudes ≤ 1800 meters or < 92% at altitudes > 1800 meters), OR
- Clinical signs of severe respiratory disease (eg, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid).

TARGET SUBJECT POPULATION

This study will be conducted in healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA who would not be recommended to receive palivizumab per AAP or local or national guidelines, and who are entering their first RSV season at the time of screening.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Subjects will be randomly assigned to receive a single dose of MEDI8897 [redacted] mg IM) or placebo.

STATISTICAL ANALYSIS PLAN

General Considerations:

Tabular summaries will be presented by treatment group. 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 intent-to-treat (ITT) Population is defined as all subjects who are randomized. Subjects will be included in the treatment group corresponding to their randomized treatment. All analyses, with the exception of safety, will be performed on the ITT Population.

The As-treated Population will include all subjects who are randomized into the study and who receive any amount of investigational product. Subjects will be included in the treatment group corresponding to the treatment actually received. All safety analyses will be performed on the As-treated Population.

Sample size:

The sample size of 1,500 is necessary based on advice from the US FDA requesting that 1,000 preterm infants be exposed to MEDI8897 in this Phase 2b study. This sample size has approximately 99% power to detect 70% relative risk reduction, assuming a placebo group medically attended RSV LRTI incidence of 8%. Power calculations are based on Poisson regression model with robust variance (Zou, 2004) comparing MEDI8897 [redacted] versus placebo, with 2-sided significance level of $\alpha = 0.05$.

- The 70% relative risk reduction assumption is based on a placebo-controlled study in Native American infants in which there was 87% relative reduction in the incidence of RSV hospitalization (11.3% placebo; 1.5% motavizumab; $p < 0.001$) and 71% relative reduction in the incidence of outpatient RSV LRTI (10.0% placebo; 2.9% motavizumab; $p < 0.001$) in infants who received motavizumab prophylaxis (O'Brien et al, 2015).

In order to evaluate risk, a sample size of 1,000 subjects exposed to MEDI8897 will provide a 90% probability of observing at least one adverse event (AE) if the true event rate is 0.2%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.3%.

Statistical Analyses:

There are two planned analyses for this study: the primary analysis and the final analysis. The primary analysis will be conducted after all randomized subjects have completed follow-up through the 5-month RSV season (ie, Day 151 visit) and will be the primary analysis for which the study is designed to assess efficacy. For the primary analysis, all efficacy, pharmacokinetics (PK), ADA, and safety data collected through at least Day 151 will be analyzed. The final analysis for safety follow-up will be conducted when all subjects have completed the last visit of the study (ie, Day 361). Since efficacy endpoints are collected in the time interval from randomization up to Day 151, the efficacy analyses performed in the primary analysis will serve the purpose of evaluating the efficacy of MEDI8897 in the study population.

The primary and secondary efficacy hypotheses will be assessed in the primary analysis by a hierarchical order. That is, the secondary hypothesis will be tested at a significance level of 0.05 only if the treatment effect on the primary efficacy endpoint is demonstrated at the significance level of 2-sided 0.05. With that, the overall Type I error is controlled at 0.05. Therefore, no further multiplicity adjustment is necessary.

Primary Endpoint Analysis:

Primary Efficacy Analysis

The incidence of RSV LRTI (inpatient and outpatient) during 5 months of the RSV season will be based on RSV test results (performed centrally via RT-PCR) and objective clinical LRTI criteria will be summarized by treatment group. For subjects with multiple medically attended RSV LRTI events, only the first occurrence will be used in the primary analysis.

The primary efficacy analysis will be conducted on the ITT Population. LRTI caused by RSV that occurs prior to discontinuation from participation in the study will contribute to the primary efficacy analysis. For subjects who do not have an RSV LRTI prior to discontinuation from participation, their event status will be imputed assuming the observed placebo RSV LRTI rate. This will be implemented by imputations based on repeated simulations and will be described in the Statistical Analysis Plan. A Poisson regression model with robust variance will be used as the primary efficacy analysis model to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo, including treatment group, age at the time of randomization (ie, ≤ 3 months, $> 3 - \leq 6$ months, > 6 months), and dichotomous temperate (northern and southern) hemispheres as covariates. In addition, the 2-sided p-value and corresponding 2-sided 95% CI on the relative risk will be provided from the model. Relative risk reduction is defined as (1 - Pn/Ps) where Pn is the incidence of RSV LRTI during 5 months of the RSV season in the MEDI8897 group and Ps is the incidence of RSV LRTI during 5 months of the RSV season in the placebo group generated by the model. Statistical significance will be achieved if the 2-sided p-value is ≤ 0.05.

Additional Analyses of the Primary Endpoint

A CMH (Cochran-Mantel-Haenszel) approach stratified by hemisphere and age group at the time of randomization (ie, ≤ 3 months, > 3 – ≤ 6 months, > 6 months) will be used to compare the incidence of RSV LRTI during 5 months of the RSV season between treatment groups as a sensitivity analysis for the primary endpoint. In addition, a time-to-event analysis assessing time to first RSV LRTI may be performed as a supplementary analysis.

An analysis may also include all RSV positive LRTI endpoints, using results from either the central lab or local lab.

Different approaches to handle missing data (ie, early discontinuation and no RSV LRTI prior to discontinuation) may be considered for sensitivity analyses. Additional analyses or subgroup summaries may be performed to adjust duration of efficacy follow-up and/or other possible confounding factors. These analyses will be described in the Statistical Analysis Plan.

Secondary Endpoint Analyses:

Efficacy

The incidence of RSV hospitalization during 5 months of the RSV season will be summarized by treatment group. The same methods described above for the primary efficacy endpoint will be used to assess treatment effect on RSV hospitalization. Following a hierarchical testing procedure, the secondary efficacy endpoint is tested at the significance level of 2-sided 0.05 if the primary analysis on the primary efficacy endpoint has achieved statistical significance at the level of 2-sided 0.05.

Safety

Safety of MEDI8897 will primarily be assessed by the occurrence of treatment-emergent AEs and SAEs. Adverse events will be graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) where applicable for pediatric assessments. Adverse events will be coded by Medical Dictionary for Regulatory Activities (MedDRA) and the type, incidence, severity and relationship to study investigational product will be summarized by treatment group. Other safety assessments will include:

- Occurrence of AESIs to include targeted AEs of hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis) following investigational product administration.
- Occurrence of NOCDs following investigational product administration

Pharmacokinetics Analysis

Following a single dose of MEDI8897, individual MEDI8897 serum concentration data will be tabulated by treatment group along with descriptive statistics. Terminal phase half-life ($t_{1/2}$) will be estimated using non-compartmental analysis, if data permit.

Anti-drug Antibody Analysis

The incidence of ADA to MEDI8897 will be assessed and summarized by number and percentage of subjects that are ADA positive by treatment group. The ADA titer will be listed by subject at different time points. The impact of ADA on PK and association with TEAEs and TESAEs will be assessed.

Exploratory Endpoint Analyses:

The magnitude of HRU (eg, number of admissions to hospitals and ICUs and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of use; number and types of outpatient visits, eg, ER, urgent care, outpatient clinic; and number of prescription and OTC medications and duration of use) will be summarized overall by treatment group, and for the following subgroups: subjects with at least one medically attended LRTI caused by RT-PCR-confirmed RSV, subjects with medically attended LRTI not caused by RSV, and subjects without medically attended LRTI.

Caregiver burden (eg, caregiver missed work days, subject absence from day care) for subjects with medically attended LRTI caused by RT-PCR-confirmed RSV will be summarized by treatment group.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AAP	American Academy of Pediatrics
AE	adverse event
AESI	adverse event of special interest
BP	blood pressure
CE	*Conformité Européenne* or European Conformity
CHD	congenital heart disease
CI	confidence interval
CLD	chronic lung disease
DMC	data monitoring committee
eCRF	electronic case report form
EDC	electronic data capture
ER	emergency room
EU	European Union
Fc	fragment cystallizable
FcRn	neonatal Fc receptor
FTIH	first-time-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
HRU	healthcare resource utilization
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
IgG1κ	immunoglobulin G1 kappa
IM	intramuscular
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
LRTI	lower respiratory tract infection
mAb	monoclonal antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Diseases
NOCD	new onset chronic disease
OTC	over-the-counter

Abbreviation or Specialized Term	Definition
PEF	peak expiratory flow
PK	pharmacokinetics
RSV	respiratory syncytial virus
RT-PCR	real time reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SID	subject identification
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TK	toxicokinetics
TESAE	treatment-emergent serious adverse event
URTI	upper respiratory tract infection
US FDA	United States Food and Drug Administration
USA	United States of America
UTI	urinary tract infection
wGA	weeks gestational age
YTE	M257Y/S259T/T261E triple amino acid substitution

1 INTRODUCTION

Prevention of respiratory syncytial virus (RSV) illnesses in all infants is a major public health priority. However, despite many years of attempted vaccine development, there is no safe and effective vaccine for these children. As there is no approved RSV prophylaxis for the broader population of healthy infants and no treatment for RSV, the current management for these patients when they acquire serious RSV illness is supportive care.

Palivizumab (Synagis®) is the only approved agent for RSV prophylaxis, and its use is restricted to high-risk children (preterm infants ≤ 35 weeks gestational age [wGA], children with chronic lung disease [CLD] of prematurity, and children with hemodynamically significant congenital heart disease [CHD]). As its terminal half-life ($t_{1/2}$) is approximately 1 month, palivizumab must be administered monthly (as an intramuscular [IM] injection) throughout the RSV season, making its use in a broader infant population unfeasible. In addition, due to the cost, further restrictions have been implemented by local or national recommending bodies. For example, in the United States of America (USA), per the American Academy of Pediatrics (AAP) guidelines, palivizumab is not recommended for healthy preterm infants ≥ 29 wGA (American Academy of Pediatrics Committee on Infectious Diseases, 2014).

1.1 Disease Background

Respiratory syncytial virus is the most common cause of lower respiratory illness among infants and young children, resulting in annual epidemics worldwide (Hall et al, 2009; Hall, 2012; Nair et al, 2010; Shay et al, 1999; Stockman et al, 2012). All children, including healthy term infants, are at risk for severe RSV lower respiratory illness with primary infection during infancy. Ninety percent of children are infected with RSV in the first 2 years of life and up to 40% will have lower respiratory tract infection (LRTI) (Greenough et al, 2001; Meissner, 2003; Parrott et al, 1973). Respiratory syncytial virus LRTI, characterized predominantly as bronchiolitis or pneumonia, represents a serious illness with acute and perhaps long-term consequences to the developing lungs in these young children (Blanken et al, 2013). It is estimated that RSV causes up to 90% of childhood bronchiolitis and up to 40% of pediatric pneumonias (Hall, 2001). Respiratory syncytial virus bronchiolitis was the leading cause of hospital admissions for infants < 1 year of age for any reason in the years between 1997 and 1999 (Leader et al, 2002).

Although hospitalization is well recognized as an important consequence of RSV illness, a large percentage of the healthcare burden from RSV occurs outside the hospital (Carroll et al, 2008; Hall et al, 2009; Hall, 2012; Paramore et al, 2010) such that office visits and

emergency department visits are more frequent than subsequent hospitalization, especially in healthy infants. In children < 5 years of age in the USA, RSV is estimated to cause 1 in 13 private practice visits, 1 in 38 emergency department visits, and 1 in 334 hospitalizations (Hall, 2012). Another study demonstrated that in otherwise healthy term infants < 12 months of age in a Medicaid program (1995-2003), 13.3% had an outpatient visit, 6.2% had an emergency department visit, and 5.5% were hospitalized for bronchiolitis (Carroll et al, 2008). Additionally, Paramore and colleagues reported high rates of outpatient RSV LRTI among infants and young children, ranging from 157.5 to 252.0 per 1000 children < 1 year of age (Paramore et al, 2010). This study also showed that outpatient RSV LRTI rates for late preterm (33 to 36 wGA) infants ranged from 183.3 to 245.7 per 1000 infants, with rates for full-term infants ranging from 128.8 to 171.3 per 1000 infants.

Hospitalization rates among young children in European countries appear to be similar to those in the USA; the rates for infants within the first year of life were invariably the highest, 19 to 22 per 1,000 children, consistent with the USA and Canadian data (Jansen et al, 2007; van Gageldonk-Lafeber et al, 2005; Weigl et al, 2001). In addition, RSV hospitalization rates among German children 0 to 3 years of age were found to be 4 and 9 times greater than the hospitalization rates associated with parainfluenza and influenza viral infections, respectively.

Similarly, high rates of RSV hospitalization are evident in South Africa for infants < 6 months of age, in which the incidence (95% confidence interval [CI]) of severe LRTI was 26.2 (23.6-29.0) per 1000 in those born at ≥ 36 wGA, 125.0 (95.3-159.9) per 1000 in those born at 32 - 35 wGA, and 142.3 (89.5-212.0) per 1000 in those born at < 32 wGA (Madhi et al, 2006).

1.2 MEDI8897 Background

MEDI8897 is briefly described below. Refer to the current Investigator's Brochure for details.

MEDI8897 is a recombinant human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) directed against the prefusion conformation of the RSV F protein. The antibody has been engineered with a triple amino acid substitution (YTE; M257Y/S259T/T261E [M252Y/S254T/T256E, according to the European Union numbering system]) in the fragment crystallizable (Fc) region to prolong the $t_{1/2}$, which is expected to provide protection from serious RSV disease for the duration of the RSV season. MEDI8897 neutralizes RSV by binding the prefusion conformation of the RSV F protein at a site distinct from that bound by palivizumab. In preclinical studies, MEDI8897 was > 150-fold more

potent than palivizumab in vitro and approximately 9-fold more potent than palivizumab in vivo in the cotton rat model. MEDI8897 is currently under development by MedImmune for the passive immunization of all infants entering their first RSV season and children with CLD or CHD entering their first and second RSV season for the prevention of LRTI caused by RSV. MEDI8897 may provide a cost-effective opportunity to protect all infants from RSV disease based on an improvement in potency and the extended $t_{1/2}$ that is expected to support once-per-RSV-season dosing.

1.3 Summary of Nonclinical Experience

The potential clinical utility of MEDI8897 and dose predictions of the antibody were evaluated in the cotton rat model of RSV infection. The pharmacokinetics (PK) of 1G7, the non-YTE version of MEDI8897, was evaluated in cotton rats following a single IM dose of 0.25 to 3.0 mg/kg. Serum concentrations increased dose proportionally across the entire dose range with a terminal-phase elimination $t_{1/2}$ of approximately 1 day. In cotton rats, a serum concentration of 6.8 μg/mL resulted in a 3-log reduction in lung RSV titers and was identified as the target serum concentration to maintain in children to provide antiviral activity against RSV over a typical 5-month RSV season.

The YTE amino acid substitutions introduced into MEDI8897 do not impact RSV neutralizing activity when compared to the parental mAb, 1G7. MEDI8897/1G7 showed potent antiviral activity in vitro against RSV A and B laboratory strains, clinical isolates, as well as palivizumab-resistant viruses. MEDI8897/1G7 was > 150- fold more potent than palivizumab in vitro against the laboratory strains and > 50-fold more potent than palivizumab against clinical isolates based on the median half-maximal inhibitory concentration (IC_{50}).

Toxicity, toxicokinetics (TK) and immunogenicity of MEDI8897 were evaluated in a Good Laboratory Practice (GLP)-compliant repeat-dose intravenous (IV) and IM toxicology study conducted in cynomolgus monkeys. Cynomolgus monkeys represent a pharmacologically relevant model for nonclinical safety assessment based on similar binding of MEDI8897 to cynomolgus monkey neonatal Fc receptor (FcRn) compared to human FcRn. Toxicology studies in cynomolgus monkeys indicate that there is no evidence of MEDI8897 toxicity in these animal models. Once weekly IV or IM administration (5 doses total) of MEDI8897 to monkeys, up to and including 300 mg/kg IV or 300 mg IM dose levels, was not associated with any treatment-related adverse effects locally or systemically. The no-observed-adverse-effect-level (NOAEL) was considered to be 300 mg/kg IV and 300 mg IM. No anti-drug antibody (ADA) was detected in any of the monkeys during the treatment phase. During the recovery phase, 4 of 12 animals treated with MEDI8897 and 0 of 6 control animals were

ADA positive with variable impact on TK. In addition, tissue cross-reactivity against cryosections of a full panel of adult and a selected panel of juvenile, neonatal, and fetal human tissues showed no staining of any tissues, as expected, given the target for MEDI8897 is a non-endogenous viral-specific target. Overall, data from nonclinical studies do not reveal any MEDI8897-related safety concerns.

Details of these studies are included in the current Investigator's Brochure.

1.4 Summary of Clinical Experience

Two clinical studies of MEDI8897 have been conducted so far. The Phase 1a, first-time-in human (FTIH) study (Study D5290C00001; ClinicalTrials.gov Identifier NCT02114268) in healthy adult volunteers was completed in June 2015, and the second study, a Phase 1b/2a study (D5290C00002; ClinicalTrials.gov Identifier NCT02290340), in healthy preterm infants of 32-35 wGA has completed enrollment and dosing; follow-up is ongoing.

The FTIH study, D5290C00001, was a Phase 1a, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and tolerability, PK, and ADA for MEDI8897 when administered as a single fixed dose of 300, 1000, or 3000 mg IV, or 100 or 300 mg IM to healthy adult subjects. Subjects completed 1 year of follow-up in June 2015. A total of 136 subjects were randomly assigned to receive a single dose of MEDI8897 (6 subjects each at doses of 300 mg IV, 1,000 mg IV, 3,000 mg IV, and 100 mg IM; 78 subjects at 300 mg IM) or placebo (34 subjects). The mean $t_{1/2}$ of MEDI8897 ranged from 85 to 117 days across the IV and IM dose groups, and model-estimated systemic bioavailability after IM administration was 87%. The predicted 3- to 4-fold increase in the $t_{1/2}$ of MEDI8897 compared to a standard immunoglobulin G (IgG) antibody was confirmed. In healthy adults, the safety profile of MEDI8897 was favorable, with similar proportions of adverse events (AEs) reported in placebo (21/34; 61.8%) and MEDI8897 recipients (64/102; 62.7%). Two SAEs (gunshot wound and appendicitis) were reported in 2 MEDI8897 recipients. AEs judged to be related to study drug were reported in 29.4% (10/34) of placebo recipients and 17.6% (18/102) of MEDI8897 recipients. The most frequently reported AEs in the MEDI8897 cohorts were upper respiratory tract infection (URTI; 19/102; 18.6%), headache (9/102; 8.8%), urinary tract infection (UTI; 6/102; 5.9%); and dermatitis contact, musculoskeletal pain, nausea and vomiting (5/102, 4.9% each). All other AEs occurred in 4 or fewer subjects. There were no events designated as adverse events of special interest (AESI). One event of Type 2 diabetes was reported as a new onset chronic disease (NOCD) in the placebo group. There were no deaths. No safety signals in this healthy adult population were observed. Post-baseline ADA was detected in a similar proportion of placebo recipients (5/33, 15.2%) and MEDI8897 recipients (14/102, 13.7%), and the presence and titer of ADA

had no effect on PK or the safety profile. These results demonstrated an acceptable safety profile for MEDI8897.

The Phase 1b/2a first-in-pediatric study (D5290C00002) is an ongoing, randomized, double-blind, placebo-controlled, dose-escalation study designed to evaluate the safety and tolerability, PK and ADA for MEDI8897 in healthy preterm infants of 32 - 35 wGA who would not receive RSV prophylaxis based on the AAP (American Academy of Pediatrics Committee on Infectious Diseases, 2014) or any other local or national recommending bodies' guidelines. This study population was selected based on advice from the United States Food and Drug Administration (US FDA) to perform initial clinical evaluations of MEDI8897 in a population where the benefit of RSV prophylaxis has been proven. Enrolment and dosing have been completed in 89 infants from sites in the United States, Chile, and South Africa. Infants were randomized and received a single IM dose of 10 mg, 25 mg, or 50 mg MEDI8897 (N = 71) or placebo (N = 18). All subjects are being followed for 1 year. The first interim analysis was conducted 30 days (October 2015) after the last subject was dosed to evaluate MEDI8897 serum concentrations, ADA, and safety. At the interim analysis, 1 infant in the placebo group had been withdrawn from the study because the mother could no longer bring the infant in for follow-up visits. At study entry, infants had a mean age (± SD) and mean weight (± SD) of 6.95 (± 2.63) months and 7.31 (± 1.84) kg in the placebo group and 6.50 (± 2.64) months and 6.82 (± 1.90) kg in the MEDI8897 group. MEDI8897 serum concentrations were consistent with the expected extended $t_{1/2}$ in infants. Model-based simulations predict the MEDI8897 median $t_{½}$ to range from 83 to 94 days for the 50 mg dose in infants with normal clearance. In healthy preterm infants the safety profile of MEDI8897 was favorable with similar proportions of AEs reported in the placebo (12/18, 66.7%) and MEDI8897 (51/71, 71.8%) recipients. No safety signals were observed with the ascending dose levels. There was 1 serious adverse event (SAE) that occurred in an infant who received 25 mg of MEDI8897. The infant was hospitalized for LRTI and, upon subsequent testing, was found to be negative for RSV by the real time reverse transcriptase-polymerase chain reaction (RT-PCR) assay. The illness resolved. All of the AEs were Grade 1 or 2 in severity. The most frequently reported AEs were URTI (placebo, 7/18, 38.9%; MEDI8897 27/71, 38%), anemia (placebo 5/18, 27.8%; MEDI8897, 9/71, 12.7%), cough (placebo 2/18, 11.1%; MEDI8897, 9/71, 12.7%), pyrexia (placebo 0, MEDI8897, 8/71, 11.3%), bronchiolitis (placebo 5.6%, MEDI8897 7/71, 9.9%), and rhinorrhea (placebo, 1/18, 5.6%; MEDI8897 7/71, 9.9%). There were no AESIs, NOCDs, or deaths. ADA levels at the 30-day interim analysis were similar for placebo and MEDI8897 recipients, with rates of 12.5% (2/18) and 4.4% (3/71) for placebo and MEDI8897 recipients, respectively. A second interim analysis is planned for 6 months after the last subject was dosed (March 2016) to evaluate MEDI8897 serum concentrations, ADA, and safety.

Additional data from these studies is available in the Investigator's Brochure.

1.5 Rationale for Conducting the Study

Prevention of RSV illnesses in all infants is a major public health priority but, despite almost 50 years of attempted vaccine development and extensive ongoing work (www.clinicaltrials.gov), there is not yet a safe and effective vaccine. While RSV prevention exists in the form of a specific RSV IgG (Synagis®, palivizumab) requiring 5 monthly injections, it is licensed only for infants who experience the greatest morbidity and mortality from RSV (preterm infants ≤ 35 wGA, children with CLD of prematurity, and children with hemodynamically significant CHD). In addition, due to the cost of prophylaxis, further restrictions have been implemented by local or national recommending bodies. For example, in the USA, per the AAP guidelines, palivizumab is not recommended for healthy preterm infants ≥ 29 wGA. Currently, there is no approved RSV prophylaxis for the broader population of healthy newborns and infants, and there is no treatment for active RSV infection. The current standard of care for these patients with serious RSV illness is supportive care. Thus, there is a significant unmet medical need in healthy infants. MEDI8897 is being developed as a cost-effective opportunity to protect all infants from RSV disease based on improved potency and an extended $t_{1/2}$, which is expected to support once-per-RSV-season dosing.

Based on advice from the US FDA, this initial pivotal study to demonstrate efficacy and safety of MEDI8897 will be conducted in healthy preterm infants who are not eligible to receive palivizumab according to AAP or other local guidelines. After 500 preterm infants are dosed with MEDI8897, a benefit: risk assessment will be conducted, and if favorable, a Phase 3 study in healthy infants > 35 wGA can be initiated.

1.6 Research Hypotheses

1.6.1 Primary Hypothesis

Compared to placebo, a single [redacted] mg IM dose of MEDI8897 will be efficacious in reducing medically attended LRTI caused by RT-PCR-confirmed RSV in healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age (GA) and entering their first RSV season, and the safety profile will be acceptable.

1.6.2 Secondary Hypotheses

1. There will be a reduction in the incidence of hospitalizations attributable to RSV
2. The predicted extended $t_{1/2}$ will be adequate for the duration of the RSV season

3. ADA to MEDI8897 will not significantly impact the serum concentrations or safety of MEDI8897 over the 5-month RSV season.

2 OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

To assess the efficacy of MEDI8897 when administered as a single [redacted] mg IM dose to healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and entering their first RSV season for the reduction of medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo.

2.1.2 Secondary Objectives

1. To assess the efficacy of MEDI8897 for the reduction of hospitalizations due to RT-PCR-confirmed RSV, compared to placebo
2. To evaluate the safety and tolerability of MEDI8897 when administered as a single fixed IM dose, compared to placebo
3. To evaluate single-dose serum concentrations of MEDI8897
4. To evaluate ADA responses to MEDI8897 in serum

2.1.3 Exploratory Objective

To assess healthcare resource utilization (HRU) and caregiver burden for MEDI8897 recipients compared to placebo recipients

2.1.4

2.2 Study Endpoints

2.2.1 Primary Endpoint

Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season

2.2.2 Secondary Endpoints

1. Incidence of hospitalizations due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season
2. Safety and tolerability of MEDI8897 as assessed by the occurrence of all treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), AESIs, and NOCDs
3. Single-dose MEDI8897 serum concentrations

4. Incidence of ADA to MEDI8897 in serum

2.2.3 Exploratory Endpoints

1. Magnitude of HRU (eg, number of admissions to hospitals and intensive care units [ICUs] and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of use; number and types of outpatient visits, eg, emergency room [ER], urgent care, outpatient clinic; and number of prescription and over-the-counter [OTC] medications and the duration of use) for MEDI8897 recipients compared to placebo recipients.
2. Caregiver burden (eg, caregiver missed work days, subject absence from day care) for subjects with medically attended LRTI caused by RT-PCR-confirmed RSV.

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This pivotal Phase 2b study is a randomized, double-blind, placebo-controlled, single-dose study to determine if MEDI8897 will be efficacious in reducing medically attended RSV-confirmed LRTI in healthy preterm infants entering their first RSV season. The population to be enrolled is healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA who would not receive RSV prophylaxis based on the AAP or other local or national guidelines. These infants will not be receiving palivizumab, allowing for a placebo comparator group for the determination of efficacy and the safety profile. A total of 1,500 infants will be randomized 2:1 to receive a [redacted] mg IM dose of MEDI8897 (N = 1000) or placebo (N = 500; see Figure 3.1.1-1). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age at the time of randomization (ie, ≤ 3 months, > 3 – ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500. Based on preclinical efficacy results in the cotton rat and pharmacokinetic (PK) modeling and simulation, the predicted efficacious dose in infants is a single fixed IM dose of [redacted] mg. All infants will be followed for approximately 360 days after dosing.

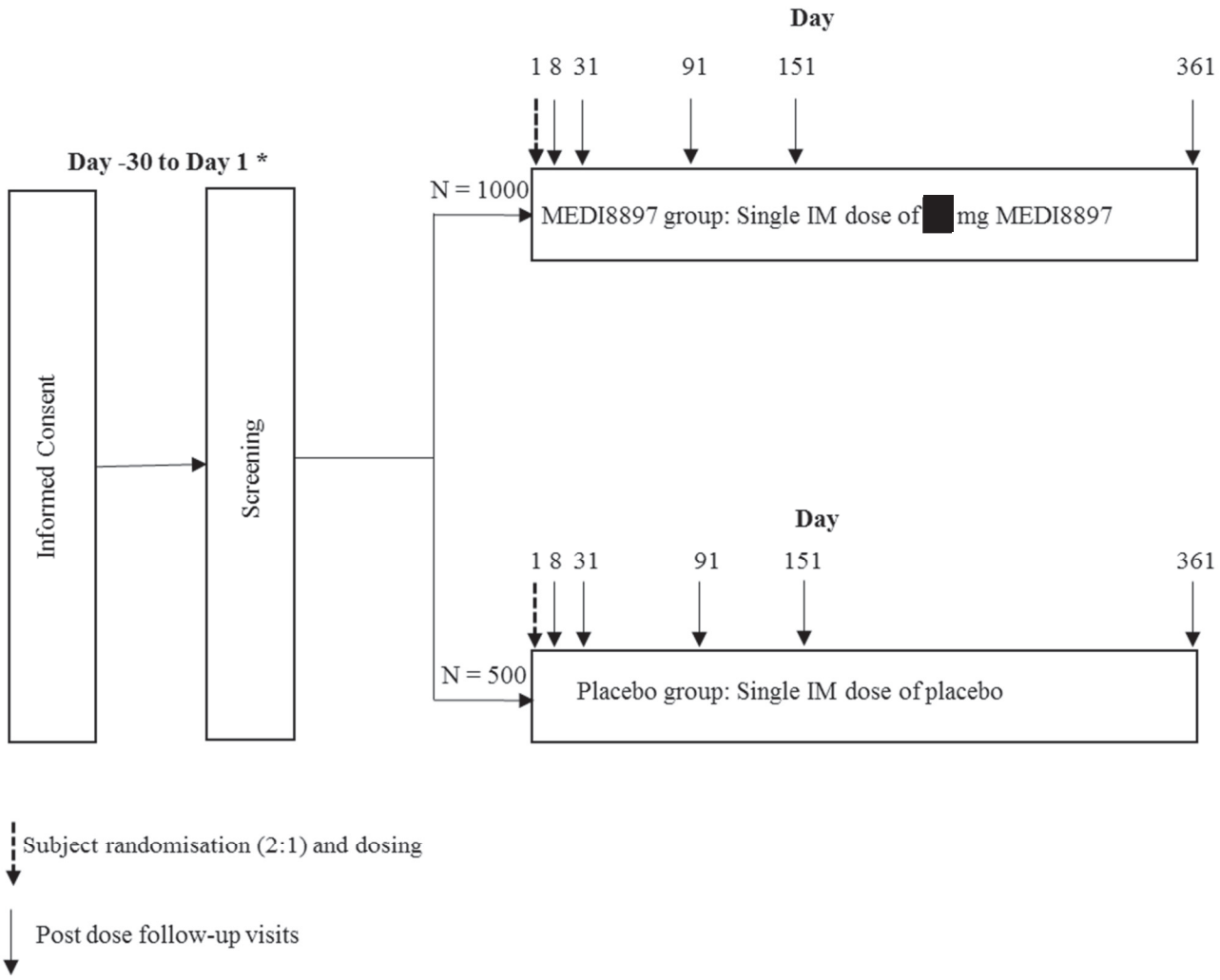
Subjects will be monitored throughout the study for LRTI. All subjects seeking medical attention for a respiratory illness (inpatient or outpatient setting) will be evaluated for the occurrence of LRTI. Subjects who have a primary hospitalization for a respiratory illness, a respiratory deterioration during a hospitalization, or who seek outpatient medical attention, including ER visits for a respiratory illness, will be assessed for RSV by diagnostic testing of respiratory secretions and clinical assessment of the presence of LRTI. Testing for RSV will

be performed centrally using the FDA-approved and *Conformité Européenne* or European Conformity (CE) - marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + human metapneumovirus [hMPV] Assay, Quidel, San Diego, CA www.quidel.com). A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by RT-PCR.

Subjects with signs of LRTI must have documented physical exam findings of rhonchi, rales, crackles, or wheeze AND any of the following:

- Increased respiratory rate at rest (age < 2 months, ≥ 60 breaths/min; age 2–6 months, ≥ 50 breaths/min; age > 6 months – 2 years, ≥ 40 breaths/min) OR
- Hypoxemia (in room air - oxygen saturation < 95% at altitudes ≤ 1800 meters or < 92% at altitudes > 1800 meters), OR
- Clinical signs of severe respiratory disease (eg, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid).

A study schematic is presented in Figure 3.1.1-1.



PK and ADA samples will be collected during screening, on Day 91, 151 and 361 and at hospitalization for LRTI
Safety assessments will be performed from screening through Day 361
* Screening and Day 1 visits may occur on the same day

Figure 3.1.1-1 Study Flow Diagram

ADA = anti-drug antibody; IM = intramuscular; N = number; PK = pharmacokinetic

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

3.1.2 Treatment Regimen

Subjects will be randomly assigned in a 2:1 ratio to receive a single dose of either [redacted] mg MEDI8897 (1000 subjects) or placebo (500 subjects) by IM injection on Day 1.

3.2 Study Design and Dose Rationale

3.2.1 Dose Rationale

In preclinical cotton rat efficacy studies, MEDI8897 serum concentrations of 6.8 µg/mL were shown to result in a 3-log decrease in RSV titers in cotton rat lungs. A population PK model developed using PK data from the Phase 1a study in healthy adults and Day 30 interim data from the Phase 1b/2a study in healthy preterm infants was used to simulate PK profiles in the Phase 2b population. PK profiles were simulated in 1,000 infants for each of the following populations: preterm infants (29-35 weeks GA) at birth, full-term infants at birth, and full-term infants at 12 months of age. A single [redacted] mg fixed IM dose of MEDI8897 is predicted to be the likely efficacious dose that will sustain serum concentrations above the target level of 6.8 µg/mL in the majority of infants over the entire RSV season and provide complete protection for infants entering their first RSV season.

3.2.2 Rationale for Study Population

The population of healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and who do not meet AAP criteria (American Academy of Pediatrics Committee on Infectious Diseases, 2014) to receive palivizumab was selected based on advice from the US FDA. The US FDA made the recommendation based on the higher risk of serious RSV disease in this population compared to older GA infants and the proven benefit shown in previous studies of RSV prophylaxis in this preterm population. In addition, since this population would not be eligible to receive palivizumab (per AAP or other local or national guidelines), a study conducted with a placebo control group is acceptable and protective efficacy can be directly evaluated.

3.2.3 Rationale for Endpoints

MEDI8897 is being developed to provide RSV immunoprophylaxis for all infants entering their first RSV season. The primary endpoint will examine the efficacy of MEDI8897 compared to placebo in preventing LRTI due to RSV. Respiratory syncytial virus results in a significant burden of disease consisting of hospitalization, visits to the ER, and visits to outpatient clinics. This primary endpoint is designed to allow the capture of this total burden of disease and the efficacy of MEDI8897 in reducing that burden.

A separate secondary endpoint of RSV hospitalization, which would indicate the most serious illnesses, will also be evaluated. Additionally, descriptive statistics of the serum concentrations of MEDI8897 at selected time points will be evaluated as a secondary endpoint and to confirm that serum concentrations are maintained above the target value of

6.8 µg/mL for 5 months. The serum concentration data will be used to characterize the PK of MEDI8897 in infants using a population PK approach. For infants who require hospitalization for LRTI, an additional serum sample for measurement of MEDI8897 concentration and ADA will be obtained around the time of hospitalization. Exposure-response analysis will be performed to relate MEDI8897 serum concentrations and efficacy endpoints (LRTI including RSV-associated hospitalization).

To determine the duration of MEDI8897 serum levels post dosing and to correlate with the development of ADA, serum concentrations will be measured at 360 days post dosing. ADA will be measured at selected time points throughout the study and at 360 days post dosing, when MEDI8897 levels are expected to be low and to not interfere with detection of ADA, if present.

Exploratory endpoints will examine magnitude of healthcare resource utilization and caregiver burden due to RSV illness in the current population. This will allow the determination of social and economic resources that are required for infants who have LRTI.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

A total of 1,500 infants will be enrolled and randomized in a 2:1 ratio to receive a single IM dose of [redacted] mg MEDI8897 (N = 1000) or placebo (N = 500).

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Healthy infants born between 29 weeks 0 days and 34 weeks 6 days GA
2. Infants who are entering their first full RSV season at the time of screening
3. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] in the USA, European Union [EU] Data Privacy Directive in the EU) obtained from the subject's parent(s)/legal representative prior to performing any protocol-related procedures, including screening evaluations
4. Subject's parent(s)/legal representative is able to understand and comply with the requirements of the protocol including follow-up and illness visits as judged by the investigator
5. Subject is available to complete the follow-up period, which will be 1 year after receipt of the dose of study drug

4.1.3 Exclusion Criteria

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

1. Meets AAP or other local criteria to receive commercial palivizumab
2. Any fever (≥ 100.4°F [≥ 38.0°C], regardless of route) or lower respiratory illness within 7 days prior to randomization
3. Acute illness (defined as the presence of moderate or severe signs and symptoms) at the time of randomization
4. Active RSV infection (a child with signs/symptoms of respiratory infection must have negative RSV testing) or known prior history of RSV infection
5. Any drug therapy (chronic or other) within 7 days prior to randomization or expected receipt during the study with the exception of: 1) multivitamins and iron; 2) infrequent use of over the counter medications for the systemic treatment of common childhood symptoms (eg, pain relievers, decongestants or cough suppressants) that may be permitted according to the judgment of the investigator
6. Any current or expected receipt of immunosuppressive agents including steroids (except for the use of topical steroids according to the judgment of the investigator)
7. History of receipt of blood transfusion or immunoglobulin products or expected receipt through the duration of the study
8. Receipt of any investigational drug
9. Known renal impairment
10. Known hepatic dysfunction including known or suspected active or chronic hepatitis infection
11. History of CLD/bronchopulmonary dysplasia
12. Clinically significant congenital anomaly of the respiratory tract
13. Chronic seizure or evolving or unstable neurologic disorder
14. Congenital heart disease, except for children with uncomplicated CHD (eg, patent ductus arteriosus, small septal defect)
15. Prior history of a suspected or actual acute life-threatening event
16. Known immunodeficiency, including human immunodeficiency virus (HIV)
17. Mother with HIV infection (unless the child has been proven to be not infected)
18. Any known allergy, including to immunoglobulin products, or history of allergic reaction
19. Receipt of palivizumab or other RSV monoclonal antibody or any RSV vaccine, including maternal RSV vaccination
20. Receipt of any monoclonal or polyclonal antibody (for example, Hepatitis B immune globulin, intravenous immunoglobulin)
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 interventional study
23. Children of employees of the sponsor, clinical study site, or any other individuals involved with the conduct of the study, or immediate family members of such individuals

Note: An individual who initially is excluded from study participation based on one or more of the above time-limited criteria (eg, acute illness) may be reconsidered for enrollment once the condition has resolved as long as the subject continues to meet all other entry criteria.

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 a central system (eg, 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 administered investigational product. The investigator must consult with the sponsor before a subject who has failed screening may be considered for rescreening.

4.1.5 Withdrawal from the Study

Subjects are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). The caregivers of such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, the subject will be seen and assessed by an investigator. Adverse events will be followed up. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Criteria for Discontinuation of Investigational Product for Individual Subjects

Each subject in this study will receive a single IM dose of investigational product. An individual subject will not receive investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent
2. Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation

Subjects who have received investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn specifically from further study participation or the subject is lost to follow-up. Subjects who have not received investigational product, regardless of reason, will not be followed.

4.1.7 Replacement of Subjects

Subjects who are randomized but not dosed or who are randomized but do not complete any study evaluation after dosing may be replaced. At the discretion of the sponsor, subjects who prematurely discontinue study participation at any time through Day 91 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 an 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's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any 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, which may be used for future research, will be labeled with a sample identification number. If the subject withdraws consent for participating in the future research, the sponsor will locate the subject's sample and destroy it after protocol specified analyses are completed.

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, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples 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.

The sites must keep a log of all subjects who sign the informed consent form for the main study and the informed consent form for future use, this log contains subject SID and must be supplied to the sponsor at the end of the study, or closure of the site whichever is sooner.

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at the screening visit.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws.

Table 4.2.1-1 Schedule of Screening Procedures

Study Period	Screening
Visit Number	**V1**
Procedure / Study Day	**Day -30 to Day 1**
Written informed consent/ assignment of SID number	X
Medical history	X
Physical examination	X
Weight	X
Vital signs	X
PK blood sample	X
ADA blood sample	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Verify eligibility criteria	X

ADA = anti-drug antibody; AEs = adverse events; PK = pharmacokinetic; SAEs = serious adverse events; SID = subject identification; V = visit.

Screening and Day 1 visits may occur on the same day.

4.2.2 Treatment and Follow-up Period

The day of dosing is Day 1 of the study. Table 4.2.2-1 shows all procedures to be conducted on day of dosing and during the follow-up period. Assessments should be performed in the order shown in the table.

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

Study Period	Treatment Period	Follow-up Period							
Visit Number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Telephone Call**	**Telephone Call**	**LRTI**
Procedure / Study Day	**Day 1**	**Day 8 (± 2 days)**	**Day 31 (± 5 days)**	**Day 91 (± 7 days)**	**Day 151 (± 7 days)**	**Day 361 (± 7 days)**	**Q2W from Day 1 to Day 151 (± 5 days)**	**Monthly after Day 151 to Day 361 (± 5 days)**	**As needed**
Medical history update	X	X	X	X	X	X			
Physical examination (abbreviated)	X	X	X	X	X	X			
Weight	X	X	X	X	X	X			
Vital signs	X [a]	X	X	X	X	X			
PK blood sample				X	X	X			X[b]
ADA blood sample				X	X	X			X[b]
Assessment of AEs/SAEs	X	X	X	X	X	X			
Assessment of AESI and NOCDs	X	X	X	X	X	X			
Concomitant medications	X	X	X	X	X	X			
Verify eligibility criteria	X								
Randomization	X								
Investigational product administration	**X**								
Assessment of LRTI									X[b]
Nasal swab collection									X[b]
Telephone contact							X	X	
HRU [c]									X

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

Study Period	Treatment Period	Follow-up Period							
Visit Number	V2	V3	V4	V5	V6	V7	Telephone Call	Telephone Call	LRTI
Procedure / Study Day	Day 1	Day 8 (± 2 days)	Day 31 (± 5 days)	Day 91 (± 7 days)	Day 151 (± 7 days)	Day 361 (± 7 days)	Q2W from Day 1 to Day 151 (± 5 days)	Monthly after Day 151 to Day 361 (± 5 days)	As needed

ADA = anti-drug antibody; AEs = adverse events; AESI = adverse event of special interest; ER = emergency room; HRU = healthcare resource utilization; ICU = intensive care unit; LRTI = lower respiratory tract infection; NOCDs = new onset of chronic disease; OTC = over-the-counter; PK = pharmacokinetic; Q2W = once every two weeks; RSV = respiratory syncytial virus; SAEs = serious adverse events; SID = subject identification; V = visit.

[a] All vital signs (temperature, blood pressure, heart rate, and respiratory rate) should be obtained within 60 minutes prior to dosing, at 30 minutes (± 5 minutes) and at 60 minutes (± 5 minutes) post dose

[b] Nasal samples will be collected for all LRTI within 2 days and up to 14 days after the diagnosis. PK and ADA samples will be collected only for subjects hospitalized with LRTI within 2 days and up to 14 days following hospitalization.

[c] HRU includes admission and duration of hospital and ICU stay, number of subjects who require respiratory support and supplemental oxygen use, duration of respiratory support and supplemental oxygen use, number and type of outpatient visits (eg, ER, urgent care, outpatient clinic), and number and days of prescription and OTC medication

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Lower Respiratory Tract Infection

Subjects will be monitored throughout the study for LRTI. All subjects seeking medical attention for a respiratory illness (defined as new onset events indicating a change from the child's baseline medical status referable to the lower respiratory tract) will be evaluated for the occurrence of LRTI (Table 4.3.1.1-1). These events may occur in the inpatient or outpatient setting. Subjects who have a primary hospitalization for a respiratory illness, or who have a respiratory deterioration during a hospitalization, or who seek outpatient medical attention, including ER visits, for a respiratory illness will be assessed for RSV by diagnostic testing of respiratory secretions. Testing for RSV will be performed centrally using the FDA-approved and CE-marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + hMPV Assay, Quidel, San Diego, CA www.quidel.com). A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by RT-PCR.

To meet the protocol-specified criteria for LRTI, subjects with signs of LRTI must have documented physical exam findings of rhonchi, rales, crackles, or wheeze AND any of the following:

- Increased respiratory rate at rest (age: < 2 months, ≥ 60 breaths/min; 2–6 months, ≥ 50 breaths/min; > 6 months – 2 years, ≥ 40 breaths/min), OR
- Hypoxemia (in room air - oxygen saturation < 95% at altitudes ≤ 1800 meters or < 92% at altitudes > 1800 meters), OR
- Clinical signs of severe respiratory disease (eg, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid).

Table 4.3.1.1-1 Elements to Evaluate for Case Definition of RSV LRTI

Specificity	Sensitivity	Medical Significance
RSV Confirmed: • Positive RT-PCR	**Documented PE findings localizing to lower respiratory tract**: • Rhonchi • Rales • Crackles • Wheeze	**Objective measures of clinical severity**: • Increased respiratory rate • Hypoxemia • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration • Prescription medications (only for children with underlying lung disease)

LRTI = lower respiratory tract infection; PE = physical examination; RSV = respiratory syncytial virus; RT-PCR = real time reverse transcriptase-polymerase chain reaction;

Note: One item from each column is required to meet the case definition of RSV LRTI.

Respiratory Syncytial Virus Hospitalization

A RSV hospitalization is defined as either 1) a respiratory hospitalization with a positive RSV test within 2 days of hospitalization (primary) or 2) new onset of respiratory symptoms in an already hospitalized child, with an objective measure of worsening respiratory status and positive RSV test (nosocomial). Primary and nosocomial RSV hospitalization are further defined below.

Primary RSV Hospitalization

RSV diagnostic testing will be performed on respiratory secretions obtained within 2 days before or after admission for children who are hospitalized for respiratory illness. If the RSV diagnostic test (performed centrally via RT-PCR) is positive, the hospitalization will be classified as a primary RSV hospitalization. Deaths which can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as primary RSV hospitalization endpoints.

Nosocomial RSV Hospitalization

Children hospitalized for a respiratory illness or non-respiratory illness whose RSV diagnostic test is negative may develop nosocomial RSV illness during the study.

If signs (such as retractions, rhonchi, wheezing, crackles or rales) of a new lower respiratory illness occur during a hospitalization, whatever the reason for hospitalization, and there is an objective measure of worsening respiratory status (that is, new requirement for supplemental oxygen, increase in supplemental oxygen requirement from prior to the onset of symptoms, or need for new or additional mechanical ventilation), a specimen will be collected within 2 days from worsening of respiratory status for RSV diagnostic testing by the central laboratory. For any child who is hospitalized for a respiratory event, the child must return to his/her baseline respiratory status or be clearly resolving the preceding respiratory illness before a subsequent respiratory deterioration for a nosocomial RSV hospitalization event can be determined.

If the RSV test (performed centrally via RT-PCR) is positive, the subsequent hospital days will count as a nosocomial RSV hospitalization. The days of RSV hospitalization will be counted beginning with the start of the respiratory deterioration that resulted in the RSV test.

RSV LRTI Outpatient Events

Children who seek outpatient medical attention, including emergency room and urgent care visits, for a respiratory illness should have respiratory secretions obtained within 2 days of the visit.

Respiratory Secretions for RSV Detection

Respiratory secretions for RSV testing must be collected within 2 days of diagnosis for medically attended outpatient lower respiratory tract infections and hospital admission for, or new onset in hospital of, a respiratory illness. Nasal secretions will be obtained unless the child is intubated, and then tracheal secretions may be obtained.

Respiratory secretions in all cases will be tested in a central laboratory for RSV using the FDA-approved and CE-marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + hMPV Assay, Quidel, San Diego, CA www.quidel.com) and testing may include other respiratory pathogens.

Monitoring for RSV Resistance

Nasal samples collected from study subjects that fail MEDI8897 prophylaxis will be evaluated by genotypic and phenotypic methods to monitor potential susceptibility changes to MEDI8897. The subtype and genotypic analysis of RSV will be performed directly on the nasal specimens that are collected from all subjects who are confirmed RSV-positive using the Lyra RSV + hMPV real-time PCR (RT-PCR) assay manufactured by Quidel Corporation

(Lyra RSV + hMPV Assay, Quidel Corporation, San Diego CA, www.quidel.com). The full length fusion (F) gene from RSV-positive nasal samples will be amplified using a standard, single-tube population-based RT-PCR method and sequenced by Sanger sequencing methodology. Amino acid substitution(s) within the MEDI8897 binding site in F protein will be reported. If Sanger sequencing does not detect resistance-associated changes within the MEDI8897 binding site in the F gene of virus isolated from individuals who received MEDI8897, deep sequencing will be employed to detect minority variants. Recombinant viruses containing identified amino acid changes in the MEDI8897 binding region will be constructed through reverse genetics, and will be tested for susceptibility to MEDI8897 neutralization in a cell-based microneutralization assay.

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

A complete medical history will be obtained at screening and a medical history update will be obtained on Day 1, Day 8, Day 31, Day 91, Day 151 and Day 361 and will include history and current medical conditions, past or present cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, drug and surgical history, or any other diseases or disorders.

A complete physical examination will be performed at screening, and an abbreviated physical examination will be performed on Day 1, Day 8, Day 31, Day 91, Day 151 and Day 361. The physical examination will include assessment of weight at screening and at each study visit mentioned above.

Vital signs (temperature, blood pressure, respiratory rate, and heart rate measurements) will be collected at screening and at each study visit on Day 1, Day 8, Day 31, Day 91, Day 151 and Day 361. On Day 1, vital signs will be monitored before and after administration of investigational product.

4.3.3 Pharmacokinetic and Anti-drug Antibody Samples

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.

4.3.4 Pharmacokinetic Evaluation and Methods

Blood will be collected to evaluate the PK of MEDI8897 in serum at screening and on Day 91, Day 151, Day 361 and as needed (PK samples will be collected for subjects hospitalized

with LRTI within 2 days and up to 14 days following hospitalization; see Table 4.2.1-1 and Table 4.2.2-1 for schedule of tests). The concentration of MEDI8897 in serum will be measured by MedImmune using validated assays.

4.3.5 Anti-drug Antibody Response Evaluation and Methods

Blood samples will be collected to evaluate ADA responses to MEDI8897 in serum (see Table 4.2.1-1and Table 4.2.2-1 for the schedule of tests) at screening and on Day 91, Day 151 and Day 361 and as needed (ADA samples will be collected for subjects hospitalized with LRTI within 2 days and up to 14 days following hospitalization; see Table 4.2.1-1 and Table 4.2.2-1 for schedule of tests). Evaluations will be performed by MedImmune, using a validated immunoassay.

4.3.6 Healthcare Resource Utilization and Caregiver Burden Evaluation

Information on HRU and caregiver burden will be collected for all events of medically attended LRTI. This will include admission to and duration of hospital and ICU stay, number of subjects who require respiratory support and supplemental oxygen use, duration of respiratory support and supplemental oxygen use, number and type of outpatient visits (eg, ER, urgent care, outpatient clinic), and the number of prescription and OTC medications and their duration of use. Caregiver burden will be assessed through, for example, caregiver missed work days and the subject's absence from day care.

4.3.7 Estimates of Blood Volume to be Collected

Blood volume estimates are provided in Table 4.3.7-1 by visit.

Table 4.3.7-1 Volume of Blood to be Collected

Visit	Estimated Blood Volume (mL)
Screening	1.5 mL
Day 91	1.5 mL
Day 151	1.5 mL
Day 361	1.5 mL
Total	6.0 mL

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. Death in any subject in which the cause of death is assessed as related to investigational product (in this case the study will be paused for the MedImmune safety review committee to evaluate the events)
2. Anaphylactic reaction that is related to investigational product (see Appendix 3 for a definition of anaphylaxis) (in this case the study will be paused for the MedImmune safety review committee to evaluate the events)
3. Grade 3 and/or 4 hypersensitivity AEs based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading scale that are assessed as related to MEDI8897 in 2 or more subjects
4. Two SAEs of the same type that are assessed as related to MEDI8897
5. Other events that, in the judgment of the sponsor or site investigator, are deemed serious enough to warrant immediate review by the MedImmune safety review committee
6. Subject enrollment is unsatisfactory
7. Non-compliance that might significantly jeopardize the validity or integrity of the study
8. Sponsor decision to terminate development

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 advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the institutional review board (IRB)/ independent ethics committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 4.5.1-1) using designated distribution centers.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI8897	MedImmune	Liquid formulation at 100 mg/mL in 2R glass vials (0.5 mL nominal fill volume) containing [redacted]
Placebo	To be provided by study sites	Commercially available 0.9% (w/v) saline (sterile for human use)

HCl = hydrochloride; w/v = weight/volume

Investigational product should be stored at 2°C to 8°C.

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

Investigational product will be supplied to the site in open-labeled kits. Each kit has a unique number printed on all labels within the kit (ie, the outer carton label and the label of each vial).

Refer to Section 4.6.2 for information on coding of the container for blinding purposes.

4.5.1.1 Investigational Product Dose Administration

Investigational Product Inspection

Each vial selected for dose administration should be inspected. MEDI8897 is supplied as a sterile liquid formulation with a concentration of 100 mg/mL in 2R glass vials (0.5 mL nominal fill volume).

If there are any defects noted with the investigational product, the Investigator and Site Monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.4) for further instructions.

Dose Administration Steps

No incompatibilities between MEDI8897 and plastics passing compatibility tests (ie, polycarbonate or polypropylene syringes) have been observed.

MEDI8897 does not contain preservatives and any unused portion must be discarded. Total in-use storage time from needle puncture of the investigational product vial to administration

should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used.

The dose administration steps are as follows:

1. Each vial of MEDI8897 contains 0.5 mL nominal fill volume of [redacted] mg/mL MEDI8897.
2. The required 0.5 mL volume of MEDI8897 or placebo will be obtained by withdrawing the contents of the investigational vial with an appropriately sized syringe. Syringes used must be polycarbonate or polypropylene. For ease of preparation, a 1.5 inch 19-gauge withdrawal needle should be used.
3. Switch the needle prior to administration.
4. Administer investigational product using the appropriate size needle ranging from 22 to 25 gauge and 5/8 to 1.0 inches based on muscle size and weight of the subject.

4.5.1.2 Treatment Administration

The first day of dosing is considered Day 1.

Investigational product (MEDI8897 or placebo) will be supplied by an unblinded investigational product manager. Blinding will be performed at the site level to ensure that MEDI8897 and placebo are indistinguishable in appearance and are not labeled to reveal treatment identity.

Investigational product (MEDI8897 or placebo) should be administered in the anterolateral aspect of the thigh according to standard practice procedures for IM injections.

4.5.1.3 Monitoring of Dose Administration

Subjects will be monitored before and after investigational product administration through assessment of vital signs (temperature, blood pressure, heart rate, and respiratory rate). All vital signs should be obtained within 60 minutes prior to dosing, at 30 minutes (± 5 minutes) and at 60 minutes (± 5 minutes) post dose.

As with any antibody, 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.

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

[redacted]

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 GMP and local regulatory guidelines. Label text will be translated into local languages, as required.

4.5.4 Storage

Store investigational product at 2°C to 8°C.

4.5.5 Treatment Compliance

Investigational product is administered by study site personnel who will monitor compliance.

4.5.6 Accountability

The investigator's or site's designated 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

An IWRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. 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 kit numbers to the subject.

Subjects will be randomized at a 2:1 ratio to receive a [redacted] mg IM dose of MEDI8897 (N = 1,000) or placebo (N = 500). Randomization will be stratified by temperate zones in the northern and southern hemisphere and by subject age at the time of randomization (ie, ≤ 3 months, > 3 – ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500.

The procedure for using IWRS is as follows:

- The investigator or designee contacts the IWRS and provides the SID number and subject's baseline characteristic(s) used to verify that it is the same subject
- Placebo (provided by site) or a vial from a MEDI8897 kit will be assigned to the subject
- Confirmation of this information is sent to the unblinded investigational product manager who prepares the investigational product to be dispensed to the subject per the response system and records the appropriate information in the investigational product accountability log

Investigational product (MEDI8897 or placebo) must be administered the same day the investigational product is assigned. Total in-use storage time from needle puncture of the investigational product vial to administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the unblinded investigational product monitor must be notified immediately.

4.6.2 Methods for Ensuring Blinding

This is a double-blind study in which sites are using commercially available saline as the placebo. MEDI8897 and placebo are visually indistinguishable once in syringes. Neither the subject/legal representative nor any of the investigator or site staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Council for Harmonisation [ICH] E9). In the event that treatment allocation for a subject becomes known to the investigator or other blinded 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*. 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. 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 SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

4.6.3.2 Unblinding for Primary Analysis Purposes

The primary analysis will be conducted when all randomized subjects have completed the Day 151 visit and will include all efficacy data for all randomized subjects. All efficacy and safety data collected up to the Day 151 visit and available safety data beyond Day 151 at the time of that data cut-off date will be included in the primary analysis. Efficacy and safety for MEDI8897 will be evaluated in this unblinded analysis.

Sponsor personnel will be unblinded at this primary analysis. Study site personnel and the subjects' parent(s)/legal guardian will remain blinded to the treatment assignment of individual subjects until the last subject completes the study and the final database is locked.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the electronic case report form (eCRF).

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care including routine vitamins and iron.

4.7.2 Prohibited Concomitant Medications

Use of concomitant medications including over-the-counter medications (except for routine vitamins and iron), herbal supplements, etc from Day 1 through Day 15 post dose is discouraged. Subjects' legal representatives must be instructed not to administer any medications, including over-the-counter products, without first consulting with the investigator.

4.8 Statistical Evaluation

4.8.1 General Considerations

There are two planned analyses for this study: the primary analysis and the final analysis. The primary analysis will be conducted after all randomized subjects have completed the Day 151 visit, and the final analysis will be conducted when all subjects have completed the last visit of the study (Day 361).

Tabular summaries will be presented by treatment group. 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 intent-to-treat (ITT) Population is defined as all subjects who are randomized. Subjects will be included in the treatment group corresponding to their randomized treatment. All analyses, with the exception of safety, will be performed on the ITT Population.

The As-treated Population will include all subjects who are randomized into the study and who receive any amount of investigational product. Subjects will be included in the treatment group corresponding to the treatment actually received. All safety analyses will be performed on the As-treated Population.

4.8.2 Sample Size and Power Calculations

The sample size of 1,500 is necessary based on advice from the US FDA requesting that 1,000 preterm infants be exposed to MEDI8897 in this Phase 2b study. This sample size has approximately 99% power to detect 70% relative risk reduction, assuming a placebo group medically attended RSV LRTI incidence of 8%. Power calculations are based on Poisson

regression model with robust variance (Zou, 2004) comparing MEDI8897 [redacted] mg versus placebo, with 2-sided significance level of $\alpha = 0.05$.

- The 70% relative risk reduction assumption is based on a placebo-controlled study in Native American infants in which there was 87% relative reduction in the incidence of RSV hospitalization (11.3% placebo; 1.5% motavizumab; $p < 0.001$) and 71% relative reduction in the incidence of outpatient RSV LRTI (10.0% placebo; 2.9% motavizumab; $p < 0.001$) in infants who received motavizumab prophylaxis (O'Brien et al, 2015)

In order to evaluate risk, a sample size of 1,000 subjects exposed to MEDI8897 will provide a 90% probability of observing at least one AE if the true event rate is 0.2%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.3%.

4.8.3 Efficacy Analysis

The primary analysis will be conducted after all randomized subjects have completed the Day 151 visit. At the time of this primary analysis, approximately half of all subjects enrolled (722 subjects) will have completed the Day 361 visit. The remaining 731 subjects will have completed approximately 8 months of the study.

The primary and secondary efficacy hypotheses will be assessed in the primary analysis by a hierarchical order. That is, the secondary hypothesis will be tested at a significance level of 0.05 only if the treatment effect on the primary efficacy endpoint is demonstrated at the significance level of 2-sided 0.05. With that, the overall Type I error is controlled at 0.05. Therefore, no further multiplicity adjustment is necessary.

4.8.3.1 Primary Efficacy Analysis

The incidence of RSV LRTI (inpatient and outpatient) during 5 months of the RSV season will be based on RSV test results (performed centrally via RT-PCR) and objective clinical LRTI criteria and will be summarized by treatment group. For subjects with multiple medically attended RSV LRTI events, only the first occurrence will be used in the primary analysis.

The primary efficacy analysis of the primary endpoint will be conducted with the ITT Population. LRTI caused by RSV that occurs prior to discontinuation from participation in the study will contribute to the primary efficacy analysis. For subjects who do not have an RSV LRTI prior to discontinuation from participation, their event status will be imputed assuming the observed placebo RSV LRTI rate. This will be implemented by imputations based on repeated simulations and will be described in the Statistical Analysis Plan. A Poisson regression model with robust variance (Zou, 2004) will be used as the primary

efficacy analysis model to compare the incidence of medically attended RSV LRTI between MEDI8897 and placebo, including treatment group, age at the time of randomization (ie, ≤ 3 months, > 3 – ≤ 6 months, > 6 months) and dichotomous temperate (northern and southern) hemispheres as covariates. In addition, the 2-sided p-value and corresponding 2-sided 95.1% CI on the relative risk will be provided from the model. Relative risk reduction is defined as (1 - Pn/Ps) where Pn is the incidence of RSV LRTI during 5 months of the RSV season in the MEDI8897 group and Ps is the incidence of RSV LRTI during 5 months of the RSV season in the placebo group generated from the model. Statistical significance will be achieved if the 2-sided p-value is ≤ 0.05.

4.8.3.2 Additional Analyses of the Primary Endpoint

A CMH (Cochran-Mantel-Haenszel) approach stratified by hemisphere and age at the time of randomization (ie, ≤ 3 months, > 3 – ≤ 6 months, > 6 months) will be used to compare the incidence of RSV LRTI during 5 months of the RSV season between treatment groups as a sensitivity analysis for the primary endpoint. In addition, a time-to-event analysis assessing time to first RSV LRTI may be performed as a supplementary analysis.

An analysis may also include all RSV positive LRTI endpoints, using results from either the central lab or local lab.

Different approaches to handle missing data (ie, early discontinuation and no RSV LRTI prior to discontinuation) may be considered for sensitivity analyses. Additional analyses or subgroup summaries may be performed to adjust duration of efficacy follow-up and/or other possible confounding factors. These analyses will be described in the Statistical Analysis Plan.

4.8.3.3 Secondary Efficacy Analyses

The incidence of RSV hospitalization during 5 months of the RSV season will be summarized by treatment group. The same methods described above for the primary efficacy endpoint will be used to assess treatment effect on RSV hospitalization. Following a hierarchical testing procedure, the secondary efficacy endpoint will be tested at the significance level of 2-sided 0.05 if the primary analysis on the primary efficacy endpoint has achieved statistical significance at the level of 2-sided 0.05.

4.8.4 Safety Analysis

Safety of MEDI8897 will primarily be assessed by the occurrence of treatment-emergent AEs and SAEs. Adverse events will be graded according to the current version of the NCI CTCAE where applicable for pediatric assessments. Adverse events will be coded by

Medical Dictionary for Regulatory Activities (MedDRA) and the type, incidence, severity and relationship to study investigational product will be summarized by treatment group. Other safety assessments will include:

- Occurrence of AESIs to include targeted AEs of hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, and glomerulonephritis) following investigational product administration.
- Occurrence of NOCDs following investigational product administration.

4.8.5 Analysis of Pharmacokinetics and Anti-drug Antibody

4.8.5.1 Analysis of Pharmacokinetics

Following a single dose of MEDI8897, individual MEDI8897 serum concentration data will be tabulated by treatment group along with descriptive statistics. Terminal-phase half-life ($t_{1/2}$) will be estimated using non-compartmental analysis, if data permit.

4.8.5.2 Analysis of Anti-drug Antibodies

The incidence of ADA to MEDI8897 will be assessed and summarized by number and percentage of subjects that are ADA positive by treatment group. The ADA titer will be listed by subject at different time points. The impact of ADA on PK, and association with TEAEs and TESAEs will be assessed.

4.8.6 Exploratory Analyses

The magnitude of HRU (eg, number of admissions to hospitals and ICUs and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of use; number and types of outpatient visits, eg, ER, urgent care, outpatient clinic; and number of prescription and OTC medications and duration of use) will be summarized overall by treatment group, and for the following subgroups: subjects with at least one medically attended LRTI caused by RT-PCR confirmed RSV, subjects with medically attended LRTI not caused by RSV, and subjects without medically attended LRTI.

Caregiver burden (eg, caregiver missed work days, subject absence from day care) for subjects with medically attended LRTI caused by RT-PCR-confirmed RSV will be summarized by treatment group.

4.8.7 Data Monitoring Committee

An independent DMC will review safety data regularly and make recommendations regarding further study conduct.

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 electrocardiogram [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 cells [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 (that was 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

A 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, blood dyscrasias, 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 non-serious. 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.

5.3.1 Hypersensitivity, Including Anaphylaxis

Administration of polyclonal immunoglobulin preparations and mAbs has been associated with hypersensitivity (including anaphylaxis) that occurs during or after dosing. A hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both during administration of investigational product (but does not meet the definition of anaphylaxis). Anaphylaxis is a rare event, usually occurring after subsequent exposure to antigen, and it is most commonly accompanied by severe systemic skin and or mucosal reactions. It is potentially a fatal, systemic allergic reaction that is distinct from simple allergic reactions (eg, rash, pruritus) because of the simultaneous involvement of several organ systems (Sampson et al, 2006). A full definition of anaphylaxis is provided in Appendix 3. See Section 5.5 for recording AEs.

5.3.2 Immune Complex Disease

Immune complex disease can manifest in the form of a number of conditions such as vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, and arthralgias. Drug-induced immune complex (type III) hypersensitivity reactions can occur when host immune system generates antibodies to drug resulting in soluble circulating antigen-antibody complexes formation and their deposition in blood vessels. Subsequently this initiates tissue

damaging inflammatory reactions mediated by complement and/or leukocytes and mast cells. The pathology and clinical manifestations are dependent on the tissues/organs involved, with vascular, skin and renal tissues being common sites of injury. Common examples of immune complex hypersensitivity reactions are serum sickness (systemic) and Arthus reactions (local). The clinical manifestations of serum sickness include skin rash, fever, malaise and polyarthralgias or polyarthritis. Symptoms typically develop 1 to 2 weeks after first exposure to antigen and usually resolve in several weeks after withdrawal of the causative agent. Serum sickness needs to be differentiated from other 'serum-sickness-like' reactions that have a similar clinical presentation (eg, viral infections, anti-seizure drugs), but are believed to have different pathogenic mechanisms. Both serum sickness and serum sickness-like reactions have been reported with mAbs (eg, rituximab, infliximab). Clinical presentation and time to onset should be taken into account for the diagnosis and differentiation of these reactions. Diagnosis of these suspected reactions is best confirmed via biopsy of the affected tissues. See Section 5.5 for recording AEs.

5.3.3 Thrombocytopenia

Thrombocytopenia is a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150,000 to 450,000 platelets per μL. The 3 major causes of low platelet counts include: 1) insufficient platelet synthesis in the bone marrow; 2) increased breakdown of platelets in the bloodstream; and 3) increased breakdown of platelets in the spleen or liver. General symptoms of thrombocytopenia include bleeding in the mouth and gums, bruising, nosebleeds, and petechiae (pinpoint red spots/rash). Severe bleeding is the major complication, which may occur in the brain or gastrointestinal tract. Drug-induced thrombocytopenia is a reversible form of thrombocytopenia that should be suspected in a subject who presents with new onset thrombocytopenia or recurrent episodes of acute thrombocytopenia, without an obvious alternative etiology. It is commonly induced by drug-dependent antibodies that cause platelet destruction or clearance by the reticuloendothelial system (drug-induced immune thrombocytopenia), and less commonly by drug-induced bone marrow suppression or autoimmune thrombocytopenia that is initiated by exposure to the offending drug but persists in its absence. The initial approach to the subject with suspected drug-induced thrombocytopenia involves confirming thrombocytopenia, establishing a temporal relationship to a drug, and eliminating other causes of thrombocytopenia. The diagnosis is made clinically by documenting prompt resolution of thrombocytopenia after discontinuation of the suspected drug (typically within 1 week). Most subjects with drug-induced thrombocytopenia require no specific treatment, as their platelet counts will recover promptly following withdrawal of the causative agent. See Section 5.5 for recording AEs.

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 as NOCDs are mild eczema, diagnosis of a congenital anomaly present at study entry, or acute illness (eg, upper respiratory infection, otitis media, bronchitis). See Section 5.5 for recording AEs.

5.5 Recording of Adverse Events

Adverse events, including SAEs, 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 study procedure(s), possible etiologies, and whether the event meets criteria of an SAE (see Section 5.2 and 5.6), or is an AESI or NOCD (see Section 5.3, 5.4 and 5.7) and therefore requires immediate notification to the sponsor. See Appendix 2 for guidelines for assessment of AE severity and relationship to IP. If an AE evolves into a condition that meets the definition of "serious," it will be reported on the AE form in the eCRF as a serious adverse event.

5.5.1 Time Period for Collection of Adverse Events

Adverse events and SAEs will be collected from the time of signature of informed consent through the follow-up period (Day 361 visit).

All AESIs and NOCDs will be collected from the time of dosing through the follow-up period (Day 361 visit).

5.5.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit are followed up by the investigator for as long as medically indicated but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.6 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel must inform the appropriate sponsor study representative(s) within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated sponsor study representative works with the investigator to ensure that all the necessary information is provided to the sponsor patient safety data entry site within 1 calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel must inform sponsor study representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the Electronic Data Capture (EDC) system, an automated email alert is sent to inform the designated sponsor study representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate sponsor study representative by telephone. The sponsor study representative will advise the investigator/study site personnel how to proceed.

5.7 Other Events Requiring Immediate Reporting

5.7.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

- An overdose with associated AEs is recorded as the AE diagnosis on the relevant AE modules in the eCRF and on the overdose eCRF module.
- An overdose associated with an SAE must be recorded as an SAE.
- An overdose without associated symptoms is only reported on the overdose eCRF module.

If an overdose on a MedImmune study drug occurs in the course of the study, then the investigator or other site personnel must inform appropriate sponsor study representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it. The designated sponsor study representative works with the investigator to ensure that all relevant

information is provided to the sponsor's patient safety data entry site. For all overdoses, reporting to the data entry site must occur within 24 hours.

5.7.2 Adverse Events of Special Interest

5.7.2.1 Hypersensitivity, Including Anaphylaxis

Events of hypersensitivity, including anaphylaxis (as defined in Appendix 3), require that the investigator or other site personnel inform appropriate sponsor study representatives immediately, or **no later than 24 hours** of when he or she becomes aware of the event. The designated sponsor study representative works with the Investigator to ensure that all relevant information is provided and entered in EDC. If the event is considered serious it must be reported as an SAE (see Section 5.6).

Signs of hypersensitivity include urticaria, pruritis, angioedema, skin rash, difficulty breathing, and wheezing. Parent(s)/legal representatives will be provided a card with this information to aid in prompt identification and reporting of these signs. Parent(s)/legal representatives will be instructed to immediately report the occurrence of any of these findings to the site investigator who should then report the events to appropriate sponsor study representatives immediately, or **no later than 24 hours** of when he or she becomes aware of the event.

5.7.2.2 Immune Complex Disease

Events of immune complex disease (as defined in Section 5.3.2) require that the investigator or other site personnel inform appropriate sponsor study representatives immediately, or **no later than 24 hours** of when he or she becomes aware of the event. The designated sponsor study representative works with the Investigator to ensure that all relevant information is provided and entered into EDC. If the event is considered serious it must be reported as an SAE (see Section 5.6).

5.7.2.3 Thrombocytopenia

Events of thrombocytopenia (platelet count < 120,000 per µL) require that the investigator or other site personnel inform appropriate sponsor study representatives immediately, or **no later than 24 hours** of when he or she becomes aware of the event. The designated sponsor study representative works with the Investigator to ensure that all relevant information is provided and entered into EDC. If the event is considered serious it must be reported as an SAE (see Section 5.6).

5.7.3 New Onset Chronic Disease

If a case of NOCD occurs in the course of this study, the investigator or other site personnel must inform appropriate sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it. The designated sponsor study representative works with the Investigator to ensure that all relevant information is provided and entered into EDC. If the event is considered serious it must be reported as an SAE (see Section 5.6).

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 sponsor representative will have regular contacts 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 accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug 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 withdrawal of informed consent to 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 study site 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 follows 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 will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Sections 4.1.5 and 4.1.6).

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.

6.4 Data Management

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

A Web Based Data Capture 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 site.

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 (GCP), 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 enrolment 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 ICF 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 ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

The Sponsor 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's legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject's legal guardian is notified that they are free to discontinue the subject from the study at any time
- Ensure that each subject's legal guardian is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject's legal guardian provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject's legal guardian
- Ensure that any incentives for subjects and/or their legal guardians who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

7.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the 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 and if applicable, also the national regulatory authority approval, 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 ICF, MedImmune and the site's IRB/IEC are to approve the revised ICF 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 centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine 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.

8 REFERENCES

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9 CHANGES TO THE PROTOCOL

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

9.1 Protocol Amendment 1, 25Jan2018

Major changes to the protocol are summarized below:

1. The interim analysis was removed from the study. (Changes have been made in the synopsis and in Section 4.8 [Statistical Evaluation].)
2. As a result of the removal of the interim analysis, no alpha will be spent so the two-sided significance level of $\alpha = 0.049$ has returned to $\alpha = 0.05$ and the p value required to achieve statistical significance of < 0.049 has returned to ≤ 0.05. (Changes have been made in the synopsis and in Section 4.8 [Statistical Evaluation].)
3. A decision was made to conduct a primary analysis rather than an interim analysis; therefore, text has been added to explain that the primary analysis will now include all efficacy data from all randomized subjects through Day 151 and all available safety data up to and beyond Day 151 at the time of the final data cut-off date. (Changes have been made in the synopsis and in Section 4.8 [Statistical Evaluation].)

Appendix 1 Signatures

Sponsor Signature(s)

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

I agree to the terms of this protocol.

Signature and date: (Electronic signature appended)

[redacted]

Clinical Development Therapeutic Area Head

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: [redacted]

Signature of Principal or Coordinating Investigator

A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

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 Council for 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 is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) where applicable for pediatric assessments. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 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 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.

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 eCRF (Section 5.6). 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, nasal sample 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 (NIAID) and Food and Allergy Anaphylaxis Network (FAAN) Guidance for Anaphylaxis Diagnosis

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006; 117(2):391-7.

NIAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. 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
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP. Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years.

SIGNATURE PAGE

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