A Phase 3 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 Late Preterm and Term Infants (MELODY)

Sponsor Protocol Number:	D5290C00004
Application Number:	IND number 118524
Investigational Product:	MEDI8897
Sponsor:	MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC, [redacted], Gaithersburg, Maryland, 20878, USA
Medical Monitor:	[redacted] AstraZeneca
Contract Research Organization:	IQVIA
Protocol History, Date:	Original Protocol, 05Apr2019 Protocol Amendment 1, 01Feb2021

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 1 (01Feb2021)

Overall Rationale for the Amendment

The principal reason for this amendment was to introduce a complementary safety cohort (which will be referred to as the safety cohort throughout the protocol) and clarify the number of subjects to be enrolled and the analysis populations for the efficacy and safety analyses. The safety cohort will serve the purpose of providing additional safety assessment. Although efficacy data will be collected for the safety cohort, only descriptive summaries will be provided and there is no intent to pool the efficacy data from the safety cohort with that from the primary cohort. These changes were made to reflect mitigation of the low RSV circulation and impact on efficacy data due to the COVID-19 pandemic related measures.

Section	Description of Change	Brief Rationale
Title Page	Updated the medical monitor information	Due to the change in medical monitor for this study
Synopsis, 3.1.1 Overview	Added text and revised the study flow diagram (Figure 1) to indicate that the study will comprise 2 cohorts: a primary cohort and safety cohort	To reflect mitigation of the low RSV circulation and impact on efficacy data due to the COVID-19 pandemic related measures
Synopsis, 3.2.3 Rationale for endpoints, 4.3.1.1 Lower Respiratory Tract Infection	Revised the RSV resistance monitoring language	To improve clarity of exploratory endpoint analysis and to align with clinical virology analysis plan
Synopsis, 4.8.1 General Considerations	Added the definition of the primary cohort and safety cohort Added the definition of ITT1, ITT2, AT1, and AT2 Updated the planned analyses, and when and what data will be analyzed for each analysis	To reflect mitigation of the low RSV circulation and impact on efficacy data due to the COVID-19 pandemic related measures, and provide clarification of the analysis populations
Synopsis, 4.8.2 Sample Size	Updated the sample size and power information	Updated study power based on the sample size of the primary cohort, on which the primary efficacy analysis will be based

Section	Description of Change	Brief Rationale
Synopsis, 4.8.3 Efficacy, 4.8.4 Safety, 4.8.6 Exploratory Analysis	Specified cohorts/populations that will be analyzed for the primary, secondary, and exploratory endpoint analyses Clarified that subjects randomized from the primary cohort (ITT1) will be analyzed in the primary and secondary efficacy analyses, and subjects randomized from the safety cohort (ITT2) will be summarized descriptively Clarified that safety analyses will be conducted on the overall As-treated Population, AT1, and AT2 Clarified that the summaries of the magnitude of HRU and caregiver burden will be conducted on ITT1 and ITT2	To provide clarification of the cohorts/populations to be analyzed
Synopsis, 4.8.3 Efficacy	Removed the stratification factor "hemisphere" from the analyses for the primary efficacy endpoint	To update the analyses due to known convergence or estimation issue during blinded data review prior to the database lock for primary analysis
4.8.3.4 Subgroup Analyses of the Primary Endpoint	Updated subgroup "weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg to < 5 kg, weight ≥ 5 kg)" to "weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)"	To update based on data availability
4.2.2 Treatment and Follow-up Periods (Table 5)	Added a concomitant medications assessment for the D362-511 period and corresponding footnote to specify that it applies only to subjects with LRTIs diagnosed during this period	To collect concomitant medications for subjects with LRTIs diagnosed during this period
4.3.1.1 Lower Respiratory Tract Infection (Respiratory Secretions for RSV Detection)	Changed "Testing may include other respiratory pathogens" to "Testing <u>of all samples</u> may include other respiratory pathogens"	For clarity
4.5.1.5 Reporting Product Complaints	Removed the fax number and the [redacted] phone number	The deleted numbers are no longer in use
4.6.2 Methods to Ensure Blinding, 4.8.1 General Considerations	Added a description of the unblinding strategy	To ensure the double-blind setting and trial integrity will be maintained with the newly added safety cohort and the updated analysis strategy
4.8.3.2 Additional Analyses of the Primary Endpoint	Added sensitivity analyses	To assess the impact of the COVID-19 pandemic on the robustness of the efficacy results

Section	Description of Change	Brief Rationale
5.3.1 Hypersensitivity, Including Anaphylaxis, 5.7.3.1 Hypersensitivity, Including Anaphylaxis	Clarified hypersensitivity by adding immediate (type I)	For clarity
Throughout	Minor editorial revisions	Minor, therefore, were not summarized

AT1 = As-treated Population 1; AT2 = As-treated Population 2; COVID-19 = coronavirus disease 2019; D = Day; HRU = healthcare resource utilization; ITT1 = Intent-to-treat Population 1; ITT2 = Intent-to-treat Population 2; LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus.

PROTOCOL SYNOPSIS

TITLE

A Phase 3 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 Late Preterm and Term Infants (MELODY)

HYPOTHESES

Primary Hypothesis

Compared to placebo, a single intramuscular (IM) MEDI8897 dose, 50 mg if weight < 5 kg or 100 mg if weight ≥ 5 kg, 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 late preterm and term infants born ≥ 35 weeks 0 days gestational age (GA) and entering their first RSV season, and the safety profile will be acceptable.

Secondary Hypotheses

- There will be a reduction in the incidence of hospitalizations attributable to RT-PCR-confirmed RSV
- The predicted serum exposures of MEDI8897 will be adequate for the duration of the RSV season
- Anti-drug antibody (ADA) to MEDI8897 will not impact the serum concentrations or safety of MEDI8897 through 150 days post dosing (ie, during a 5-month RSV season)

OBJECTIVES and ASSOCIATED ENDPOINTS

Type	Objective	Endpoint
Primary		
Efficacy	To assess the efficacy of MEDI8897 when administered as a single fixed IM dose to infants ≥ 35 weeks 0 days GA and entering their first RSV season, in reducing medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
Secondary		
Efficacy	To assess the efficacy of MEDI8897 in reducing hospitalizations due to RT-PCR-confirmed RSV, compared to placebo	Incidence of hospitalizations due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
Safety	To evaluate the safety and tolerability of MEDI8897 when administered as a single fixed IM dose, compared to placebo	Safety and tolerability of MEDI8897 as assessed by the occurrence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and new onset chronic diseases (NOCDs)
PK	To evaluate single-dose serum concentrations of MEDI8897	Summary of MEDI8897 serum concentrations and estimated PK parameters: apparent clearance, $AUC_{0-\infty}$, if data permit
ADA	To evaluate ADA responses to MEDI8897 in serum	Incidence of ADA to MEDI8897 in serum

Type	Objective	Endpoint
Exploratory		
Healthcare resource utilization and caregiver burden	To assess healthcare resource utilization and caregiver burden for MEDI8897 recipients compared to placebo recipients	• Magnitude of healthcare resource utilization (HRU; eg, number of admissions to hospitals and intensive care units 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 medications and duration of use) • Caregiver burden (eg, caregiver missed work days, subject absence from day care) for subjects with medically attended LRTI caused by RT-PCR-confirmed RSV
RSV neutralizing antibody	To determine anti-RSV neutralizing antibody levels in serum afforded by a single dose of MEDI8897 compared to maternally derived RSV neutralizing antibody levels and those elicited by RSV infection in the placebo group	Anti-RSV neutralizing antibody levels (IU/mL) in serum for MEDI8897 recipients compared to placebo recipients
RSV serology	To evaluate exposure to RSV by measuring seroresponse to different RSV proteins	• Antibody levels to RSV pre-F, post-F, Ga, Gb, and N at different time points • Changes in antibody levels (seroresponse) indicating exposure to RSV
RSV resistance monitoring	To characterize resistance to MEDI8897 through genotypic and phenotypic analyses	Genotypic analysis and susceptibility of RSV variants to neutralization by MEDI8897
RSV LRTI after Day 151	To assess the incidence of medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo after Day 151	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV from Day 152 to Day 361

STUDY DESIGN

Study D5290C00004 (MELODY) is a pivotal Phase 3 randomized, double-blind, placebo-controlled, single-dose study to determine if MEDI8897 will prevent medically attended RSV-confirmed LRTI in healthy infants entering their first RSV season. The population to be enrolled is healthy late preterm and term infants born ≥ 35 weeks 0 days GA who would not receive RSV prophylaxis based on the American Academy of Pediatrics (AAP) or other local or national guidelines. A total of approximately 3,000 infants will be randomized 2:1 to receive a 50-mg (if weight < 5 kg) or 100-mg (if weight ≥ 5 kg) IM dose of MEDI8897 (N = 2,000) or placebo (N = 1,000). Randomization will be stratified by hemisphere (northern hemisphere [NH], southern hemisphere [SH]) and by subject age at the time of randomization (≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500. The study will comprise 2 cohorts: a primary cohort (N = ~1,500) and a complementary safety cohort (hereafter referred to as the safety cohort; N = ~1,500) for a total of approximately 3,000 subjects. The primary cohort will include subjects from the NH2019, SH2020, and NH2020 enrollment seasons. The safety cohort will include subjects enrolled after the NH2020 enrollment season. Given the largely reduced circulation of RSV due to the coronavirus disease 2019 (COVID-19) pandemic related measures, the efficacy analyses performed in the primary analysis for the primary cohort will serve the purpose of evaluating the efficacy of MEDI8897 in the study population. Although efficacy data will also be collected for the safety cohort, only descriptive

summaries will be provided and there is no intent to pool the efficacy data from the safety cohort with that from the primary cohort. Both the primary and safety cohorts, individually and combined, will serve the purpose of evaluating the safety of MEDI8897.

All subjects will be followed for approximately 510 days after dosing. An independent data monitoring committee will review safety data regularly and make recommendations regarding further study conduct.

Subjects will be monitored throughout the study for LRTI. All subjects seeking medical attention for a respiratory illness (in either the inpatient or outpatient setting) will be evaluated for the occurrence of LRTI. All subjects found to have an LRTI and all subjects who require hospitalization for a respiratory infection, even if there is not a diagnosis of LRTI, should have respiratory samples obtained and respiratory assessment forms completed. Samples should be collected for all of these events (even those not meeting the protocol definition of LRTI). Subjects who have a primary hospitalization for a respiratory infection (ie, upper or lower tract) or a respiratory deterioration during a hospitalization, or who seek outpatient medical attention (including ER visits) for a lower respiratory illness, will be assessed clinically for the presence of LRTI and for RSV by central laboratory diagnostic testing of respiratory secretions.

In addition to the clinical assessment of LRTI, there is a protocol definition using objective criteria for the determination of a medically attended protocol-defined LRTI. To meet the protocol-defined endpoint of medically attended LRTI, subjects with signs of LRTI must have documented at least one physical exam finding of rhonchi, rales, crackles, or wheeze AND at least one of the following clinical signs:

- Increased respiratory rate at rest (age < 2 months, ≥ 60 breaths/min; age 2 to 6 months, ≥ 50 breaths/min; age > 6 months, ≥ 40 breaths/min) OR
- Hypoxemia (in room air: oxygen saturation < 95% at altitudes ≤ 1,800 meters or < 92% at altitudes > 1,800 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)

Testing for RSV will be performed centrally using the United States Food and Drug Administration-cleared and *Conformité Européenne* or European Conformity-marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + human metapneumovirus [hMPV] assay; Quidel Corporation, San Diego, CA). A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by the central laboratory RT-PCR.

TARGET SUBJECT POPULATION

Healthy late preterm and term infants ≥ 35 weeks 0 days GA entering their first RSV season

TREATMENT GROUPS AND REGIMENS

Subjects will be randomly assigned in a 2:1 ratio to receive a single IM dose of MEDI8897 (N = 2,000) or placebo (N = 1,000). The MEDI8897 dose level will be stratified by body weight at time of dosing: 50 mg MEDI8897 for infants < 5 kg or 100 mg MEDI8897 for infants ≥ 5 kg.

STATISTICAL METHODS

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 (SAP).

There will be 2 study cohorts: a primary cohort and a safety cohort. The primary cohort will include subjects from the NH2019, SH2020, and NH2020 enrollment seasons (enrollment was paused after one subject from NH2020 was enrolled due to the impact of the COVID-19 pandemic). The safety cohort will include subjects enrolled after the NH2020 enrollment season.

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 unless otherwise specified. Subjects in the ITT Population and from the primary cohort will be ITT Population 1 (ITT1). Subjects in the ITT Population and from the safety cohort will be ITT Population 2 (ITT2).

The As-treated Population will include all subjects who are randomized 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. Subjects in the As-treated Population and from the primary cohort will be As-treated Population 1 (AT1). Subjects in the As-treated Population and from the safety cohort will be As-treated Population 2 (AT2).

Sample Size:

This Phase 3 study will enroll approximately 3,000 subjects of whom approximately 2,000 will receive MEDI8897 and 1,000 will receive placebo. The 2,000 subjects to be dosed with MEDI8897 in this study, together with the 968 subjects dosed with MEDI8897 in the Phase 2b Study D5290C00003 and at least 600 subjects dosed with MEDI8897 in the palivizumab-controlled Phase 2/3 Study D5290C00005, will contribute to a safety database of at least approximately 3,600 subjects exposed to MEDI8897.

For this Phase 3 study, the original sample size of 3,000 was driven by the safety database requirement, and the study had at least 99% power for the primary efficacy endpoint. Reducing the sample size to 1,500 still allows the study to be sufficiently powered. More specifically, the sample size of approximately 1,500 subjects in the primary cohort has at least 99% power to detect 70% relative risk reduction (RRR), assuming a placebo group medically attended RSV LRTI incidence of 8% with a 2-sided $\alpha = 0.05$.

The 70% RRR assumption is based on the Phase 2b Study D5290C00003 in which there was 70% RRR in the incidence of medically attended RSV LRTI (9.5% placebo, 2.6% MEDI8897; $p < 0.001$) and 79% RRR in the incidence of RSV hospitalization (4.1% placebo, 0.8% MEDI8897; $p < 0.001$) in subjects who received MEDI8897 prophylaxis. In addition, the assumption is supported by a placebo-controlled study in Native American term infants in which there was a [redacted] in infants who received motavizumab prophylaxis. In the event that the incidence rate in the placebo group drops due to the impact of the COVID-19 pandemic (eg, social distancing), the sample size of 1,500 still provides at least 90% power to detect 70% RRR if the placebo incidence rate is 4% or higher.

To evaluate risk, a sample size of 2,000 subjects exposed to MEDI8897 in this Phase 3 study will provide a > 99% probability of observing at least one adverse event (AE) if the true event rate is 0.3%; if no AEs are observed, this study provides 98% confidence that the true event rate is < 0.2%.

Statistical Analyses:

There are 3 planned analyses for this study: the primary analysis, safety analysis, and final analysis. The primary analysis will be conducted after all randomized subjects (except for one subject enrolled in the NH2020 season) from the primary cohort have been followed through Day 361 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 for the primary cohort through at least Day 361 will be analyzed. The safety analysis will be conducted when all subjects from the safety cohort have been followed through Day 151. For the safety analysis, in addition to the analyses conducted during the primary analysis based on the primary cohort, all available efficacy, PK, ADA, RSV neutralizing antibody, RSV serology, and safety data collected for the safety cohort will be analyzed (only descriptive summaries will be provided for the efficacy data collected for the safety cohort). The final analysis will be conducted when all subjects have completed the last visit of the study (ie, Day 511). Given the largely reduced circulation of RSV due to the COVID-19 pandemic related measures, the efficacy analyses performed in the primary analysis for the primary cohort will serve the purpose of evaluating the efficacy of MEDI8897 in the study population. Although efficacy data will also be collected for the safety cohort, only descriptive summaries will be

provided and there is no intent to pool the efficacy data from the safety cohort with that from the primary cohort. Both the primary and the safety cohorts, individually and combined, will serve the purpose of evaluating the safety of MEDI8897.

The primary and secondary efficacy hypotheses will be assessed in the primary analysis for the primary cohort 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 and will be presented 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 on ITT1. RSV LRTI that occurs through 150 days post dose will contribute to the primary efficacy analysis. For subjects who do not have a medically attended RSV LRTI and are not followed through 150 days post dose, their event status will be imputed assuming the observed placebo RSV LRTI rate conditional on stratification factors using multiple imputation techniques and will be described in the SAP. 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, $\leq$ 3 months, $>$ 3 to $\leq$ 6 months, $>$ 6 months), and dichotomous temperate hemispheres (NH and SH) as covariates. In addition, the 2-sided p-value and corresponding 2-sided 95% confidence interval on the relative risk will be provided from the model. RRR is defined as (1 - Pn/Ps) where Pn is the incidence of RSV LRTI through 150 days post dose in the MEDI8897 group and Ps is the incidence of RSV LRTI through 150 days post dose in the placebo group generated by the model. Statistical significance will be achieved if the 2-sided p-value is $\leq$ 0.05.

During blinded data review prior to database lock for the primary analysis, it was decided to drop the stratification factor hemisphere from the full model due to no incidence of medically attended RSV LRTI events through 150 days post dose for SH in the primary cohort, which would cause a known convergence or estimation issue. Similar consideration also applies to other analyses for the primary efficacy endpoint, where hemisphere will be dropped from the corresponding models.

Additional Analyses of the Primary Endpoint

A Cochran-Mantel-Haenszel approach stratified by age group at the time of randomization (ie, $\leq$ 3 months, $>$ 3 to $\leq$ 6 months, $>$ 6 months) will be used to compare the incidence of RSV LRTI through 150 days post dose between treatment groups as a secondary analysis for the primary endpoint. The additional analyses will be conducted on ITT1. 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 laboratory or local laboratory.

Different approaches to handle missing data (ie, early discontinuation and no RSV LRTI prior to discontinuation) may be considered for supplementary analyses. Additional analyses may be performed to adjust duration of efficacy follow-up and to assess the efficacy within subgroups. These analyses will be described in the SAP.

The incidence of medically attended RSV LRTI through 150 days post dose will also be summarized by treatment group on ITT2.

Secondary Endpoint Analyses:

Efficacy

The incidence of RSV LRTI hospitalization through 150 days post dose will be presented by treatment group. Similar methods as described above for the primary efficacy endpoint will be used to assess efficacy on RSV LRTI hospitalization on ITT1.

The incidence of RSV LRTI hospitalization through 150 days post dose will also be summarized by treatment group on ITT2.

Safety

The safety analyses will be conducted on the overall As-treated Population, AT1, and AT2. Safety of MEDI8897 will primarily be assessed by the occurrence of TEAEs and TESAEs. Adverse events will be graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events where applicable for pediatric assessments. Adverse events will be coded by Medical Dictionary for Regulatory Activities and the type, incidence, severity, and relationship to 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. PK parameters, eg, C_{max}, AUC, apparent clearance, and terminal half-life, 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, efficacy, and association with TEAEs and TESAEs will be assessed. These summaries will be conducted on the overall As-treated Population, AT1, and AT2, unless specified otherwise.

Exploratory Endpoint Analyses:

HRU and Caregiver Burden

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 over-the-counter 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 with non-protocol defined LRTIs, which may be further broken down by RSV status. These summaries will be conducted on ITT1 and ITT2 (if data permit).

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 on ITT1 and ITT2 (if data permit).

RSV Neutralizing Antibody and RSV Serology

RSV neutralizing antibody levels afforded by MEDI8897 will be compared to maternal RSV neutralizing antibody levels and those elicited following infection in the placebo group.

RSV seroresponses will be evaluated as a measure of RSV exposure in the placebo and MEDI8897 groups.

Monitoring RSV Resistance to MEDI8897

Genotypic analysis of the full-length mature F protein will be conducted on all RSV-positive isolates confirmed centrally using the Lyra RSV + hMPV real-time RT-PCR assay manufactured by Quidel Corporation. RSV genotypic analysis will report amino acid changes in the mature F protein sequence compared to contemporary RSV A and RSV B reference strains. Phenotypic analyses will report changes in susceptibility of engineered recombinant RSV variants to MEDI8897 and palivizumab neutralization compared to laboratory-derived reference viruses.

RSV LRTI Occurring From Day 152 to Day 361

The incidence of medically attended RSV LRTI (inpatient and outpatient) from Day 152 to Day 361 will be based on RSV test results (performed centrally via RT-PCR) and objective clinical LRTI criteria and will be summarized by treatment group on ITT1 and ITT2.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
aa	amino acid
AAP	American Academy of Pediatrics
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AT1	As-treated Population 1
AT2	As-treated Population 2
AUC	area under the concentration time-curve
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
CHD	congenital heart disease
CI	confidence interval
CLD	chronic lung disease
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
eCRF	electronic case report form
EDC	electronic data capture
ER	emergency room
EU	European Union
F	fusion
Fc	fragment cystallizable
FcRn	neonatal Fc receptor
GA	gestational age
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
HRU	healthcare resource utilization
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgG1κ	immunoglobulin G1 kappa
IM	intramuscular

Abbreviation or Specialized Term	Definition
IRB	Institutional Review Board
ITT	Intent-to-treat
ITT1	Intent-to-treat Population 1
ITT2	Intent-to-treat Population 2
IV	intravenous
IWRS	interactive web response system
JCVI	Joint Committee on Vaccination and Immunisation
LRTI	lower respiratory tract infection
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MELODY	Study D5290C00004
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NH	northern hemisphere
NOCD	new onset chronic disease
OTC	over-the-counter
PK	pharmacokinetic(s)
RRR	relative risk reduction
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SH	southern hemisphere
SID	subject identification
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TK	toxicokinetic(s)
TESAE	treatment-emergent serious adverse event
UK	United Kingdom
URTI	upper respiratory tract infection
US FDA	United States Food and Drug Administration
USA	United States of America
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 more than 50 years of attempted vaccine development, there are no licensed vaccines. 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.

The only currently approved prophylaxis for RSV, palivizumab (Synagis®), was developed by MedImmune and is only indicated for use in high-risk children: preterm infants ≤ 35 weeks gestational age (GA), children with chronic lung disease (CLD) of prematurity, and children with haemodynamically significant congenital heart disease (CHD). In addition, further restrictions have been implemented by local or national recommending bodies on the use of palivizumab. 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 weeks GA (American Academy of Pediatrics, 2014). In the United Kingdom (UK), palivizumab is recommended by the Joint Committee on Vaccination and Immunisation (JCVI) for preterm infants with CLD or haemodynamically significant, acyanotic CHD based on the GA at birth and chronological age at the start of the RSV season (JCVI, 2010a, 2010b).

1.1 Disease Background

Respiratory syncytial virus is the most common cause of lower respiratory tract infection (LRTI) among infants and young children, resulting in annual epidemics worldwide (Hall et al, 2009; Hall, 2012; Madhi et al, 2006; Shay et al, 1999; Shi et al, 2017; Stockman et al, 2012). All children, including healthy term infants, are at risk for severe RSV LRTI with primary RSV infection during infancy. Ninety percent of children are infected with RSV in the first 2 years of life and up to 40% of those will have LRTI with the initial episode (American Academy of Pediatrics, 2014; Greenough et al, 2001; Meissner, 2003; Parrott et al, 1973). RSV 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). In 2015, an estimated 33.1 million (uncertainty range, 21.6 to 50.3 million) new episodes of RSV-associated LRTI occurred worldwide in children younger than 5 years (28% of LRTI episodes), with approximately 3.2 million (range, 2.7 to 3.8 million) episodes necessitating hospitalizations, leading to 59,600 (range, 48,000 to 74,500) in-hospital deaths (Shi et al, 2017). Children younger than 1 year of age had an estimated 2.3 million hospital admissions. The overall mortality due to RSV LRTI was estimated to be as high as 118,200 (uncertainty range, 94,600 to 149,400 (Shi et al, 2017).

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) as office visits and emergency department visits, 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). Paramore and colleagues reported high rates of outpatient RSV LRTI among infants and young children, ranging from 157.5 to 252.0 per 1,000 children < 1 year of age (Paramore et al, 2010). This study also showed that outpatient RSV LRTI rates for late preterm (33 to 36 weeks GA) infants ranged from 183.3 to 245.7 per 1,000 infants, with rates for full-term infants ranging from 128.8 to 171.3 per 1,000 infants.

Hospitalization rates among young children in European countries appear to be similar to those in the US; 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 (König et al, 2004).

Similarly, high rates of RSV hospitalization are evident in South Africa. For infants < 6 months of age, the incidence (95% confidence interval [CI]) of severe LRTI was 26.2 (range, 23.6 to 29.0) per 1,000 in those born at ≥ 36 weeks GA, 125.0 (range, 95.3 to 159.9) per 1,000 in those born at 32 to 35 weeks GA, and 142.3 (range, 89.50 to 212.0) per 1,000 in those born at < 32 weeks GA (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 (EU) numbering system]) in the fragment crystallizable (Fc) region to prolong the terminal half-life ($t_{1/2}$), 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 (Zhu et al, 2017). 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 intramuscular (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 for Phase 2b 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}) (Zhu et al, 2017).

Toxicity, toxicokinetics (TK), and immunogenicity of MEDI8897 were evaluated in a Good Laboratory Practice-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. [redacted] 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

MEDI8897 has been investigated in 3 completed clinical studies.

1.4.1 Study D5290C00001

The first-time-in-human Study D5290C00001 (Griffin et al, 2017) was a Phase 1a, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, tolerability, and PK of MEDI8897 compared to placebo. A total of 136 subjects were randomized and received 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 confirming the predicted 3- to 4-fold increase in the $t_{1/2}$ of MEDI8897 compared to a standard immunoglobulin G (IgG) antibody. The safety profile of MEDI8897 was favorable, with similar proportions of treatment-emergent adverse events (TEAEs) reported in placebo (61.8%) and MEDI8897 recipients (62.7%). Two treatment-emergent serious adverse events (TESAEs; gunshot wound and appendicitis) were reported in 2 MEDI8897 recipients. TEAEs judged to be related to investigational product were reported in 29.4% of placebo recipients and 17.6% of MEDI8897 recipients. The most frequent TEAEs in the MEDI8897 total group included upper respiratory tract infection (URTI; 18.6%), headache (8.8%), urinary tract infection (5.9%), dermatitis contact (4.9%), musculoskeletal pain (4.9%), nausea (4.9%), and vomiting (4.9%). The most frequent TEAEs in the placebo group were headache (17.6%), URTI (8.8%), nausea (5.9%), increased blood creatine phosphokinase level (5.9%), and paresthesia (5.9%). There were no events designated as an adverse event of special interest (AESI) or new onset chronic disease (NOCD). There were no deaths. No safety signals in this healthy adult population were observed. Post-baseline ADA was detected in 13.7% of adults receiving MEDI8897 and 15.2% of adults in the placebo group. On Day 361, ADA was detected in 5.3% of subjects in the MEDI8897 total group and 10.7% of subjects in the placebo group. The highest titer at Day 361 was 1:200 for both the MEDI8897 total and placebo groups. The presence and titer of ADA had no effect on the PK or safety profile. These results confirmed the extended half-life and demonstrated an acceptable safety profile for MEDI8897, including no observed hypersensitivity reactions, thus supporting further clinical studies of IM administration of 1 dose of MEDI8897 in the target population of infants to provide protection for the duration of the RSV season.

1.4.2 Study D5290C00002

The first-time-in-infant Study D5290C00002 (Domachowske et al, 2018) was a Phase 1b/2a, randomized, double-blind, placebo-controlled, single ascending-dose study to evaluate safety, PK, and ADA in healthy preterm infants. The population enrolled was healthy preterm infants born between 32 weeks 0 days and 34 weeks 6 days gestation who would not receive RSV

prophylaxis based on the AAP or other national or local guidelines. These subjects would not be receiving palivizumab, allowing for a placebo comparator group. A total of 89 infants from sites in the USA, Chile, and South Africa were randomized and received a single IM dose of MEDI8897 (10, 25, or 50 mg; N = 71) or placebo (N = 18) and were followed for approximately 360 days after dosing.

A total of 66 subjects (93%) in the MEDI8897 group and 17 subjects (94.4%) in the placebo group reported at least 1 TEAE. No safety signals were observed with ascending dose levels. The majority of the events were mild or moderate in severity; only 2 TEAEs were assessed as ≥ Grade 3 severity, and neither was considered to be related to investigational product by the investigator. There were no deaths, AESIs, or NOCDs in any dose group.

Three MEDI8897 subjects (4.2%) had a total of 5 TESAEs, none of which were considered related to investigational product by the investigator; no subjects in the placebo group had a TESAE. One infant who received 25 mg of MEDI8897 was hospitalized for LRTI. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing from the central laboratory was negative for RSV (but positive for human metapneumovirus [hMPV]); the illness resolved. [redacted]

The most frequently reported TEAEs for the MEDI8897 group were URTI (69.0%), gastroenteritis (29.6%), cough (25.4%), pyrexia (22.5%), and otitis media (21.1%). There were no trends by dose of MEDI8897 for these events. The most frequently reported TEAEs in the placebo group were URTI (66.7%), anemia (33.3%), gastroenteritis (22.2%), cough (22.2%), and otitis media (22.2%). Skin rashes (defined as adverse events [AEs] that coded to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms of dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, dermatitis diaper, dry skin, eczema, rash, and rash papular) were reported for 38.9% of subjects in the placebo group and 47.9% of subjects in the MEDI8897 group. No skin events were consistent with hypersensitivity.

MEDI8897 exhibited a less-than-dose-proportional exposure increase between the 10 and 25 mg doses; however, exposure increase was dose proportional between 25 and 50 mg doses. Following a single IM dose of 10, 25, or 50 mg, the estimated t½ of MEDI8897 ranged from 62.5 to 72.9 days. On Day 151, 87% of the MEDI8897 serum concentrations following the 50 mg IM dose were above the EC_{90} threshold of 6.8 μg/mL.

ADA was not detected in any subject at Day 151. Post-baseline ADA was detected at Day 361 only in 18/68 (26.5%) subjects, and there were 2 subjects with transient ADA positive titers at Day 50 only who were ADA negative at Day 361. Overall, post-baseline ADA was detected in

20/71 subjects (28.2%) in the MEDI8897 group and 0/17 subjects (0%) in the placebo group. None of the post-baseline MEDI8897 ADA-positive subjects were ADA positive at baseline; only one subject (in the placebo group) was ADA-positive at baseline. The highest titer detected was 1:25,600 (observed in 2 subjects [2.8%]). The 20 subjects in the MEDI8897 group who had ADA detected were positive for the presence of ADA targeting the YTE domain and 4 of the 20 subjects with samples available had neutralizing ADA antibody.

There was no impact of the presence of ADA on safety. ADAs did not appear to impact PK for 150 days after dosing, but there may have been an impact between Day 151 and Day 361. Serum anti-RSV neutralizing antibody titers increased dose-dependently following administration of MEDI8897 and were higher than placebo by Day 8 and through Day 151. Serum MEDI8897 concentrations were correlated with serum anti-RSV neutralizing antibody across all the dose levels, confirming anti-RSV activity of MEDI8897.

1.4.3 Study D5290C00003

The Phase 2b Study D5290C00003 was a randomized, double-blind, placebo-controlled single-dose study that evaluated the safety, efficacy, PK, and ADA response of MEDI8897 in healthy preterm infants. Subjects were 29 to < 35 weeks GA entering their first RSV season who would not receive RSV prophylaxis based on the JCVI, AAP, or other local or national guidelines. Overall, 1,453 subjects were randomized 2:1 to receive a single dose of 50 mg IM MEDI8897 (n = 969) or placebo (n = 484). A total of 1,447 subjects were dosed, including 966 subjects in the MEDI8897 group and 481 subjects in the placebo group. Subjects were followed for approximately 360 days after dosing. The study was completed on 06Dec2018 (last subject last visit).

Results from the planned primary analysis conducted after all randomized subjects who remained in the study completed the Day 151 visit demonstrated a statistically significant relative risk reduction (RRR) in the incidence of the primary endpoint of RSV-confirmed LRTI (inpatient and outpatient) and the secondary endpoint of RSV hospitalization. [redacted]

Based on the primary analysis, the safety profile for the MEDI8897 group was comparable to the placebo group, with no identified risks. Overall, [redacted] of subjects in the MEDI8897 group and [redacted] of subjects in the placebo group had at least 1 TEAE. The majority of the TEAEs were mild or moderate in severity. TEAEs ≤ 1 day post dose occurred in 2.5% of subjects in both groups. In comparison to the placebo group, the MEDI8897 group had a

lower incidence of TEAEs occurring ≤ 7 days post dose (15.2% vs 12.5%, respectively), TEAEs ≥ Grade 3 in severity (12.3% vs 7.4%, respectively), and TESAEs (16.7% vs 10.4%, respectively). The most common TESAEs, based on the MEDI8897 group, were bronchiolitis (2.1% MEDI8897, 4.2% placebo), LRTI (1.4% MEDI8897, 2.7% placebo), pneumonia (1.4% MEDI8897, 2.1% placebo), and bronchitis (1.2% MEDI8897, 2.3% placebo). None of the TESAEs were considered related to study treatment by the investigator. Five deaths were reported during the study through Day 361, including 2 subjects (0.2%) in the MEDI8897 group and 3 subjects (0.6%) in the placebo group. None of the deaths were related to study drug according to the investigator.

Overall, the incidence of investigational product-related TEAEs (MEDI8897 2.3%, placebo 2.1%); AESIs, including hypersensitivity, immune complex disease, and thrombocytopenia (MEDI8897 0.5%, placebo 0.6%); and NOCDs (MEDI8897 0.3%, placebo 0.8%) was low and generally comparable between the placebo and MEDI8897 groups. AESIs were reported in 5 subjects (4 subjects with rash or rash macular and 1 subject with petechiae) in the MEDI8897 group and 3 subjects (rash or rash papular) in the placebo group. All events were Grade 1 in severity. The TEAE of petechiae that was reported as an AESI was 1-day duration and was reported by the site investigator based on description by the parent. There were no laboratory assessments for the petechiae.

TEAEs that involved the skin and subcutaneous tissues (including diaper rash) were collected as skin reactions, with a few exceptions for skin reactions that could be definitively diagnosed such as impetigo, varicella, and scabies. [redacted]

Following a single fixed 50 mg IM dose of MEDI8897, over 95% of measurable Day 151 concentrations were greater than the nonclinical EC_{90} target of 6.8 µg/mL. The median area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) and estimated apparent t½ were 5.3 day.mg/mL (range, 3.2 to 10.2 day.mg/mL) and 56.5 days (range, 46.8 to 81.1 days), respectively.

Overall, the rate and titers of ADA were low, and in ADA-positive subjects there was no effect on PK or safety. Of the subjects who had serum samples available for testing, ADA was detected post baseline in 4.3% (40/921) of subjects in the MEDI8897 group and 2.8% (13/466) of subjects in the placebo group; with less than 5% of subjects in either group being ADA positive at any visit. ADA titers ranged from 1:50 to 1:3,200 in the MEDI8897 group and 1:50 to 1:200 in the placebo group. Of the MEDI8897 subjects who were post-baseline ADA positive, ADA targeting the YTE domain was observed in 4/17 subjects on Day 151 and 10/15 on Day 361. Two MEDI8897 subjects had neutralizing ADA antibody on Day 361.

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 born ≤ 35 weeks GA, 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, the USA national guidelines provided by the AAP (American Academy of Pediatrics, 2014) limit the recommendation for palivizumab to (a) preterm infants born before 29 weeks GA who are younger than 12 months of age at the start of the RSV season, (b) preterm infants with a GA of < 32 weeks and CLD for the first year of life with consideration of prophylaxis during the second year if continued medical support is required, and (c) infants with hemodynamically significant CHD who are 12 months of age or younger. In the UK, palivizumab is recommended by the JCVI for preterm infants with CLD or hemodynamically significant, acyanotic CHD based on the GA at birth and chronological age at the start of the RSV season (JCVI, 2010a, 2010b). Currently, there is no approved RSV prophylaxis for the broader population of healthy 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 United States Food and Drug Administration (US FDA), a pivotal Phase 2b study was conducted in healthy preterm infants born 29 to 35 weeks GA to demonstrate efficacy and safety of MEDI8897 in healthy preterm infants who are not eligible to receive palivizumab according to AAP or other local guidelines. Based on favorable benefit-risk results following the primary analysis, this Phase 3 study in healthy infants ≥ 35 weeks GA will be initiated.

1.6 Benefit-Risk and Ethical Assessment

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

Prevention of RSV illness 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 once they acquire serious RSV illness, the medical management for these patients is supportive care.

Based on the risk of serious RSV disease in younger infants and in high-risk children, there is an established unmet medical need for the use of MEDI8897 as a prophylactic mAb in all infants entering their first RSV season and in high-risk preterm infants and children up to 2 years of age with CLD or CHD. Infants in this study who receive MEDI8897 may potentially benefit by being protected against serious RSV disease; however, this has not yet been proven in this population.

MEDI8897 has no endogenous targets, and no safety concerns were identified in nonclinical studies. The potential risks are based primarily on common safety risks observed with any immunoglobulin, including mAbs such as palivizumab. These potential risks include, but are not limited to, hypersensitivity (including anaphylaxis), immune complex disease, thrombocytopenia, and injection site reactions. To date, there have been no observed events of anaphylaxis, significant hypersensitivity reactions, immune complex disease, or thrombocytopenia attributable to MEDI8897 in the clinical studies. Nonetheless, subjects in MEDI8897 clinical studies will be monitored for important potential risks, and routine pharmacovigilance and risk minimization activities will be performed accordingly.

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

Compared to placebo, a single IM MEDI8897 dose, 50 mg if weight < 5 kg or 100 mg if weight ≥ 5 kg, will be efficacious in reducing medically attended LRTI caused by RT-PCR-confirmed RSV in healthy late preterm and term infants born ≥ 35 weeks 0 days GA and entering their first RSV season, and the safety profile will be acceptable.

1.7.2 Secondary Hypotheses

- There will be a reduction in the incidence of hospitalizations attributable to RT-PCR-confirmed RSV
- The predicted serum exposure of MEDI8897 will be adequate for the duration of the RSV season
- ADA to MEDI8897 will not significantly impact the serum concentrations or safety of MEDI8897 through 150 days post dosing (ie, during a 5-month RSV season)

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoint

Table 1 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
Efficacy	To assess the efficacy of MEDI8897 when administered as a single fixed IM dose to infants ≥ 35 weeks 0 days GA and entering their first RSV season, in reducing medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)

GA = gestational age; IM = intramuscular; LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction.

2.1.1 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Efficacy	To assess the efficacy of MEDI8897 in reducing hospitalizations due to RT-PCR-confirmed RSV, compared to placebo	Incidence of hospitalizations due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
Safety	To evaluate the safety and tolerability of MEDI8897 when administered as a single fixed IM dose, compared to placebo	Safety and tolerability of MEDI8897 as assessed by the occurrence of TEAEs, TESAEs, AESIs, and NOCDs
PK	To evaluate single-dose serum concentrations of MEDI8897	Summary of MEDI8897 serum concentrations and estimated PK parameters (apparent clearance and AUC, if data permit)
ADA	To evaluate ADA responses to MEDI8897 in serum	Incidence of ADA to MEDI8897 in serum

ADA = anti-drug antibody; AESI = adverse event of special interest; AUC = area under the concentration time-curve; IM = intramuscular; NOCD = new onset chronic diseases; PK = pharmacokinetic; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

2.1.2 Exploratory Objectives and Associated Endpoints

Table 3 Exploratory Objectives and Endpoints

Type	Objective	Endpoint
Healthcare resource utilization	To assess healthcare resource utilization and caregiver burden for MEDI8897 recipients compared to placebo recipients	• Magnitude of healthcare resource utilization (eg, number of admissions to hospitals and intensive care units 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, urgent care, outpatient clinic; and number of prescription and over-the-counter medications and duration of use) • Caregiver burden (eg, caregiver missed work days, subject absence from day care) for subjects with medically attended LRTI caused by RT-PCR-confirmed RSV
RSV neutralizing antibody	To determine anti-RSV neutralizing antibody levels in serum afforded by a single dose of MEDI8897 compared to maternal RSV neutralizing antibody levels and those elicited following infection in the placebo group	Anti-RSV neutralizing antibody levels (IU/mL) in serum for MEDI8897 recipients compared to placebo recipients
RSV serology	To evaluate exposure to RSV by measuring seroresponses to different RSV proteins	• Antibody levels to RSV pre-F, post-F, Ga, Gb, and N at different time points • Changes in antibody levels (seroresponse) indicating exposure to RSV
RSV resistance monitoring	To characterize resistance to MEDI8897 through genotypic and phenotypic analyses	Genotypic analysis and susceptibility of RSV variants to neutralization by MEDI8897
RSV LRTI after Day 151	To assess the incidence of medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo after Day 151	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV from Day 152 to Day 361

LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction.

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

Study D5290C00004 (MELODY) is a pivotal Phase 3 randomized, double-blind, placebo-controlled, single-dose study to determine if MEDI8897 will prevent medically attended RSV-confirmed LRTI in healthy infants entering their first RSV season (Figure 1). The population to be enrolled is healthy late preterm and term infants born ≥ 35 weeks 0 days GA who would not receive RSV prophylaxis based on the AAP or other local or national guidelines. The study will be conducted over 5 respiratory virus seasons (3 northern

hemisphere [NH] and 2 southern hemisphere [SH] seasons) to better characterize RSV cases over multiple seasons. A total of approximately 3,000 infants will be randomized in a 2:1 ratio to receive a single 50-mg (if < 5 kg weight at the time of dosing) or 100-mg (if ≥ 5 kg weight at the time of dosing) IM dose of MEDI8897 (N = 2,000) or placebo (N = 1,000). The study may continue to enroll through 5 enrollment seasons even if the target of 3,000 subjects is met. Randomization will be stratified by hemisphere (NH, SH) and by subject age at the time of randomization (≤ 3 months, > 3 to ≤ 6 months, > 6 months). Enrollment of infants > 6 months of age will be limited to approximately 500. The study will comprise 2 cohorts: a primary cohort (N = ~1,500) and a complementary safety cohort (hereafter referred to as the safety cohort; N = ~1,500) for a total of approximately 3,000 subjects. Given the largely reduced circulation of RSV due to the coronavirus disease 2019 (COVID-19) pandemic related measures, the primary cohort will include subjects from the NH2019, SH2020, and NH2020 enrollment seasons. The safety cohort will include subjects enrolled after the NH2020 enrollment season. The efficacy analyses performed in the primary analysis for the primary cohort will serve the purpose of evaluating the efficacy of MEDI8897 in the study population. Although efficacy data will also be collected for the safety cohort, only descriptive summaries will be provided and there is no intent to pool the efficacy data from the safety cohort with that from the primary cohort. Both the primary and the safety cohorts, individually and combined, will serve the purpose of evaluating the safety of MEDI8897. All subjects will be followed for approximately 510 days after dosing. An independent data monitoring committee will review safety data regularly and make recommendations regarding further study conduct.

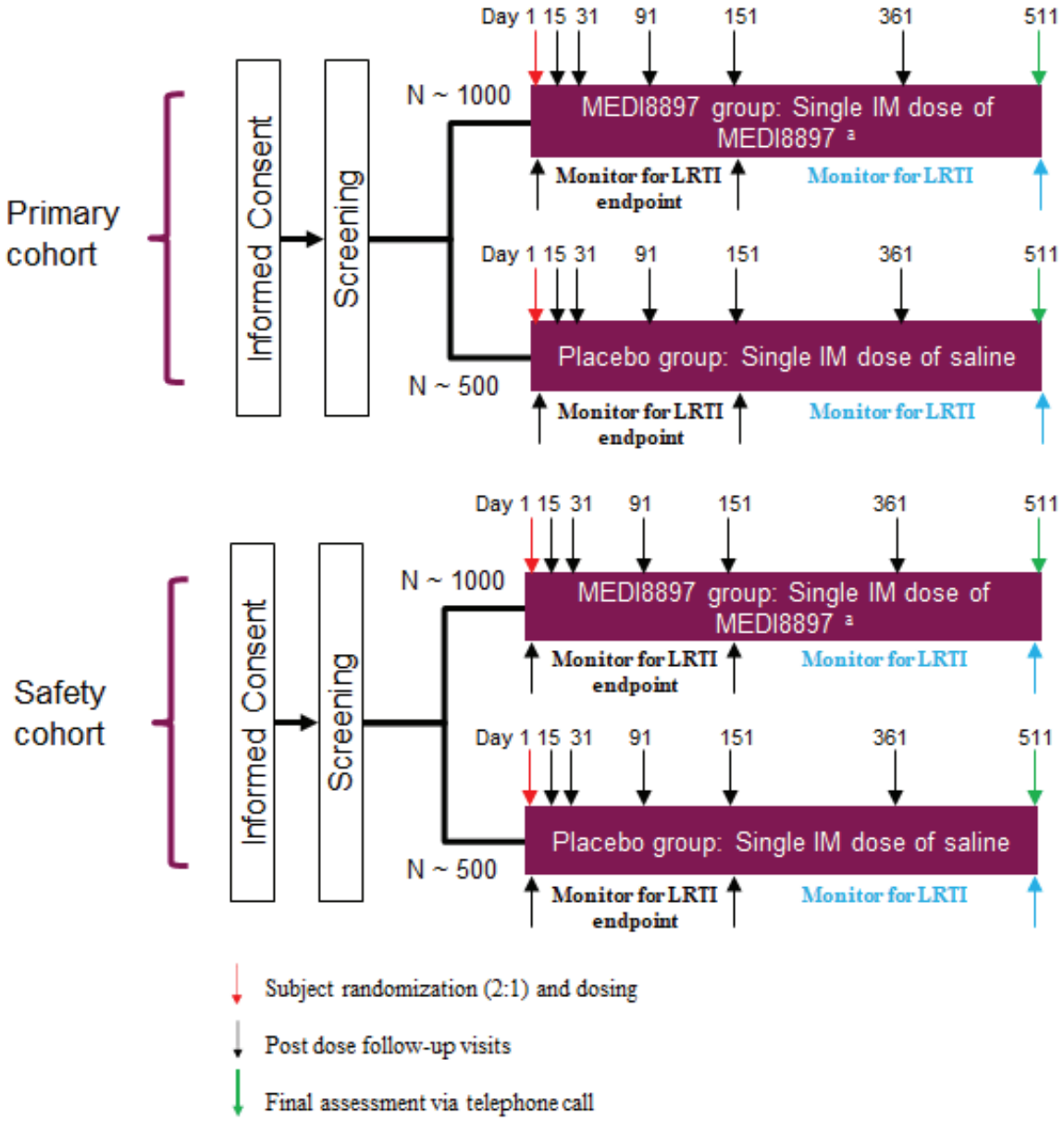
Subjects will be monitored throughout the study for LRTI. All subjects seeking medical attention for a respiratory illness (in either the inpatient or outpatient setting) will be evaluated for the occurrence of LRTI. All subjects found to have an LRTI and all subjects who require hospitalization for a respiratory infection, even if there is not a diagnosis of LRTI, should have respiratory samples obtained and respiratory assessment forms completed. Samples should be collected for all of these events (even those not meeting the protocol definition of LRTI). Subjects who have a primary hospitalization for a respiratory infection (ie, upper or lower tract) or a respiratory deterioration during a hospitalization, or who seek outpatient medical attention (including emergency room [ER] visits) for a lower respiratory illness, will be assessed clinically for the presence of LRTI and for RSV by central laboratory diagnostic testing of respiratory secretions.

In addition to the clinical assessment of LRTI, there is a protocol definition using objective criteria for the determination of a medically attended protocol-defined LRTI. To meet the protocol-defined endpoint of medically attended LRTI, subjects with signs of LRTI must have documented at least one physical exam finding of rhonchi, rales, crackles, or wheeze AND at least one of the following clinical signs:

- Increased respiratory rate at rest (age < 2 months, ≥ 60 breaths/min; age 2 to 6 months, ≥ 50 breaths/min; age > 6 months, ≥ 40 breaths/min) OR
- Hypoxemia (in room air: oxygen saturation < 95% at altitudes ≤ 1,800 meters or < 92% at altitudes > 1,800 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 IV fluid)

Testing for RSV will be performed centrally using the US FDA-cleared and *Conformité Européenne* or European Conformity-marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + hMPV assay; Quidel Corporation, San Diego, CA, www.quidel.com). A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by the central laboratory RT-PCR.

Figure 1 Study Flow Diagram



ADA = anti-drug antibody; IM = intramuscular; LRTI = lower respiratory tract infection; PK = pharmacokinetic.
Blood samples for PK and ADA will be collected at screening or Day 1 predose, on Days 31, 151, and 361, and from subjects hospitalized for a respiratory infection through Day 361.
Safety assessments will be performed through Day 361.

[a] Dose level will be stratified by body weight at time of dosing. In the MEDI8897 group, subjects will receive 50 mg (0.5 mL) MEDI8897 if < 5 kg or 100 mg (1.0 mL) MEDI8897 if ≥ 5 kg. Subjects in the placebo group will receive a corresponding volume of normal saline, ie, 0.5 mL if < 5 kg or 1.0 mL if ≥ 5 kg.

The endpoints to be measured in this study are described in Section 2.

3.1.2 Treatment Regimen

Subjects will be randomly assigned in a 2:1 ratio to receive a single IM dose of MEDI8897 (N = 2,000) or placebo (N = 1,000). The MEDI8897 dose level will be stratified by body weight at time of dosing: 50 mg MEDI8897 for infants < 5 kg or 100 mg MEDI8897 for infants ≥ 5 kg.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

A single fixed 50-mg IM dose was shown to be efficacious in the Phase 2b Study D5290C00003 in preterm infants (29 to < 35 weeks GA) in their first RSV season (see Section 1.4). Model-based analyses of the Phase 2b clinical PK and efficacy data identified a projected serum $AUC_{0-\infty}$ of [redacted] as the protective exposure threshold. The risk of medically attended RSV-confirmed LRTI over the course of the RSV season was significantly lower in infants with higher projected $AUC_{0-\infty}$. Infants with $AUC_{0-\infty}$ above 13.4 day.mg/mL had a statistically significantly higher probability of protection based on exposure-response analysis using Cox proportional hazard regression. [redacted] Additionally, a cut-point analysis of the weight-normalized doses of all treated infants revealed that a 10 mg/kg dose was the corresponding clinically efficacious and protective threshold dose. Henceforth, based on these analyses, a stratified fixed dosing strategy by weight bands is proposed to ensure maintenance of MEDI8897 serum concentrations above the target AUC throughout the RSV season. Based on dose optimization analysis designed to maximize the proportion of infants with clinically efficacious MEDI8897 serum exposure, a single fixed 50-mg IM dose is proposed for infants < 5 kg in their first RSV season while a single fixed 100-mg dose is proposed for infants weighing ≥ 5 kg entering their first RSV season.

3.2.2 Rationale for Study Population

MEDI8897 has the potential to address a serious unmet medical need by protecting all infants from RSV disease with once per season dosing. A dose of 50 mg MEDI8897 was first evaluated in healthy preterm infants 29 to < 35 weeks GA (per US FDA advice) in the pivotal Phase 2b Study D5290C00003 with favorable benefit-risk results following the primary analysis (see Section 1.4). This study proposes to further extend the population to healthy late preterm and term infants (≥ 35 weeks GA) to meet the overall goal of evaluating MEDI8897 for prevention of RSV disease in all infants entering their first RSV season.

3.2.3 Rationale for Endpoints

The endpoints for this Phase 3 pivotal study are the same as the endpoints used in the completed Phase 2b pivotal study. The primary endpoint is the incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season). This endpoint will examine the efficacy of MEDI8897 compared to placebo in preventing LRTI due to RSV. RSV 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 the total burden of RSV disease and the efficacy of MEDI8897 in reducing that burden. A separate secondary endpoint of RSV hospitalization will also be evaluated.

Safety endpoints include TEAEs, TESAEs, AESIs (defined as hypersensitivity including anaphylaxis, immune complex disease, and thrombocytopenia), NOCDs, and concomitant medications.

Serum concentration of MEDI8897 at selected time points will be evaluated as a secondary endpoint to confirm that adequate serum exposures are maintained for at least 5 months after dosing. Additionally, serum concentration data will be used to characterize the PK of MEDI8897 in infants using a population PK approach separately. For infants who require hospitalization for LRTI or any respiratory infection, an additional serum sample for measurement of MEDI8897 concentration and ADA will be obtained contemporaneous with time of hospitalization. Exposure-response analysis will be performed to relate MEDI8897 serum concentrations and efficacy endpoints (LRTI including RSV-associated hospitalization).

To determine MEDI8897 serum levels post dosing and correlation with the development of ADA, serum concentrations will be measured up to 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.

Exploratory endpoints will examine magnitude of healthcare resource utilization (HRU) and caregiver burden due to RSV illness in the studied population. This will allow the determination of social and economic resources that are required for infants who have RSV-confirmed LRTI. Serum anti-RSV neutralizing antibody levels will be evaluated for correlation with serum MEDI8897 levels and maternally-derived RSV neutralizing antibody levels in the placebo group. RSV serology will be performed to identify potential exposure to RSV. To monitor for RSV resistance, the F protein from collected RSV isolates will be genetically characterized and novel variants will be phenotypically characterized for susceptibility to MEDI8897 and palivizumab neutralization. The incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV from Day 152 to Day 361 will be assessed to determine if there is a possible effect of MEDI8897 past Day 151.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

A total of approximately 3,000 infants will be enrolled and randomized in a 2:1 ratio to receive a single IM dose of MEDI8897 (N = 2,000) or placebo (N = 1,000).

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Healthy infants in their first year of life and born ≥ 35 weeks 0 days GA (infants who have an underlying illness such as cystic fibrosis or Down syndrome with no other risk factors are eligible)
2 Infants who are entering their first RSV season at the time of screening
3 Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the USA, 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 17 months after receipt of study drug

4.1.3 Exclusion Criteria

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

1 Meets national or other local criteria to receive commercial palivizumab
2 Any fever (≥ 100.4°F [≥ 38.0°C], regardless of route) or acute illness within 7 days prior to randomization
3 Any history of LRTI or active LRTI prior to, or at the time of, randomization
4 Known history of RSV infection or active RSV infection prior to, or at the time of, randomization
5 Any drug therapy (chronic or other) within 7 days prior to randomization or expected receipt during the study with the exception of: a) multivitamins and iron; b) infrequent use of over-the-counter (OTC) medications for the systemic treatment of common childhood symptoms (eg, pain relievers) 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, blood products, 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 CHD, 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 mAb or any RSV vaccine, including maternal RSV vaccination
20 Receipt of any monoclonal or polyclonal antibody (for example, hepatitis B immune globulin, IV 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

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 may at any time be withdrawn from the study without prejudice to further treatment (withdrawal of consent). The caregivers of such subjects will always be asked about the reason(s) for withdrawal and the presence of any AEs. If possible, the subject will be seen and assessed by the investigator. AEs 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 Discontinuation of Investigational Product

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 from further study participation (Section 4.1.5) 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 Withdrawal of Informed Consent for Data and Biological Samples

MedImmune ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, MedImmune is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to MedImmune.
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the subject and MedImmune are informed about the sample disposal.

MedImmune ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

4.2 Schedule of Study Procedures

Whenever vital signs and blood draws are scheduled for the same nominal time, vital signs should occur prior to blood draws.

4.2.1 Enrollment/Screening Period

Table 4 shows all procedures to be conducted at the screening visit.

Table 4 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
Blood sample for PK, ADA, RSV neut Ab, and RSV serology [a]	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Verify eligibility criteria	X

ADA = anti-drug antibody; AEs = adverse events; neut Ab = neutralizing antibody; PK = pharmacokinetic; RSV = respiratory syncytial virus; SAEs = serious adverse events; SID = subject identification; V = visit.

Visit 1/Screening and Visit 2/Day 1 may occur on the same day.

[a] If Visit 1/Screening and Visit 2/Day 1 do not occur on the same day, blood sample for PK, ADA, RSV neut Ab, and RSV serology can be collected at either Visit 1/Screening or Visit 2/Day 1 predose.

4.2.2 Treatment and Follow-up Periods

Study drug is administered on Day 1. Table 5 shows all procedures to be conducted during the treatment and follow-up periods.

Table 5 Schedule of Treatment Period and Follow-up Period Study Procedures

Study Period	Treatment Period	Follow-up Period											
Visit Number	**V2** [a]	**TC**	**V3**	**V4**	**V5**	**V6**	**V7**	**TC**			**LRTI**		**Skin Reaction**
Procedure / Study Day	**D1**	**D8 (± 2 days)**	**D15 (± 2 days)**	**D31 (± 5 days)**	**D91 (± 7 days)**	**D151 (± 7 days)**	**D361 (± 7 days)**	**D1-151 Q2W (± 5 days)**	**D152-361 monthly (± 5 days)**	**D362-511 Q2W (± 5 days)**	**D1-361 as needed**	**D362-511 as needed**	**D1-361 as needed**
Medical history update	X		X	X	X	X	X						
Physical examination	X		X	X	X	X	X						
Weight	X		X	X	X	X	X						
Vital signs	X [b]		X	X	X	X	X						
Blood sample for PK, ADA, RSV neut Ab, and RSV serology	X [c]			X		X	X				X [d]		
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X		X		X
Assessment of AESIs and NOCDs	X	X	X	X	X	X	X	X	X		X		X
Concomitant medications	X	X	X	X	X	X	X	X	X		X	X [i]	X
Verify eligibility criteria	X												
Randomization	X												
Investigational product administration	**X**												
Assessment of LRTI (inpatient or outpatient) or any respiratory infection that requires hospitalization											X [d, e]	X [e]	
Nasal swab collection											X [e]	X [e]	
Assessment of skin reaction													X [f]

Table 5 Schedule of Treatment Period and Follow-up Period Study Procedures

Study Period	Treatment Period	Follow-up Period											
Visit Number	**V2** [a]	**TC**	**V3**	**V4**	**V5**	**V6**	**V7**	**TC**			**LRTI**		**Skin Reaction**
Procedure / Study Day	**D1**	**D8 (± 2 days)**	**D15 (± 2 days)**	**D31 (± 5 days)**	**D91 (± 7 days)**	**D151 (± 7 days)**	**D361 (± 7 days)**	**D1-151 Q2W (± 5 days)**	**D152-361 monthly (± 5 days)**	**D362-511 Q2W (± 5 days)**	**D1-361 as needed**	**D362-511 as needed**	**D1-361 as needed**
Telephone contact [g]		X						X	X	X (respiratory illness inquiry only)			
HRU and caregiver burden [h]											X		

ADA = anti-drug antibody; AEs = adverse events; AESIs = adverse events of special interest; D = study day; ER = emergency room; HRU = healthcare resource utilization; ICU = intensive care unit; LRTI = lower respiratory tract infection; neut Ab = neutralizing antibody; NOCDs = new onset chronic diseases; OTC = over-the-counter; PK = pharmacokinetic; Q2W = once every two weeks; RSV = respiratory syncytial virus; SAEs = serious adverse events; TC = telephone call; V = visit.

[a] Visit 2/Day 1 and Visit 1/Screening can occur on the same day.

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

[c] If Visit 1/Screening and Visit 2/Day 1 do not occur on the same day, blood sample for PK, ADA, RSV neut Ab, and RSV serology can be collected at either Visit 1/Screening or Visit 2/Day 1 predose.

[d] Blood samples will be collected from all subjects hospitalized with LRTI or any respiratory infection within approximately 2 days following hospital admission.

[e] Nasal samples will be collected from all subjects with LRTIs (inpatient or outpatient) and from all subjects hospitalized with any respiratory infection (upper or lower) within approximately 2 days after the initial healthcare provider assessment and diagnosis.

[f] Skin reaction assessment will be done for any post-dosing skin or skin-related reaction regardless of severity, duration, time of onset post dosing, or relationship to investigational product.

[g] Telephone contact must be verbal communication. Written communication via text, email, or other written form is not acceptable.
Telephone contact from Days 362 to 511 is only to determine whether there were any respiratory illnesses that required a medical visit.

[h] 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. Caregiver burden includes days of worked missed by the parent(s)/legal representative or other household member as a result of the subject's illness, and days of day care/babysitting missed by the subject as a result of illness.

[i] Only for subjects with LRTIs diagnosed during this period.

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 (see Table 5). All subjects seeking medical attention for a respiratory illness (in either the inpatient or outpatient setting) will be evaluated for the occurrence of LRTI (Table 6). All subjects found to have an LRTI and all subjects who require hospitalization for a respiratory infection, even if there is not a diagnosis of LRTI, should have respiratory samples obtained and respiratory assessment forms completed. Samples should be collected for all of these respiratory events even those not meeting the protocol definition of LRTI. Subjects who have a primary hospitalization for a respiratory infection (ie, upper or lower tract) or a respiratory deterioration during a hospitalization, or who seek outpatient medical attention (including ER visits) for a lower respiratory illness, will be assessed clinically for the presence of LRTI and for RSV by central laboratory diagnostic testing of respiratory secretions. Testing for RSV will be performed using the US FDA-cleared and CE-marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + hMPV assay; Quidel Corporation, San Diego, CA, www.quidel.com). A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by the central laboratory RT-PCR assay.

In addition to the clinical assessment of LRTI, there is a protocol definition using objective criteria for the determination of a medically attended protocol-defined RSV LRTI. To meet the protocol-defined endpoint of medically attended RSV LRTI, subjects with signs of LRTI must have documented at least one physical exam finding of rhonchi, rales, crackles, or wheeze AND at least one of the following clinical signs:

- Increased respiratory rate at rest (age: < 2 months, ≥ 60 breaths/min; 2 to 6 months, ≥ 50 breaths/min; > 6 months, ≥ 40 breaths/min), OR
- Hypoxemia (in room air: oxygen saturation < 95% at altitudes ≤ 1,800 meters or < 92% at altitudes > 1,800 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 IV fluid).

Table 6 Criteria for Meeting the Protocol-defined Endpoint of Medically Attended RSV LRTI

RSV	Lower Respiratory Tract	Medical Significance
RSV Confirmed: • Positive by central laboratory RT-PCR assay	**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 due to respiratory distress

LRTI = lower respiratory tract infection; PE = physical examination; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction.
Note: One item from each column is required to meet the protocol-defined endpoint of RSV LRTI.

RSV Hospitalization

An RSV hospitalization is defined as either (1) a respiratory hospitalization with a positive RSV test within approximately 2 days of hospital admission (primary) or (2) a new onset of respiratory symptoms in an already hospitalized subject, 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 approximately 2 days before or after admission for subjects hospitalized for respiratory infection (upper or lower respiratory tract). If the RSV diagnostic test (performed centrally via RT-PCR) is positive, the hospitalization will be classified as a primary RSV hospitalization. Deaths that 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

Subjects 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 approximately 2 days from worsening of respiratory status for RSV diagnostic testing by the central laboratory. For any subject who is hospitalized for a respiratory infection (upper or lower respiratory tract), the subject 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 diagnostic 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 diagnostic test.

RSV LRTI Outpatient Events

Subjects who seek outpatient medical attention, including ER and urgent care visits, for an LRTI should have respiratory secretions obtained within approximately 2 days after the initial healthcare provider assessment.

Respiratory Secretions for RSV Detection

Respiratory secretions for RSV testing must be collected from all subjects with LRTIs (inpatient or outpatient) and from all hospitalized subjects with any new respiratory infection (upper or lower) within approximately 2 days after the initial healthcare provider assessment and diagnosis. Nasal secretions will be obtained unless the subject is intubated, and then tracheal secretions may be obtained.

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

Monitoring for RSV Resistance

As an exploratory endpoint, novel RSV F variants identified in RSV positive nasal specimens collected from study subjects will be evaluated by genotypic and phenotypic methods to monitor potential susceptibility changes to MEDI8897 neutralization. The subtype and genotypic determination 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 RT-PCR assay manufactured by Quidel Corporation (Lyra RSV + hMPV assay; Quidel Corporation, San Diego CA, www.quidel.com).The full-length F gene 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 (amino acid [aa] 62-69 and aa 196-212) and outside the binding site in the extracellular regions of mature F protein (aa 24-109 and aa 137-524), including the palivizumab binding site (aa 267-275), will be reported and compared to F protein sequences of contemporary reference RSV strains. In vitro phenotypic analysis (susceptibility to MEDI8897 and palivizumab neutralization) will be attempted using an RSV neutralization assay with either RSV viruses constructed through site-directed mutagenesis of the F gene and reverse genetics..

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 the day of dosing and during the follow-up period as defined in Section 4.2. Assessment 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 physical examination will be performed at screening, on the day of dosing, and during the follow-up period as defined in Section 4.2. 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, on the day of dosing, and during the follow-up period as defined in Section 4.2. On Day 1, vital signs will be monitored before and after administration of investigational product.

Baseline information will be collected on breastfeeding, smoking in the household, and if the infant attends day care.

4.3.3 Pharmacokinetics, Anti-drug Antibody, and RSV Serology

A blood sample for assessment of PK, ADA, RSV neutralizing antibody, and RSV serology will be collected through Day 361 according to the schedule defined in Section 4.2. 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.

4.3.3.1 Pharmacokinetic Evaluation

Blood samples to evaluate the PK of MEDI8897 in serum will be collected according to scheduled time points. Blood samples for PK evaluation will also be collected from subjects hospitalized with LRTI or any respiratory infection within approximately 2 days following hospitalization. See the collection schedule in Section 4.2. The concentration of MEDI8897 in serum will be measured using validated assays.

4.3.3.2 Anti-drug Antibody Evaluation

Blood samples to evaluate ADA responses to MEDI8897 in serum will be collected according to scheduled time points. Blood samples will also be collected for ADA response from subjects hospitalized with LRTI or any respiratory infection within approximately 2 days following hospitalization. See the collection schedule in Section 4.2. Evaluations will be performed using validated immunoassays.

4.3.3.3 RSV Neutralizing Antibody Evaluation

Blood samples to measure RSV neutralizing antibody levels in serum will be collected according to scheduled time points. Blood samples will also be collected for measuring RSV neutralizing antibody levels from subjects hospitalized with LRTI or any respiratory infection within approximately 2 days following hospitalization. See the collection schedule in Section 4.2. Analyses will be performed using an RSV neutralizing antibody assay previously described (Shambaugh et al, 2017).

4.3.3.4 RSV Serology Evaluation

Blood samples to measure RSV antigen-specific antibody levels in serum will be collected according to scheduled time points. Blood samples will also be collected for measuring RSV antigen-specific antibody levels from subjects hospitalized with LRTI or any respiratory infection within approximately 2 days following hospitalization. See the collection schedule in Section 4.2. Analyses will be performed using an updated version of an assay previously described (Maifeld et al, 2016).

4.3.4 Healthcare Resource Utilization and Caregiver Burden

Information on HRU and caregiver burden will be collected for all events of medically attended LRTI through Day 361 (see Table 5). This will include admission to and duration of hospital and intensive care unit 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.

4.3.5 Skin Reactions

Skin reaction assessment will be done for any post-dosing skin or skin-related reaction through Day 361 to assist in determination of the etiology of the reaction (see Table 5). Information will be collected regardless of event severity, duration, time of onset post dosing, or relationship to investigational product. Parents/legal representatives of study subjects will be given a hypersensitivity card and instructed to call the study site immediately for signs of hypersensitivity or allergic reaction. Sites must notify MedImmune within 24 hours of knowledge of such events. For any skin or skin-related reactions, including all rashes that

occur within 7 days after dosing, the infant will be brought to the study site as soon as possible for evaluation.

4.3.6 Estimate of Volume of Blood to be Collected

Blood volume estimates are provided in Table 7 by visit/study day.

Table 7 Volume of Blood to be Collected

Visit/Study Day	Estimated Blood Volume (mL)
Visit 1/Screening or Visit 2/Day 1	1.5 mL
Visit 4/Day 31	1.5 mL
Visit 6/Day 151	1.5 mL
Visit 7/Day 361	1.5 mL
Total	6.0 mL

4.4 Study Suspension or Termination

MedImmune reserves the right to temporarily suspend or permanently terminate this study at any time. The reasons for temporarily suspending or permanently 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 B 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 Common Terminology Criteria for Adverse Events (NCI CTCAE) grading scale that are assessed as related to MEDI8897 in 2 or more subjects
4 Two serious adverse events (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 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 Products

MedImmune will provide the investigator(s) with investigational product (Table 8) using designated distribution centers.

Table 8 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI8897	MedImmune	Supplied as 50 mg (nominal) per vial solution. The solution contains 100 mg/mL MEDI8897, [redacted] The nominal fill volume is 0.5 mL.
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 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 Inspection

Each vial selected for dose administration should be inspected. Refer to Table 8 for identification of investigational product.

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 4.5.1.5) for further instructions.

4.5.1.2 Dose Administration Steps

No incompatibilities between MEDI8897 and 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 A dose of 50 mg (ie, 0.5 mL) of MEDI8897 will be obtained by withdrawing the entire contents of 1 investigational vial with an appropriately sized syringe.
2 A dose of 100 mg (ie, 1.0 mL) of MEDI8897 will be obtained by withdrawing the entire contents of 2 investigational vials with an appropriately sized syringe.
3 For subjects randomized to placebo, a corresponding volume of placebo (0.5 mL for infants < 5 kg or 1.0 mL for infants ≥ 5 kg) should be administered.
4 Switch the needle prior to administration.
5 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.

4.5.1.3 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.

4.5.1.4 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, and 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.

4.5.1.5 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: [redacted]

Phone: [redacted]

Mail: MedImmune
Attn: Product Complaint Department
[redacted]
Gaithersburg, MD USA 20878

4.5.2 Additional Study Medications

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

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice 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 MEDI8897 (N = 2,000) or placebo (N = 1,000). Randomization will be stratified by hemisphere (NH and SH) and by subject age at the time of randomization (ie, ≤ 3 months, > 3 to ≤ 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 manager must be notified immediately.

4.6.2 Methods to Ensure 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 the investigator or any of the site staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (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.

Details of maintaining the double-blind setting until database lock for the primary and safety analyses are provided in Section 4.8.1.

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.

4.7 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 OTC 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 OTC products, without first consulting with the investigator.

4.8 Statistical Evaluation

4.8.1 General Considerations

There will be 2 study cohorts: a primary cohort and a safety cohort. The primary cohort will include subjects from the NH2019, SH2020, and NH2020 enrollment seasons (enrollment was paused after one subject from the NH2020 was enrolled due to the impact of the COVID-19 pandemic). The safety cohort will include subjects enrolled after the NH2020 enrollment season.

There are 3 planned analyses for this study: the primary analysis, safety analysis, and final analysis. The primary analysis will be conducted after all randomized subjects (except for one subject enrolled in the NH2020 season) from the primary cohort have been followed through Day 361 and will be the primary analysis for which the study is designed to assess efficacy. For the primary analysis, all efficacy, PK, ADA, and safety data collected for the primary cohort through at least Day 361 will be analyzed. The safety analysis will be conducted when all subjects from the safety cohort have been followed through Day 151. For the safety analysis, in addition to the analyses conducted during the primary analysis based on the primary cohort, all available efficacy, PK, ADA, RSV neutralizing antibody, RSV serology, and safety data collected for the safety cohort will be analyzed (only descriptive summaries will be provided for the efficacy data collected for the safety cohort). The final analysis will be conducted when all subjects have completed the last visit of the study (ie, Day 511). Given the largely reduced circulation of RSV due to the COVID-19 pandemic related measures, the efficacy analyses performed in the primary analysis for the primary cohort will serve the purpose of evaluating the efficacy of MEDI8897 in the study population. Although efficacy data will also be collected for the safety cohort, only descriptive summaries will be provided and there is no intent to pool the efficacy data from the safety cohort with that from the primary cohort. Both the primary and the safety cohorts, individually and combined, will serve the purpose of evaluating the safety of MEDI8897.

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 (SAP).

The Intent-to-treat (ITT) Population will include all subjects who are randomized. In this population, data will be analyzed according to the randomized treatment. All analyses, with the exception of safety, will be performed on the ITT Population unless otherwise specified. Subjects in the ITT Population and from the primary cohort will be ITT Population 1 (ITT1). Subjects in the ITT Population and from the safety cohort will be ITT Population 2 (ITT2).

The As-treated Population will include all subjects who are randomized and who receive any amount of investigational product. In this population, data will be analyzed according to the

treatment actually received. All safety analyses will be performed on the As-treated Population. Subjects in the As-treated Population and from the primary cohort will be As-treated Population 1 (AT1). Subjects in the As-treated Population and from the safety cohort will be As-treated Population 2 (AT2).

The Per-protocol Population will include subjects in the ITT Population who receive the correct dose of randomized treatment and who do not have a serious protocol violation. Detailed criteria defining this population will be determined and documented prior to performing the primary analysis.

The study will maintain a double-blind setting (ie, blind for subjects, Investigators/site staff, and Sponsor/designated clinical research organization) until database lock for the primary and safety analyses. More specifically, at the time of the primary analysis (where the analyses will be based only on the primary cohort), the data from the primary cohort will be unblinded to the Sponsor/designated clinical research organization associated with the analysis, write-up, and submission. To maintain the double-blind setting for the safety cohort until the safety analysis, any data with potential unblinding risk will be split by primary cohort and safety cohort by the corresponding third party data vendors and when the primary database lock occurs, no potential unblinded information will be transferred from subjects not in the primary cohort. The unblinded data from the safety cohort will not be transferred to the Sponsor until the database lock for safety analysis occurs. The site personnel, subjects, and the study team members involved in advice or decisions involving study subjects and/or day-to-day interactions with the site will remain blinded until the end of the study (ie, all subjects have completed the Day 511 visit) to ensure the trial integrity is maintained. Further details will be specified in the unblinding plan prior to unblinding of the primary cohort data.

4.8.2 Sample Size

This Phase 3 study will enroll approximately 3,000 subjects of whom approximately 2,000 will receive MEDI8897 and 1,000 will receive placebo. The 2,000 subjects to be dosed with MEDI8897 in this study, together with the 968 subjects dosed with MEDI8897 in the Phase 2b Study D5290C00003 and at least 600 subjects dosed with MEDI8897 in the palivizumab-controlled Phase 2/3 Study D5290C00005, will contribute to a safety database of at least approximately 3,600 subjects exposed to MEDI8897.

For this Phase 3 study, the original sample size of 3,000 was driven by the safety database requirement, and the study had at least 99% power for the primary endpoint. Reducing the sample size to 1,500 still allows the study to be sufficiently powered. More specifically, the sample size of approximately 1,500 subjects in the primary cohort has at least 99% power to detect 70% RRR, assuming a placebo group medically attended RSV LRTI incidence of 8%, with a 2-sided $\alpha = 0.05$. The assumption of 8% incidence is supported both by literature

(Paramore et al, 2010) and the observed placebo incidence rate (9.6%) in the Phase 2b Study D5290C00003.

The 70% RRR assumption is based on the Phase 2b Study D5290C00003 in which there was 70% RRR in the incidence of medically attended RSV LRTI (9.5% placebo, 2.6% MEDI8897; $p < 0.001$) and [redacted] RRR in the incidence of RSV hospitalization (4.1% placebo, 0.8% MEDI8897; $p < 0.001$) in subjects who received MEDI8897 prophylaxis (see Section 1.4.3). In addition, the assumption is supported by a placebo-controlled study in Native American term infants in which there was a [redacted] in infants who received motavizumab prophylaxis (O'Brien et al, 2015). In the event that the incidence rate in the placebo group drops due to the impact of the COVID-19 pandemic (eg, social distancing), the sample size of 1,500 still provides at least 90% power to detect 70% RRR if the placebo incidence rate is 4% or higher.

To evaluate risk, a sample size of 2,000 subjects exposed to MEDI8897 in this Phase 3 study will provide a > 99% probability of observing at least one AE if the true event rate is 0.3%; if no AEs are observed, this study provides 98% confidence that the true event rate is < 0.2%.

4.8.3 Efficacy

The primary and secondary efficacy hypotheses will be assessed in the primary analysis for the primary cohort 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. More specifically, after the significance of the primary efficacy endpoint is demonstrated, the secondary efficacy endpoint will first be tested from pooling all ITT subjects from the Phase 2b Study D5290C00003 and ITT1 in the Phase 3 Study D5290C00004. If the significance of the pooled efficacy based on pooling all subjects from Phase 2b and Phase 3 is demonstrated (at 2-sided 0.05), the secondary efficacy endpoint will be further tested from pooling the 860 subjects weighing < 5 kg on Day 1 (ie, 290 subjects randomized to placebo and 570 subjects randomized to MEDI8897) in the Phase 2b Study D5290C00003 and ITT1 subjects in the Phase 3 Study D5290C00004. If the significance of the pooled efficacy based on pooling the subjects weighing < 5 kg from Phase 2b and Phase 3 ITT1 subjects is again demonstrated (at 2-sided 0.05), the secondary efficacy endpoint will be tested using ITT1 subjects from this Phase 3 study alone. 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 primary endpoint is the incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose. For subjects with multiple events, only the first

occurrence will be used in the primary analysis. The determination of medically attended RSV LRTI will be based on RSV test results (performed centrally using RT-PCR) and objective clinical LRTI criteria.

The primary efficacy analysis of the primary endpoint will be performed on ITT1 using a Poisson regression model with robust variance (Zou, 2004). The model contains the term of treatment group and age group at randomization (ie, age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months) and dichotomous temperate hemispheres (NH and SH) as covariates. The RRR, defined as 1- Relative Risk, and its corresponding 2-sided 95% CI, will be estimated from the model. In addition, the 2-sided p-value testing null hypothesis that the incidence of medically attended RSV LRTI between MEDI8897 and placebo groups are the same will be obtained from the model. Statistical significance will be achieved if the 2-sided p-value is ≤ 0.05.

During blinded data review prior to database lock for the primary analysis, it was revealed that there was no incidence of medically attended RSV LRTI events through 150 days post dose for SH in the primary cohort, which would cause a known convergence or estimation issue. Therefore, it was decided to drop the stratification factor hemisphere from the full model and a reduced model (including the term of treatment group and age at randomization stratum as covariate) will be used instead. Similar consideration also applies to other analyses for the primary efficacy endpoint, where hemisphere will be dropped from the corresponding models.

RSV LRTI that occurs through 150 days post dose will contribute to the primary efficacy analysis. For subjects who do not have a medically attended RSV LRTI and are not followed through 150 days post dose, their event status will be imputed assuming the observed placebo RSV LRTI rate conditional on stratification factor (age at randomization) using multiple imputation techniques and will be described in the SAP.

If convergence cannot be achieved using the Poisson regression analysis model, the stratified Cochran-Mantel-Haenszel (CMH) test (detailed in Section 4.8.3.2) will be used as the primary analysis model.

The above described analysis on the primary efficacy endpoint will also be conducted on the Per-protocol Population.

4.8.3.2 Additional Analyses of the Primary Endpoint

The additional analyses of the primary endpoint will be conducted on ITT1. To allow for differences in follow-up time, the primary analysis using a Poisson Regression with robust variance will be repeated, adjusting for the same covariates as well as log (follow-up time) as an offset. Since the follow-up time is adjusted in the model, there is no missing imputation for this analysis.

A CMH test stratified by age at randomization (ie, ≤ 3 months, > 3 to ≤ 6 months, > 6 months) will be used to compare between treatment groups through 150 days post dose as the key secondary analysis for the primary endpoint. The RRR and its associated 95% CI will be provided. This analysis will be performed without imputation. The Breslow-Day test and Zelen's exact test will be used to test the homogeneity of the odds ratios across strata and the corresponding p-values will be presented.

In addition, a Kaplan-Meier curve for time to first medically attended RSV LRTI will be generated based on observed events. Treatment group differences in time-to-first medically attended RSV LRTI will be compared using the stratified log-rank test with the stratification factor (age at randomization) as the strata.

Additional analyses, including summaries for age at onset of the first medically attended RSV LRTI, inpatient/outpatient visit settings, and RSV subtypes associated with the primary endpoint will be provided.

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

Additional sensitivity analyses will be conducted on ITT1 to assess the robustness of the efficacy results with regard to the impact of the COVID-19 pandemic.

4.8.3.3 Supplementary Analyses of the Primary Endpoint

The supplementary analyses of the primary endpoint will be conducted on ITT1. To evaluate the impact of the missing data on the primary analyses, the following supplementary analyses will be conducted. For subjects who do not have an RSV LRTI and are not followed through 150 days post dose:

1 Count these subjects as having not met the RSV LRTI endpoint within each treatment group
2 Perform multiple imputation using the observed event rate per treatment group for their event status
3 Perform single imputation using observed placebo rate for both groups

The details of the supplementary analyses will be described in the Statistical Analysis Plan.

4.8.3.4 Subgroup Analyses of the Primary Endpoint

Subgroup analysis will be performed for the primary efficacy endpoint, the incidence of medically attended RSV LRTI. Treatment-by-subgroup interaction will be tested using the Poisson regression with robust variance model with the terms of treatment, age group, subgroup, and treatment-by-subgroup interaction. If this full model does not achieve convergence, a reduced model of treatment, subgroup, and treatment-by-subgroup interaction

will be used. Significant treatment-by-subgroup interaction is judged at the significance level of 0.10. Within each level of a subgroup, the RRR and its corresponding 95% CI will be estimated using a Poisson regression model with robust variance with the term of treatment. A forest plot of the RRR and the 95% CI will be presented. In the event that the Poisson regression model does not converge for any stratum of a subgroup, the exact conditional method based on the number of RSV LRTIs (Breslow and Day, 1987) will be used as the analytical model to generate the RRR and its corresponding CI for all subgroup strata.

The subgroup analysis will be conducted for the following subgroups on ITT1:

- Hemisphere
- Age at randomization stratum (age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months)
- Gender
- Race (Caucasian, non-Caucasian)
- Weight at birth (weight ≤ 2.5 kg, weight > 2.5 kg)
- Weight on Day 1 (weight < 5 kg, weight ≥ 5 kg)
- Sibling also participating in the study (yes/no)

In addition, incidence of medically attended RSV LRTI will be summarized by country on ITT1.

4.8.3.5 Secondary Efficacy Analyses

The secondary efficacy endpoint is the incidence of RSV LRTI hospitalization through 150 days post dose. For subjects with multiple RSV LRTI hospitalizations, only the first occurrence will be used in the analysis.

For the pooled analysis, a Poisson regression model with robust variance (Zou, 2004) will be used to assess the treatment effect on the incidence of RSV LRTI hospitalization between MEDI8897 and placebo groups in the pooled ITT population, which includes all ITT subjects from Study D5290C00003 and ITT1 subjects from Study D52090C00004. In addition to the treatment arm, the variable “Study” (which identifies the enrolled study for each subject) will be used as a covariate to adjust for differences between the 2 studies. RRR and its corresponding 95% CI will be estimated from the model. RSV LRTI hospitalization that occurs through 150 days post dose will contribute to the analysis. For subjects who do not have an RSV LRTI and were not followed through 150 days post dose, their event status will be imputed using the observed placebo RSV LRTI hospitalization rate following the repeated imputation procedure conditional on study.

For the analysis using the primary cohort of Phase 3 data alone, a Poisson regression model with robust variance (Zou, 2004) using only the treatment term will be used to assess the treatment effect on the incidence of RSV LRTI hospitalization between MEDI8897 and

placebo groups in ITT1. RRR and its corresponding 95% CI will be estimated from the model. RSV LRTI hospitalization that occurs through 150 days post dose will contribute to the analysis. For subjects who do not have an RSV LRTI and were not followed through 150 days post dose, their event status will be imputed using the observed placebo RSV LRTI hospitalization rate following the repeated imputation procedure without involvement of stratification factors.

The additional analyses, including the CMH test stratified by study (for the pooled population) or the CMH test with the only term of treatment (for subjects from Phase 3 alone) for the incidence of RSV LRTI hospitalization, and the Kaplan-Meier for time-to-first RSV LRTI hospitalization will be conducted on ITT1. Treatment group differences in time-to-first RSV LRTI hospitalization will be compared using log-rank test.

In addition, age at onset of the first medically attended RSV LRTI hospitalization through 150 days post dose will be analyzed similar to that for the primary endpoint. Summary of incidence of RSV LRTI hospitalization by subgroup will also be provided. These analyses will be conducted on ITT1.

4.8.3.6 Additional Efficacy Analyses for the Safety Cohort

Additional efficacy summaries on ITT2 will be produced.

The incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose will be summarized by treatment group using ITT2. For subjects with multiple medically attended RSV LRTI events, only the first occurrence will be used in the summary.

The incidence of RSV hospitalization through 150 days after dosing will be summarized by treatment group using ITT2.

Additional analyses, including summaries for age at onset of the first medically attended RSV LRTI, inpatient/outpatient visit settings, and RSV subtypes associated with the incidence of medically attended RSV LRTI through 150 days post dose will be provided.

Details of the efficacy analyses for the safety cohort will be provided in the SAP.

4.8.4 Safety

Safety analyses will be conducted for the overall As-treated Population, AT1, and AT2. Safety of MEDI8897 will primarily be assessed and measured by the occurrence of all TEAEs and TESAEs. AEs will be graded according to the current version of the NCI CTCAE where applicable for pediatric assessments. AEs will be coded by MedDRA system organ class and preferred term. Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. The

type, incidence, severity, and relationship to study investigational product will be summarized by treatment group. In addition, summaries of deaths and SAEs will be provided. 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

4.8.5 Analysis of Pharmacokinetics and Anti-drug Antibody

4.8.5.1 Pharmacokinetic Analysis

Following a single dose of MEDI8897, individual MEDI8897 serum concentration data will be tabulated by treatment group along with descriptive statistics. PK parameters, eg, C_{max}, AUC, apparent clearance, and $t_{1/2}$, will be estimated using non-compartmental analysis, if data permit.

4.8.5.2 Anti-drug Antibody Analysis

The incidence of ADA to MEDI8897 will be assessed and summarized by number and percentage of subjects who are ADA positive by treatment group. The ADA titer will be listed by subject at different time points. The impact of ADA on PK, efficacy, and association with TEAEs and TESAEs, will be assessed. The summaries will be conducted on the overall As-treated Population, AT1, and AT2, unless specified otherwise.

4.8.6 Exploratory Analysis

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 with non-protocol defined LRTIs, which may be further broken down by RSV status. Summaries of the magnitude of HRU will be conducted on ITT1 and ITT2 (if data permit).

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 on ITT1 and ITT2 (if data permit).

RSV seroresponses will be evaluated as a measure of "RSV exposure" in the placebo and MEDI8897 groups.

RSV neutralizing antibody levels afforded by MEDI8897 will be compared to maternal RSV neutralizing antibody levels and those elicited following infection in the placebo group.

RSV genotypic analysis will report the sequence changes in the mature F protein from all RSV positive isolates compared to contemporary RSV A and RSV B reference strains. Susceptibility of novel RSV variants to MEDI8897 will be tested and compared to control viruses.

The incidence of medically attended RSV LRTI (inpatient and outpatient) from Day 152 to Day 361 will be based on RSV test results (performed centrally via RT-PCR) and objective clinical LRTI criteria and will be summarized by treatment group on ITT1 and ITT2.

4.8.7 Data Monitoring Committee

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

4.8.8 Interim Analysis

No interim analyses are planned.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

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

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time even if no study treatment has been administered.

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

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- 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 ER or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations

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 MedImmune. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

5.3.1 Hypersensitivity, Including Anaphylaxis

Administration of polyclonal immunoglobulin preparations and mAbs has been associated with immediate (type I) hypersensitivity (including anaphylaxis) that occurs during or after dosing. An immediate 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 B. 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

An 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, 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

AEs, 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 Sections 5.2 and 5.6), or is an AESI or NOCD (see Sections 5.3, 5.4, and 5.7) and therefore requires immediate notification to the sponsor. See Appendix A for guidelines for assessment of AE severity and relationship to investigational product. 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 an SAE.

5.5.1 Time Period for Collection of Adverse Events

AEs and SAEs will be collected from the time of signature of informed consent through Day 361.

All AESIs and NOCDs will be collected from the time of dosing through Day 361.

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.

5.5.3 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as follows:

- Deaths with an unknown cause should always be reported as an SAE. A post-mortem (autopsy) may be helpful in the assessment of the cause of death, and if performed a copy

of the post-mortem results should be forwarded to MedImmune representative(s) within the usual timeframes (refer to Section 5.6 for additional information).

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 ie, 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 AEs 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 an 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 Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for a MedImmune study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human- or process-related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not stored as instructed, eg, kept at room temperature when it should be in the refrigerator
- Wrong subject received the medication (excluding IWRS errors)
- Wrong drug administered to subject (excluding IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Accidental overdose (will be captured as an overdose)

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate MedImmune representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated MedImmune representative works with the investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 5.6) and within 30 days for all other medication errors. Medication errors should be reported using a Medication Error Report Form.

5.7.3 Adverse Events of Special Interest

5.7.3.1 Hypersensitivity, Including Anaphylaxis

Events of immediate (type I) hypersensitivity, including anaphylaxis (as defined in Appendix B), 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 immediate hypersensitivity include urticaria, pruritus, 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.

5.7.3.2 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).

5.7.3.3 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).

5.7.4 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 protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

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

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

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular 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 center needs information and advice about the study conduct.

6.2.1 Source Data

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

6.2.2 Study Agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this protocol and the Clinical Study Agreement, the terms of 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 their 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 or other party according to the Data Management Plan.

An EDC system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF 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 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the trial, eg, demographic information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc. will only be collected with the subject's informed consent. The informed consent form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation.

7.2 Ethics and Regulatory Review

The IRB/IEC responsible for each site must review and approve the final study protocol, including the final version of the informed consent form and any other written information and/or materials to be provided to the subjects. The IRB/IEC must also approve all advertising used to recruit subjects for the study. The investigator is responsible for submitting these documents to the applicable IRB/IEC, and distributing them to the study site staff.

The opinion of the IRB/IEC must be given in writing. The investigator must provide a copy of the written approval to MedImmune before enrollment of any subject into the study.

MedImmune should approve any substantive modifications to the informed consent form that are needed to meet local requirements.

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

Before the study is initiated, MedImmune will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required. MedImmune will provide safety updates/reports according to local requirements, including suspected

unexpected serious adverse reactions where relevant, to regulatory authorities, IRB/IEC, and principal investigators.

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

7.3 Informed Consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by ICH/GCP. MedImmune will develop a core informed consent form for use by all investigators in the clinical study. MedImmune must approve any modifications to the informed consent form that are needed to meet local requirements.

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 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 informed consent form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed informed consent form is given to the subject'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 informed consent form that is approved by an IRB/IEC

7.4 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the investigators and MedImmune. Any changes must be documented in a study protocol amendment.

For a substantial change to the protocol, MedImmune will distribute amended versions of the protocol to the Principle Investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (see Section 7.2) and reviewed as per local regulatory authority requirements. The IRB/IEC must also approve revisions to the informed consent form,

advertising, and any other written information and/or materials resulting from the change to the protocol.

Any non-substantial changes will be communicated to or approved by each IRB/IEC.

7.5 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to 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.

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Appendix A Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an ER is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an ER or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization

Assessment of Severity

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

Grade 1	An event of mild intensity 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	An event of moderate intensity 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	A severe 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	An event, and/or its immediate sequelae, that is associated with an imminent risk of death.
Grade 5	Death as a result of an event.

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

Assessment of Relationship

A guide to Interpreting the Causality Question

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational product.

- Time Course. Exposure to suspect investigational product. Has the subject actually received the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology) or products of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? MedImmune would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes non-TESAEs (ie, SAEs that occur prior to the administration of investigational product) as well as TESAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). 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 B National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-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;117:391-7.

National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network 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

SIGNATURE PAGE

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