A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children (MEDLEY)

Sponsor Protocol Number:	D5290C00005
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:	[redacted]
Protocol History, Date:	Original Protocol, 05Apr2019 Protocol Amendment 1, 31Mar2021

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 1 (31Mar2021)

Overall Rationale for the Amendment

The principal reason for this amendment was to update the sample size for target enrollment, introduce a primary analysis and Season 2 analysis to allow earlier assessment of Season 1 and Season 2 data, respectively, and add a description about the process to safeguard the blind.

Section	Description of Change	Brief Rationale
Title Page	Updated the medical monitor information	Change in medical monitor for this study
Synopsis, 1.7 Research Hypotheses, 4.8.2 Sample Size	Removed hypotheses section with clarification	The study is descriptive by design and there is no formal hypothesis testing, therefore the hypotheses section was removed to avoid potential confusion. Also added a clarification/rationale to describe why formal hypothesis testing for efficacy is not feasible.
Synopsis, 3.1.1 Overview, 4.1.1 Number of Subjects, 4.8.2 Sample Size, 4.8.4 Efficacy	Updated the sample size	Given the challenge of study enrollment due to the COVID-19 pandemic, the sample size was reduced from originally planned in the protocol.
Synopsis, 4.8 Statistical Evaluation	Added primary analysis and Season 2 analysis	To allow earlier assessment of Season 1 and Season 2 data
Synopsis, 4.8.4 Efficacy	Removed side-by-side efficacy summaries for 2 consecutive seasons	As the incidence of medically attended RSV LRTI and RSV hospitalization (and the relevant HRU) are expected to be lower in Season 2 (infant's second RSV season) than that in Season 1, combining the events from Season 1 and Season 2 may not confer value in addition to the individual summary for each season
Synopsis, 4.8.6.3 Healthcare Resource Utilization and Caregiver Burden	Summarized HRU overall and for subjects with at least 1 one medically attended RSV LRTI (protocol defined); other subgroups were removed	To focus HRU and caregiver burden summaries on the most important efficacy events, which are medically attended RSV LRTIs (protocol defined), especially given that COVID-19 pandemic has a high impact on the number of RSV and non-RSV LRTIs
4.5.1.4 Reporting Product Complaints	Removed the fax number and the +1-877-MEDI-411 (+1-877-633-4411) phone number	The numbers removed are no longer in use

Section	Description of Change	Brief Rationale
4.8.1 General Considerations	Added description about strategy to maintain the blind	To ensure trial integrity and the blinding of the Season 2 treatment assignment for CLD/CHD subjects who were randomized to the palivizumab arm in Season 1
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

CHD = congenital heart disease; CLD = chronic lung disease; COVID-19 = coronavirus disease 2019; HRU = healthcare resource utilization; LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus.

PROTOCOL SYNOPSIS

TITLE

A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children (MEDLEY)

OBJECTIVES and ASSOCIATED ENDPOINTS

Type	Objective	Endpoint
Primary		
Safety	To evaluate the safety and tolerability of MEDI8897 compared to palivizumab when administered to preterm infants entering their first RSV season and children with CLD or CHD entering their first and second RSV season	Safety and tolerability of MEDI8897 as assessed by the occurrence of all TEAEs, TESAEs, AESIs, and NOCDs
Secondary		
PK	To evaluate serum concentrations of MEDI8897 and palivizumab	• MEDI8897 and palivizumab serum concentrations • MEDI8897 and palivizumab PK parameters: Summary of serum concentrations and estimated PK parameters (C_{max}, AUC, apparent clearance, and $t_{1/2}$, if data permit)
ADA	To evaluate ADA responses to MEDI8897 and to palivizumab in serum	Incidence of ADA to MEDI8897 and palivizumab in serum
Efficacy	To assess the descriptive efficacy of MEDI8897 when administered as a single IM dose of 50 mg to infants < 5 kg or 100 mg to infants ≥ 5 kg in the first RSV season or a single 200-mg IM dose administered in the second RSV season, in reducing medically attended LRTI (inpatient and outpatient) and hospitalization due to RT-PCR-confirmed RSV, compared to palivizumab	• Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after Dose 1 for Season 1 and Season 2 • Incidence of hospitalizations due to RT-PCR-confirmed RSV through 150 days after Dose 1 for Season 1 and Season 2

Type	Objective	Endpoint
Exploratory		
RSV neutralizing antibody	To determine anti-RSV neutralizing antibody levels in serum afforded by a single dose of MEDI8897 compared to 5 monthly doses of palivizumab	• Anti-RSV neutralizing antibody levels (IU/mL) in serum for MEDI8897 recipients compared to palivizumab recipients • Summary of serum RSV neutralizing antibody levels (may include GMT, GMFR, C_{max}, apparent clearance, and $t_{1/2}$)
RSV serology	To evaluate exposure to RSV by measuring seroresponses to different RSV proteins in MEDI8897 and palivizumab recipients	• Antibody levels to RSV F, Ga, Gb, or N at different time points • Changes in RSV antibody levels (seroresponse) indicating exposure to RSV
	To evaluate the levels of maternal RSV-specific antibody in MEDI8897 and palivizumab recipients	• RSV antigen antibody levels (AbU/mL) to multiple RSV antigens • Summary of serum RSV antibody levels (may include GMT, GMFR, seroconversion rates, apparent clearance, and $t_{1/2}$)
HRU and caregiver burden	To assess HRU and caregiver burden for MEDI8897 recipients compared to palivizumab recipients	• 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 type of outpatient visits [eg, ER, urgent care, outpatient clinic]; and number of prescription and OTC medications and duration of use) for MEDI8897 recipients compared to palivizumab recipients • 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 resistance monitoring	To characterize resistance to MEDI8897 and palivizumab through genotypic and phenotypic analyses	Genotypic analysis and susceptibility of RSV variants to neutralization by MEDI8897 and palivizumab
RSV LRTI after Day 151	To assess the incidence of medically attended LRTI due to RT-PCR-confirmed RSV, compared to palivizumab after Day 151	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV from Day 152 to Day 361 for Season 1 and Season 2

AbU/mL = antibody unit per mL; ADA = anti-drug antibody; AESI = adverse event of special interest; AUC = area under the concentration-time curve ; CHD = congenital heart disease; CLD = chronic lung disease; C_{max} = maximum observed concentration; ER = emergency room; GMFR = geometric mean fold-rise; GMT = geometric mean titer; HRU = healthcare resource utilization; ICU = intensive care unit; IM = intramuscular; LRTI = lower respiratory tract infection; NOCD = new onset chronic disease; OTC = over-the-counter; PK = pharmacokinetic; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction; $t_{1/2}$ = terminal half-life; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

STUDY DESIGN

Study D5290C00005 (MEDLEY) is a pivotal Phase 2/3 randomized, double-blind, palivizumab-controlled study to evaluate the safety, PK, ADA response, and descriptive efficacy for MEDI8897 in high-risk infants eligible to receive palivizumab when entering their first or second RSV season (Season 1 or Season 2, respectively). Approximately 900 palivizumab-eligible infants entering their first RSV season will be enrolled into one of 2 cohorts: (1) preterm cohort, including approximately 600 preterm infants (≤ 35 weeks gestational age [GA]) without CLD/CHD, or (2) CLD/CHD cohort, including approximately 300 infants with CLD of prematurity or hemodynamically significant CHD. A minimum of 100 infants with hemodynamically significant CHD will be enrolled. Within each cohort, randomization will be stratified by hemisphere (northern, southern) and subject age at the time of Season 1 randomization (≤ 3 months, > 3 to ≤ 6 months, > 6 months).

Season 1, Preterm and CLD/CHD Cohorts

All subjects will be randomized 2:1 to either the MEDI8897 group (approximately 600 subjects, including approximately 400 subjects in the preterm cohort and approximately 200 subjects in the CLD/CHD cohort) or palivizumab group (approximately 300 subjects, including approximately 200 subjects in the preterm cohort and approximately 100 subjects in the CLD/CHD cohort). Subjects in the MEDI8897 group will receive a single fixed IM dose of MEDI8897 followed by 4 once-monthly IM doses of placebo. The MEDI8897 dose level will be stratified by weight band, ie, 50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg. Subjects in the palivizumab group will receive 5 once-monthly IM doses of 15 mg/kg palivizumab.

Season 2, CLD/CHD Cohort Only

- Subjects with CLD/CHD ≤ 24 months of age who were randomized to the MEDI8897 group for Season 1 will receive a single fixed IM dose of 200 mg MEDI8897 followed by 4 once-monthly IM doses of placebo (approximately 200 subjects).
- Subjects with CLD/CHD ≤ 24 months of age who were randomized to the palivizumab group for Season 1 will be re-randomized 1:1 to either the MEDI8897 group or the palivizumab group. Subjects in the MEDI8897 group will receive a single fixed IM dose of 200 mg MEDI8897 followed by 4 once-monthly IM doses of placebo (approximately 50 subjects). Subjects in the palivizumab group will receive 5 once-monthly IM doses of 15 mg/kg palivizumab (approximately 50 subjects).

In Season 1 or Season 2, subjects in the CLD/CHD cohort who undergo cardiac surgery with cardiopulmonary bypass after receipt of Dose 1 but prior to receipt of Dose 5 will receive a replacement dose of the study drug they received for Dose 1 immediately following the surgery when determined by the physician to be medically stable for an IM injection. Any subsequent doses of study drug will continue to be given according to the protocol-specified dosing schedule.

Subjects in the preterm cohort will be followed through 1 year after Season 1/Dose 1, and subjects in the CLD/CHD cohort will be followed through 1 year after Season 2/Dose 1. Subjects in the CLD/CHD cohort who receive a replacement dose in Season 2 will be followed through 1 year after the last replacement dose.

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 LRTI, including protocol-defined medically attended RSV LRTI. All subjects evaluated for LRTI will have respiratory samples obtained and tested centrally for RSV using the United States Food and Drug Administration-cleared and *Conformité Européenne* or European Conformity-marked in vitro diagnostic real-time RT-PCR assay.

Blood samples will be collected for PK, ADA, and RSV neutralizing antibody and RSV serology.

TARGET SUBJECT POPULATION

Preterm infants entering their first RSV season who are eligible to receive palivizumab, and children with CLD or CHD who are entering their first RSV season and the same children ≤ 24 months of age entering their second RSV season

TREATMENT GROUPS AND REGIMENS

Subjects will be randomly assigned to receive study drug as described in the Study Design section and presented below:

<table>
<tr><th>Cohort</th><th colspan="3">Season 1</th><th colspan="3">Season 2</th></tr>
<tr><td rowspan="4">Preterm
(N = 600)</td><td rowspan="2">MEDI8897
(N = 400)</td><td>Dose 1</td><td>50 mg (if < 5 kg) or
100 mg (if ≥ 5 kg) IM</td><td colspan="3" rowspan="4">Not applicable</td></tr>
<tr><td>Doses 2, 3, 4, 5</td><td>Placebo IM</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Palivizumab
(N = 200)</td><td>Doses 1, 2, 3, 4, 5</td><td>15 mg/kg IM</td></tr>
<tr><td rowspan="5">CLD/CHD
(N = 300</td><td rowspan="2">MEDI8897
(N = 200)</td><td>Dose 1</td><td>50 mg (if < 5 kg) or
100 mg (if ≥ 5 kg) IM</td><td rowspan="2">MEDI8897
(N = 200)</td><td>Dose 1</td><td>200 mg IM</td></tr>
<tr><td>Doses 2, 3, 4, 5</td><td>Placebo IM</td><td>Doses 2, 3, 4, 5</td><td>Placebo IM</td></tr>
<tr><td colspan="6"></td></tr>
<tr><td rowspan="3">Palivizumab
(N = 100)</td><td rowspan="3">Doses 1, 2, 3, 4, 5</td><td rowspan="3">15 mg/kg IM</td><td>MEDI8897
(N = 50)</td><td>Dose 1</td><td>200 mg IM</td></tr>
<tr><td rowspan="2">MEDI8897
(N = 50)</td><td>Doses 2, 3, 4, 5</td><td>Placebo IM</td></tr>
<tr><td>Palivizumab
(N = 50)</td><td>Doses 1, 2, 3, 4, 5</td><td>15 mg/kg IM</td></tr>
</table>

STATISTICAL METHODS

Sample Size: With respect to safety, 600 subjects exposed to MEDI8897 in Season 1 will provide a 95% probability of observing at least 1 adverse event (AE) if the true event rate is 0.5%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.5%. The sample size is for safety consideration.

With respect to efficacy, approximately 600 subjects will be exposed to MEDI8897 and 300 subjects will be exposed to palivizumab in Season 1 to observe numerically similar efficacy for both monoclonal antibodies. Because of the reduced incidence of RSV disease in this population following the introduction of palivizumab, a superiority or non-inferiority design is not practical. A valid non-inferiority margin cannot be established due to the lack of historical efficacy data for the medically attended RSV LRTI endpoint for palivizumab. Therefore, there is no hypothesis testing for efficacy. Using an assumption of a 6% RSV LRTI rate in palivizumab recipients, approximately 18 events will be observed in that group. The 6% RSV LRTI rate (1.9% RSV hospitalizations and 3.9% outpatient RSV illness) was based on a prior study in preterm infants with and without CLD who received palivizumab. Assuming a 6% rate of RSV LRTI in MEDI8897 recipients, 600 MEDI8897 subjects in Season 1 will provide approximately 36 events in that group. However, because of the largely reduced RSV circulation due to COVID-19 pandemic-related measures, the observed event rates could be much lower. Only summaries will be provided for efficacy unless specified otherwise.

Statistical Analyses

There are 3 planned analyses for this study: the primary analysis, Season 2 analysis, and the final analysis. The primary analysis will be conducted after all randomized subjects have completed follow-up through the first 5-month RSV season (ie, Season 1 Day 151 visit) and include all available Season 1 safety, efficacy, PK, and ADA data at the time of the data cutoff. The Season 2 analysis will be conducted after all CLD/CHD subjects have completed follow-up through the second 5-month RSV season (ie, Season 2 Day 151 visit) and include all available Season 1 data and Season 2 safety, efficacy, PK, and ADA data at the time of the data cutoff. The final analysis will be conducted when all subjects have completed the last visit of the study and include all data collected in the study.

Safety: Safety of MEDI8897 will be summarized by treatment group based on the As-treated Population (defined as all subjects who receive any investigational product analyzed according to treatment received) for each season, as well as for the 2 consecutive RSV seasons (ie, Season 1 and Season 2). For the Season 1 summary, the analysis dataset will include subjects from the preterm cohort and CLD/CHD cohort, presented

by the treatment received in Season 1; for the Season 2 summary and the 2 consecutive-season summary, the analysis dataset will include subjects from the CLD/CHD cohort, presented by the treatment received through the 2 seasons.

AEs will be graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events where applicable for pediatric assessments. AEs will be coded by Medical Dictionary for Regulatory Activities and the type, incidence, severity, and relationship to study drug will be summarized by treatment group. Other safety assessments will include the occurrence of AESIs, defined as AEs of hypersensitivity to study drug (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), and NOCDs following study drug administration.

Efficacy: All efficacy summaries will be based on the Intent-to-treat (ITT) Population (defined as all randomized subjects analyzed according to randomized treatment assignment). The incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post Dose 1 (ie, during a typical 5-month RSV season) in Season 1, based on RSV test results (performed centrally using real-time RT-PCR) and objective protocol-defined LRTI criteria, is the primary efficacy endpoint and will be summarized by Season 1 treatment group for all 900 subjects. The 95% confidence interval (CI) of the percentage of subjects meeting the primary efficacy endpoint will be presented by treatment group. In addition, the incidence of RSV LRTI through 150 days post Dose 1 in Season 2 will be summarized for the 300 subjects in the CLD/CHD cohort based on the treatment assignments through Season 1 and Season 2: ie, (a) MEDI8897 (Season 1)/MEDI8897 (Season 2), (b) palivizumab (Season 1)/MEDI8897 (Season 2), and (c) palivizumab (Season 1)/palivizumab (Season 2).

The incidence of RSV hospitalization through 150 days after dosing (ie, during the 5-month RSV season) will be summarized by treatment group using a similar strategy as described for RSV LRTI.

PK: Individual MEDI8897 and palivizumab serum concentration data will be tabulated by treatment group along with descriptive statistics. PK parameters will be estimated using non-compartmental analysis, if data permit.

ADA: The incidence of ADA to MEDI8897 and to palivizumab will be assessed and summarized by number and percentage of subjects who are ADA positive by treatment group. The impact of ADA on PK, and association with TEAEs and TESAEs, will be assessed.

RSV neutralizing antibody: Individual MEDI8897 and palivizumab serum anti-RSV neutralizing antibody levels will be tabulated by treatment group along with descriptive statistics. Anti-RSV neutralizing antibody levels in serum will be summarized by geometric mean titer and geometric mean-fold rise and corresponding 95% CI for each treatment group at each visit. Anti-RSV neutralizing antibody level $t_{1/2}$ will be estimated using non-compartmental analysis, if data permit.

RSV serology: Analysis of anti-RSV antigens antibody levels in serum in MEDI8897 and palivizumab recipients will be summarized by geometric mean titer and geometric mean-fold rise and corresponding 95% CI for each treatment group at each visit. Seroresponses in MEDI8897 and palivizumab recipients will be determined by examining the fold-rise in antibodies to Ga, Gb, and N antigens.

HRU and caregiver burden: The HRU and caregiver burden summaries will be performed on the ITT Population. 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 subjects with at least one medically attended LRTI (protocol defined) caused by RT-PCR-confirmed RSV.

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

Monitoring RSV resistance to MEDI8897 and palivizumab: Genotypic analysis of the full-length mature F protein will be conducted on all RSV-positive isolates confirmed centrally using the Lyra RSV + human metapneumovirus real-time RT-PCR assay manufactured by Quidel Corporation. 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 and palivizumab will be tested and compared to control 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 for Season 1 and Season 2 will be based on RSV test results (performed centrally via RT-PCR) and objective clinical LRTI criteria and will be summarized by treatment group.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

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
ATP	As-treated Population
AUC	area under the concentration-time curve
CE	*Conformité Européenne*
CHD	congenital heart disease
CI	confidence interval
CLD	chronic lung disease
C_{max}	maximum observed concentration
eCRF	electronic case report form
EDC	electronic data capture
ER	emergency room
EU	European Union
F	fusion
GA	gestational age
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
HRU	healthcare resource utilization
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgG1κ	immunoglobulin G1 kappa
IM	intramuscular
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	intravenous
IWRS	interactive web response system

Abbreviation or Specialized Term	Definition
JCVI	Joint Committee on Vaccination and Immunisation
LRTI	lower respiratory tract infection
mAb	monoclonal antibody
MEDLEY	Study D5290C00005
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
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
SID	subject identification
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
UK	United Kingdom
US FDA	United States Food and Drug Administration
USA	United States of America
YTE	M257Y/S259T/T261E [M252Y/S254T/T256E 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 and no approved RSV prophylaxis for the broader population of healthy infants. There are no specific RSV therapeutic options so the current medical management is limited to 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 hemodynamically 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 hemodynamically 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

RSV 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 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 them 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). RSV bronchiolitis was the leading cause of hospital admissions for infants < 1 year of age for any reason between 1997 and 1999 (Leader and Kohlhase, 2002). 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 hospitalization, leading to 59,600 (range, 48,000 to 74,500) in-hospital deaths. 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 of the hospital (Carroll et al, 2008; Hall et al, 2009; Paramore et al, 2010) such that office visits and emergency department visits are more frequent than subsequent hospitalization, especially in healthy infants. The general severity of RSV infection observed among infants in outpatient settings is almost as severe as those observed in hospitalized infants, including labored breathing requiring supplemental oxygen, wheezing, and fever (Hall, 2012). While 95% of children hospitalized with RSV had labored respirations, similar percentages of outpatients were also observed to have labored respirations (85% of children cared for in emergency departments and 73% of children treated in private practice settings (Hall et al, 2009). The outpatient burden and severity of disease accounts for a significant portion of the morbidity associated with RSV in all infants.

Palivizumab is the only approved agent for RSV prophylaxis, and its use is limited to high-risk children. Because of its terminal half-life (t½) of approximately 1 month, infants and young children need to receive monthly intramuscular (IM) doses of palivizumab throughout the typical 5-month RSV season to maintain protection. This constitutes a significant burden on healthcare providers as well as the infants/children and their families. Additionally, many infants who receive palivizumab are unable to comply with the monthly dosing schedule and non-compliance has been shown to result in increased risk of hospitalization (Frogel et al, 2010; Stewart et al, 2013). Furthermore, the cost of palivizumab prophylaxis has led to additional restrictions being implemented by many countries, including the USA (American Academy of Pediatrics, 2014) and the UK (JCVI, 2010a, 2010b).

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 fusion (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 $t_{1/2}$, 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

Toxicity, toxicokinetics, and immunogenicity of MEDI8897 were evaluated in a Good Laboratory Practice-compliant repeat-dose intravenous (IV) and IM toxicology study conducted in cynomolgus monkeys. 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, including a first-time-in-human Phase 1a study in healthy adults (Study D5290C00001), a first-time-in-pediatric Phase 1b/2a study in healthy preterm infants (Study D5290C00002), and a Phase 2b safety and efficacy study in healthy preterm infants (Study D5290C00003). MEDI8897 had a favorable safety profile, with generally similar proportions of treatment-emergent adverse events (TEAEs) reported in the MEDI8897 and placebo-control groups across the 3 studies.

A summary of Study D5290C00003 is presented below. Refer to the current Investigator's Brochure for details on all MEDI8897 clinical studies.

1.4.1 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 treatment-emergent serious adverse events (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%); adverse events of special interest (AESIs), including hypersensitivity, immune complex disease, and thrombocytopenia (MEDI8897 0.5%, placebo 0.6%); and new onset chronic diseases [redacted] 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 ADA on Day 361.

1.5 Rationale for Conducting the Study

Prevention of 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. While RSV prevention exists in the form of a specific RSV IgG (Synagis®, palivizumab) requiring 5 once-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 American Academy of Pediatrics (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 Joint Committee on Vaccination and Immunisation (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). MEDI8897 is being developed as a cost-effective opportunity to protect all infants, including those who currently receive palivizumab, from RSV disease based on improved potency and an extended $t_{1/2}$, which is expected to support once-per-RSV-season dosing.

The MEDI8897 clinical development program includes two pivotal studies for infants entering their first RSV season: the completed Phase 2b study (D5290C00003) and a planned Phase 3 study (D5290C00004 [MELODY]). Because of the significant advantage of one dose per RSV season that MEDI8897 would provide, MedImmune recognizes the potentially important benefits for the current pediatric population receiving palivizumab who must receive monthly injections during the typical 5-month RSV season for protection. Therefore, this Phase 2/3 study is planned to support an indication in the high-risk palivizumab-eligible population entering their first and second RSV seasons to compare the safety, PK, ADA, and efficacy trend of MEDI8897 once-per-RSV-season dosing with palivizumab once-per-month dosing during the RSV season.

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.

See Section 1.4 for a summary of MEDI8897 clinical safety and efficacy. More detailed information about the known and expected benefits and risks of MEDI8897 can be found in the Investigator's Brochure.

1.6.1 Potential Benefit

Palivizumab, the only currently approved RSV prophylaxis, requires 5 once-monthly injections for protection and due to cost is restricted for use only in infants at the greatest risk for morbidity and mortality from RSV. As there is no approved treatment for active RSV infection, the current standard of care for patients with serious RSV illness is supportive care. Thus, there is a significant unmet medical need for RSV prophylaxis in high-risk infants and children. Favorable efficacy and safety data from the Phase 2b Study D5290C00003 in preterm infants who received a single dose of MEDI8897, suggest that MEDI8897 may provide an important alternative and cost-effective option.

1.6.2 Potential Risk

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.

1.6.3 Overall Benefit-Risk

The current study will compare the safety, PK, ADA, and descriptive statistics of MEDI8897 with palivizumab in high-risk preterm infants and children. The single-dose regimen for MEDI8897 vs the 5 once-monthly dosing regimen for palivizumab presents a potentially important and cost-effective treatment option for RSV prophylaxis in this high-risk pediatric population of preterm infants and children up to 2 years of age with CLD or CHD.

The design of the current study aims to minimize the risks to subjects and includes the protocol inclusion and exclusion criteria, restrictions on concomitant medication during the study, safety monitoring (including review of all safety data by the independent data monitoring committee), and study stopping criteria.

Overall, the benefit-risk assessment for this Phase 2/3 study is acceptable.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoint

Table 1 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
Safety	To evaluate the safety and tolerability of MEDI8897 compared to palivizumab when administered to preterm infants entering their first RSV season and children with CLD or CHD entering their first and second RSV season	Safety and tolerability of MEDI8897 as assessed by the occurrence of all TEAEs, TESAEs, AESIs, and NOCDs

AESI = adverse event of special interest; CHD = congenital heart disease; CLD = chronic lung disease; NOCD = new onset chronic disease; RSV = respiratory syncytial virus; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

2.1.1 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
PK	To evaluate serum concentrations of MEDI8897 and palivizumab	• MEDI8897 and palivizumab serum concentrations • MEDI8897 and palivizumab PK parameters: Summary of serum concentrations and estimated PK parameters (C_{max}, AUC, apparent clearance, and $t_{1/2}$, if data permit)
ADA	To evaluate ADA responses to MEDI8897 and to palivizumab in serum	Incidence of ADA to MEDI8897 and palivizumab in serum
Efficacy	To assess the descriptive efficacy of MEDI8897 when administered as a single IM dose of 50 mg to infants < 5 kg or 100 mg to infants ≥ 5 kg in the first RSV season or a single 200-mg IM dose	• Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after Dose 1 for Season 1 and Season 2

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
	administered in the second RSV season, in reducing medically attended LRTI (inpatient and outpatient) and hospitalization due to RT-PCR-confirmed RSV, compared to palivizumab	• Incidence of hospitalizations due to RT-PCR-confirmed RSV through 150 days after Dose 1 for Season 1 and Season 2

ADA = anti-drug antibody; AUC = area under the concentration-time curve; C_{max} = maximum observed concentration; IM = intramuscular; LRTI = lower respiratory tract infection; PK = pharmacokinetic; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction; $t_{1/2}$ = terminal half-life.

2.1.2 Exploratory Objectives and Associated Endpoints

Table 3 Exploratory Objectives and Endpoints

Type	Objective	Endpoint
RSV neutralizing antibody	To determine anti-RSV neutralizing antibody levels in serum afforded by a single dose of MEDI8897 compared to 5 monthly doses of palivizumab	• Anti-RSV neutralizing antibody levels (IU/mL) in serum for MEDI8897 recipients compared to palivizumab recipients • Summary of serum RSV neutralizing antibody levels (may include GMT, GMFR, C_{max}, apparent clearance, and $t_{1/2}$)
RSV serology	To evaluate exposure to RSV by measuring seroresponses to different RSV proteins in MEDI8897 and palivizumab recipients	• Antibody levels to RSV F, Ga, Gb, or N at different time points • Changes in RSV antibody levels (seroresponse) indicating exposure to RSV
	To evaluate the levels of maternal RSV-specific antibody in MEDI8897 and palivizumab recipients	• RSV antigen antibody levels (AbU/mL) to multiple RSV antigens • Summary of serum RSV antibody levels (may include GMT, GMFR, seroconversion rates, apparent clearance, and $t_{1/2}$)
HRU and caregiver burden	To assess HRU and caregiver burden for MEDI8897 recipients compared to palivizumab recipients	• 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 type of outpatient visits [eg, ER, urgent care, outpatient clinic]; and number of prescription and OTC medications and duration of use) for MEDI8897 recipients compared to palivizumab recipients • Caregiver burden (eg, caregiver missed work days, subject absence from day care) for subjects with medically attended LRTI caused by RT-PCR-confirmed RSV

Table 3 Exploratory Objectives and Endpoints

Type	Objective	Endpoint
RSV resistance monitoring	To characterize resistance to MEDI8897 and palivizumab through genotypic and phenotypic analyses	Genotypic analysis and susceptibility of RSV variants to neutralization by MEDI8897 and palivizumab
RSV LRTI after Day 151	To assess the incidence of medically attended LRTI due to RT-PCR-confirmed RSV, compared to palivizumab after Day 151	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV from Day 152 to Day 361 for Season 1 and Season 2

AbU/mL = antibody unit per mL; C_{max} = maximum observed concentration; ER = emergency room; GMFR = geometric mean fold-rise; GMT = geometric mean titer; HRU = healthcare resource utilization; ICU = intensive care unit; LRTI = lower respiratory tract infection; OTC = over-the-counter; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction; $t_{1/2}$ = terminal half-life.

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

Study D5290C00005 (MEDLEY) is a pivotal Phase 2/3 randomized, double-blind, palivizumab-controlled study to evaluate the safety, PK, ADA response, and descriptive efficacy for MEDI8897 in high-risk infants eligible to receive palivizumab when entering their first or second RSV season (Season 1 or Season 2, respectively). Approximately 900 palivizumab-eligible infants entering their first RSV season will be enrolled into one of 2 cohorts (Figure 1): (1) preterm cohort, including approximately 600 preterm infants (≤ 35 weeks GA) without CLD/CHD, or (2) CLD/CHD cohort, including approximately 300 infants with CLD of prematurity or hemodynamically significant CHD. As minimum of 100 infants with hemodynamically significant CHD will be enrolled. Within each cohort, randomization will be stratified by hemisphere (northern, southern) and subject age at the time of Season 1 randomization (≤ 3 months, > 3 to ≤ 6 months, > 6 months).

Season 1, Preterm and CLD/CHD Cohorts

All subjects will be randomized 2:1 to either the MEDI8897 group (approximately 600 subjects, including approximately 400 subjects in the preterm cohort and approximately 200 subjects in the CLD/CHD cohort) or palivizumab group (approximately 300 subjects, including approximately 200 subjects in the preterm cohort and approximately 100 subjects in the CLD/CHD cohort). Subjects in the MEDI8897 group will receive a single fixed IM dose of MEDI8897 followed by 4 once-monthly IM doses of placebo. The MEDI8897 dose level will be stratified by weight band, ie, 50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg. Subjects in the palivizumab group will receive 5 once-monthly IM doses of 15 mg/kg palivizumab.

Season 2, CLD/CHD Cohort Only

- Subjects with CLD/CHD ≤ 24 months of age who were randomized to the MEDI8897 group for Season 1 will receive a single fixed IM dose of 200 mg MEDI8897 followed by 4 once-monthly IM doses of placebo (approximately 200 subjects).
- Subjects with CLD/CHD ≤ 24 months of age who were randomized to the palivizumab group for Season 1 will be re-randomized 1:1 to either the MEDI8897 group or the palivizumab group. Subjects in the MEDI8897 group will receive a single fixed IM dose of 200 mg MEDI8897 followed by 4 once-monthly IM doses of placebo (approximately 50 subjects). Subjects in the palivizumab group will receive 5 once-monthly IM doses of 15 mg/kg palivizumab (approximately 50 subjects).

In Season 1 or Season 2, subjects in the CLD/CHD cohort who undergo cardiac surgery with cardiopulmonary bypass after receipt of Dose 1 but prior to receipt of Dose 5 will receive a replacement dose of the study drug they received for Dose 1 immediately following the surgery when determined by the physician to be medically stable for an IM injection. Any subsequent doses of study drug will continue to be given according to the protocol-specified dosing schedule. See Section 3.1.2.3 for details on replacement dosing.

Subjects in the preterm cohort will be followed through 1 year after Season 1/Dose 1, and subjects in the CLD/CHD cohort will be followed through 1 year after Season 2/Dose 1. Subjects in the CLD/CHD cohort who receive a replacement dose in Season 2 will be followed through 1 year after the last replacement dose.

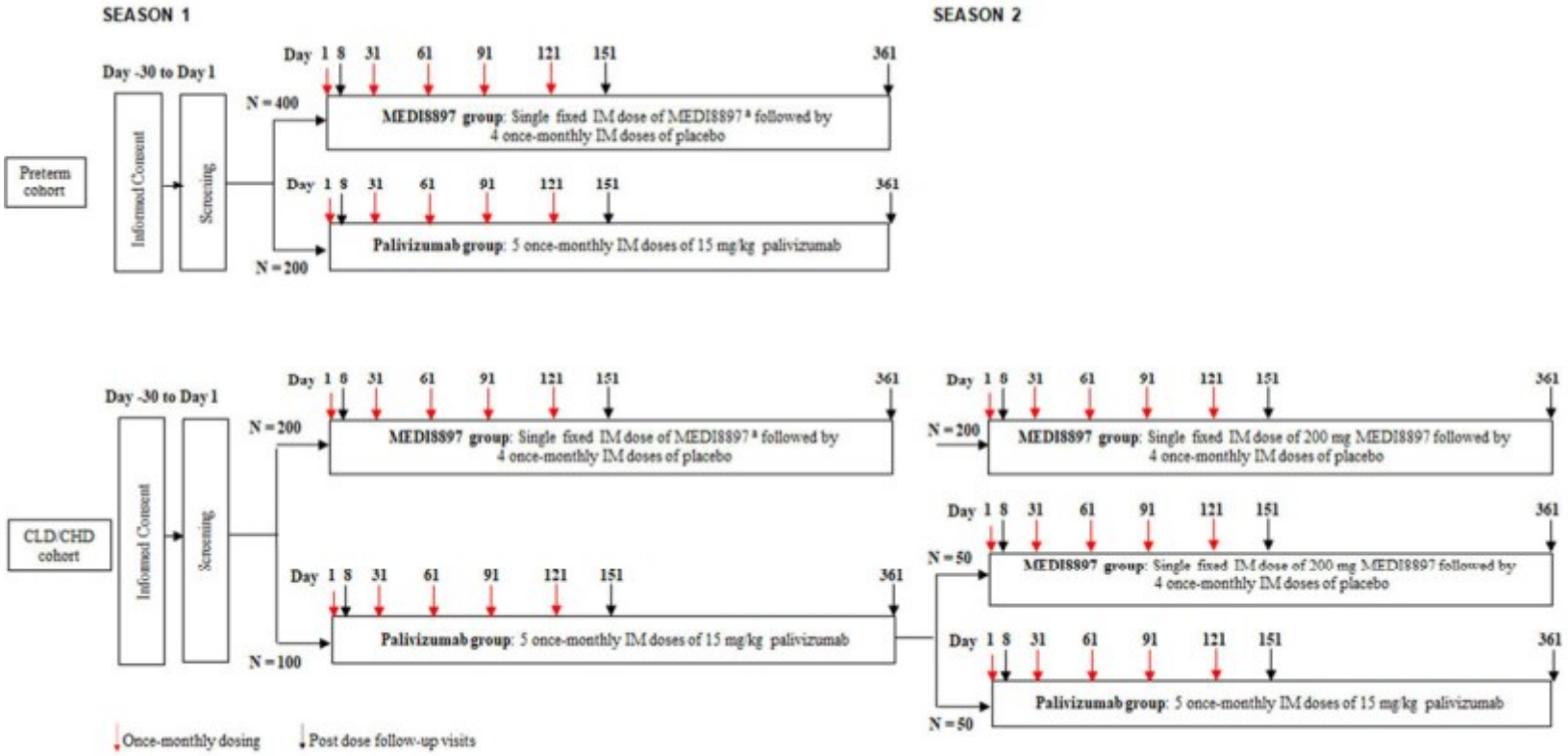
Subjects in the CLD/CHD cohort with a weight < 7 kg at the time of dosing for Season 2 will have increased monitoring of adverse events (AEs). Any SAEs or Grade 3 or Grade 4 AEs that occur in the first month after dosing will be sent to the independent data monitoring committee for immediate review.

Subjects will be monitored throughout the study for LRTI (see Section 4.3.1). All subjects seeking medical attention for a respiratory illness (in either the inpatient or outpatient setting) will be evaluated for LRTI, including protocol-defined medically attended RSV LRTI (Table 7 and Table 8). All subjects evaluated for LRTI will have respiratory samples obtained and tested centrally for RSV using the United States Food and Drug Administration (US FDA)-cleared and *Conformité Européenne* (CE) or European Conformity-marked in vitro diagnostic real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay (see Section 4.3.1.2).

Blood samples will be collected for PK, ADA, and RSV neutralizing antibody and RSV serology as defined in Sections 4.3.3, 4.3.4, and 4.3.5, respectively.

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

Figure 1 Study Flow Diagram



ADA = anti-drug antibody; CHD = congenital heart disease; CLD = chronic lung disease; IM = intramuscular; PK = pharmacokinetic.

SEASON 1: Randomization for Season 1 Day 1, 2:1 MEDI8897 or palivizumab group

SEASON 2 (CLD/CHD cohort only): Randomization for Season 2 Day 1: Subjects who were randomized in Season 1 to receive MEDI8897 will receive MEDI8897 in Season 2. Subjects who were randomized to receive palivizumab in Season 1 will receive MEDI8897 or palivizumab in Season 2

Blood samples for PK and ADA: Season 1 for both cohorts – Screening or Day 1 predose and on Days 31 (predose), 151, and 361 (for CLD/CHD cohort, prior to Season 2 dosing); Season 2 for CLD/CHD cohort only - Days 31 (predose), 151, and 361. Additionally, samples will be collected during both seasons from all subjects hospitalized for a respiratory infection, and before and after cardiac surgery with cardiopulmonary bypass for subjects with CHD requiring a replacement dose of study drug.

Safety assessments will be performed through Day 361 for each respective season.

[a] In the MEDI8897 group Season 1, dose level will be stratified by body weight at time of dosing; subjects will receive 50 mg MEDI8897 if < 5 kg or 100 mg MEDI8897 if ≥ 5 kg.

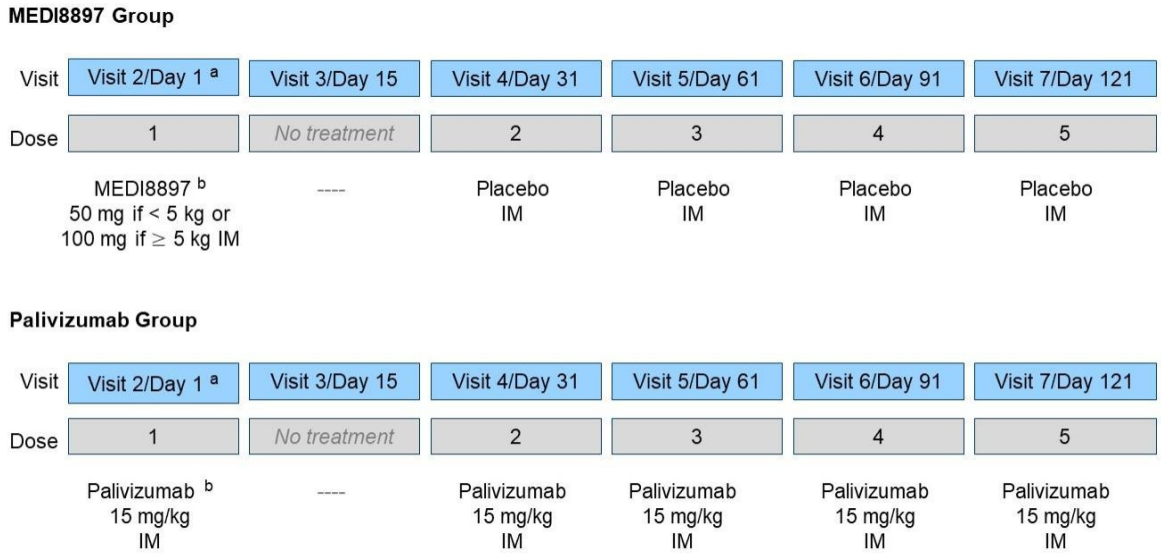
3.1.2 Dosing Regimen

Subjects will be randomly assigned to receive study drug as outlined in Figure 1.

3.1.2.1 Season 1, Preterm Cohort and CLD/CHD Cohort

In Season 1, subjects in the preterm cohort and CLD/CHD cohort will receive either MEDI8897 or palivizumab as presented in Figure 2. Section 3.1.2.3 provides details on replacement dosing for subjects in the CLD/CHD cohort who undergo cardiac surgery with cardiopulmonary bypass surgery.

Figure 2 Dosing Regimen: Season 1 – Preterm Cohort and CLD/CHD Cohort



CHD = congenital heart disease; CLD = chronic lung disease; IM = intramuscular.

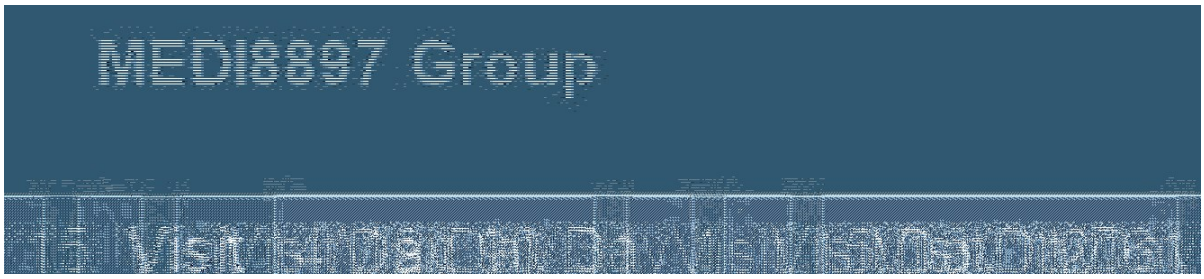
[a] Visit 1/Screening and Visit 2/Day 1 and can occur on the same day.

[b] Based on body weight at time of dosing.

3.1.2.2 Season 2, CLD/CHD Cohort

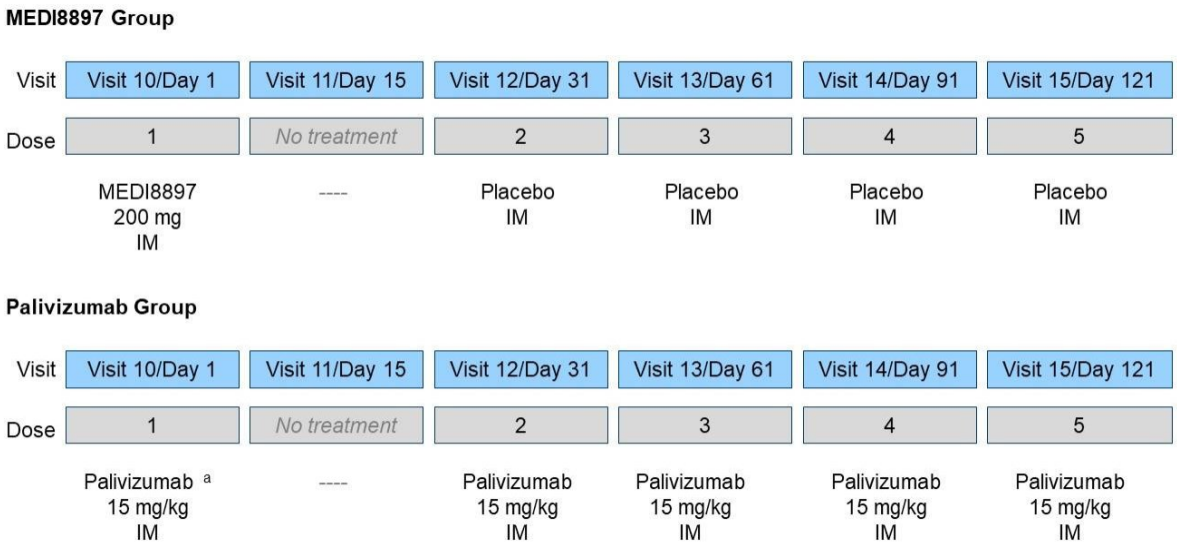
In Season 2, subjects in the CLD/CHD cohort only will receive either MEDI8897 or palivizumab based on their randomized dosing group in Season 1. Figure 3 presents the dosing regimen for subjects who were randomized to receive MEDI8897 in Season 1. Figure 4 presents the dosing regimen for subjects who were randomized to receive palivizumab in Season 1. Section 3.1.2.3 provides details on replacement dosing for subjects in the CLD/CHD cohort who undergo cardiac surgery with cardiopulmonary bypass surgery.

Figure 3 Dosing Regimen: Season 2 – CLD/CHD Cohort, MEDI8897 Group in Season 1



CHD = congenital heart disease; CLD = chronic lung disease; IM = intramuscular.

Figure 4 Dosing Regimen: Season 2 – CLD/CHD Cohort, Palivizumab Group in Season 1



CHD = congenital heart disease; CLD = chronic lung disease; IM = intramuscular.

[a] Based on body weight at time of dosing.

3.1.2.3 Season 1 or Season 2, CLD/CHD Cohort - Replacement Dose

Subjects in the CLD/CHD cohort who undergo cardiac surgery with cardiopulmonary bypass after receipt of Dose 1 but prior to receipt of Dose 5 will receive a replacement dose of the study drug that they received for Dose 1 immediately following the surgery when determined by the physician to be medically stable for an IM injection. Any subsequent doses of study drug will continue to be given according to the protocol-specified dosing schedule. In subjects requiring multiple surgeries during the same season, the dosing and timing scheme described below should be followed relative to the most recent replacement dose.

Details for the replacement dose by randomized group are presented below.

MEDI8897 Group

- Season 1
  - Subjects undergoing surgery < 90 days post first dose who originally received 50 mg MEDI8897 will receive a single 50-mg MEDI8897 IM replacement dose if < 5 kg body weight at time of replacement dosing or a single 100-mg MEDI8897 IM replacement dose if ≥ 5 kg body weight at time of replacement dosing.
  - Subjects undergoing surgery < 90 days post first dose who originally received 100 mg MEDI8897 will receive a single 100-mg MEDI8897 IM replacement dose.
  - Subjects undergoing surgery ≥ 90 days post first dose who originally received either 50 mg or 100 mg MEDI8897 will receive a single 50-mg MEDI8897 IM replacement dose.
- Season 2
  - Subjects undergoing surgery < 90 days post first dose will receive a single 200-mg MEDI8897 IM replacement dose.
  - Subjects undergoing surgery ≥ 90 days post first dose will receive a single 100-mg MEDI8897 IM replacement dose.

Palivizumab Group

Subjects will receive a 15 mg/kg palivizumab IM replacement dose. Thereafter, doses should be given according to the protocol-specified dosing schedule.

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. 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 [redacted] had a statistically significantly higher probability of protection based on exposure-response analysis using Cox proportional hazard regression. [redacted] Henceforth, based on these analyses, a stratified fixed dosing strategy by weight bands will be implemented to ensure an adequate dose to maintain 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 will be administered for infants < 5 kg in their first RSV season while a single fixed 100-mg dose will be administered for those weighing ≥ 5 kg entering their first RSV season. Additionally, the body weight range for the Phase 2/3 population in the second year of life at time of dosing is expected to be approximately 8.5 to 15 kg. Therefore, with the same rationale, a single fixed 200-mg dose of MEDI8897 is proposed for infants in the second year of life to achieve and maintain efficacious exposure during the entire second RSV season.

The approved palivizumab dosing regimen of 15 mg/kg administered IM once monthly during the RSV season (ie, once monthly for 5 months) will be used for this study.

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 based on its demonstrated increased potency and expected extended half-life that may support once per season dosing. Because of these significant advantages over palivizumab, including the potential for a single dose versus up to 5 monthly doses of palivizumab, MEDI8897 may also provide a significant improvement for prevention of RSV disease in the pediatric population indicated for palivizumab, ie, high-risk preterm infants and children up to 2 years of age with CLD or CHD. Therefore, this Phase 2/3 study is planned to evaluate MEDI8897 in high-risk palivizumab-eligible infants and young children entering their first and second RSV seasons.

3.2.3 Rationale for Endpoints

MEDI8897 is being developed to provide RSV immunoprophylaxis for all infants entering their first RSV season and children with CLD of prematurity or hemodynamically significant CHD entering their first and second seasons. The primary endpoint for this study is safety and tolerability, with the aim of comparing the profiles for MEDI8897 and palivizumab in this population. The standard measures of TEAEs/TESAEs, AESIs, and NOCDs will be used for this assessment. All subjects will be followed for approximately 1 year after the last dose of MEDI8897. Subjects with CLD/CHD who receive MEDI8897 for Season 1 and Season 2 and subjects who receive a replacement dose of MEDI8897 after cardiopulmonary bypass will provide data for the safety assessment of infants who receive more than a single dose of MEDI8897.

Serum concentration of MEDI8897 at selected time points will be evaluated as a secondary endpoint to confirm that serum concentrations are maintained at an efficacious level for at least 5 months after dosing. Palivizumab serum concentrations will also be evaluated. MEDI8897 and palivizumab PK data will be summarized by non-compartmental analysis. 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/palivizumab 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 and palivizumab serum levels post dosing and to correlate with the potential development of ADA, serum concentrations will be measured up to 360 days post Dose 1 (when MEDI8897 would be given) for both Season 1 and, as applicable, Season 2. ADA to MEDI8897 and to palivizumab will be measured at selected time points throughout the study and up to 360 days post Dose 1 for each season as well.

This study will also summarize efficacy of MEDI8897 and palivizumab in terms of incidence of RSV LRTI. Respiratory syncytial virus results in a significant burden of disease consisting of hospitalization, visits to the emergency room (ER), and visits to outpatient clinics. This endpoint is designed to allow the capture of this total burden of disease. A separate endpoint of RSV hospitalization will also be evaluated. Because of the reduced incidence of RSV disease in this population following the introduction of palivizumab, a superiority or non-inferiority design (with RRR of MEDI8897 over palivizumab as the endpoint) is not practical. This Phase 2/3 study is designed to confirm the safety and PK while incidence of RSV LRTI (and RSV hospitalization) will be summarized and no formal statistical test will be conducted. It is anticipated that efficacy from the Phase 2b and Phase 3 studies in preterm and term infants will be predictive of efficacy in the palivizumab population.

Exploratory endpoints will examine magnitude of healthcare resource utilization (HRU) and caregiver burden due to RSV illness in the current population. This will allow the determination of social and economic resources that are required for infants who have LRTI. Serum anti-RSV neutralizing antibody levels will be evaluated for correlation with serum MEDI8897 and palivizumab concentrations. RSV serology will be evaluated 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 MEDI8897 and palivizumab susceptibility. The incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV from Day 152 to Day 361 in Season 1 and Season 2 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 900 subjects will be enrolled and randomized to either the MEDI8897 group (approximately 600 subjects, including approximately 400 subjects in the

preterm cohort and approximately 200 subjects in the CLD/CHD cohort) or palivizumab group (approximately 300 subjects, including approximately 200 subjects in the preterm cohort and approximately 100 subjects in the CLD/CHD cohort).

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 For the preterm cohort (excluding subjects with CLD or hemodynamically significant CHD): preterm infants in their first year of life and born ≤ 35 weeks 0 days GA eligible to receive palivizumab in accordance with national or local guidelines, including those with:
   (a) Uncomplicated small atrial or ventricular septal defects or patent ductus arteriosus, ***or***
   (b) Aortic stenosis, pulmonic stenosis, or coarctation of the aorta alone
2 For the CLD/CHD cohort:
   (a) Subjects with CLD - infants in their first year of life and a diagnosis of CLD of prematurity requiring medical intervention/management (ie, supplemental oxygen, bronchodilators, or diuretics) within the 6 months prior to randomization
   (b) Subjects with CHD - infants in their first year of life and documented, hemodynamically significant CHD (must be unoperated or partially corrected CHD) ***Note***: Infants with hemodynamically significant acyanotic cardiac lesions must have pulmonary hypertension (≥ 40 mmHg measured pressure in the pulmonary artery) or the need for daily medication to manage CHD
3 Infants who are entering their first RSV season at the time of screening
4 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(s) prior to performing any protocol-related procedures, including screening evaluations
5 Subject's parent(s)/legal representative(s) able to understand and comply with the requirements of the protocol including follow-up and illness visits as judged by the investigator
6 Subject is available to complete the follow-up period, which will be 1 year after Season 1/ Dose 1 for subjects without CLD/CHD, or 1 year after Season 2/Dose 1 (or last replacement dose as applicable for CHD) for subjects with CLD/CHD

4.1.3 Exclusion Criteria

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

1 Any fever (≥ 100.4°F [≥ 38.0°C], regardless of route) or acute illness within 7 days prior to randomization
2 Any history of LRTI or active LRTI prior to, or at the time of, randomization
3 Known history of RSV infection or active RSV infection prior to, or at the time of, randomization

4 Hospitalization at the time of randomization, unless discharge is expected within the 7 days after randomization
5 Requirement for mechanical ventilation, extracorporeal membrane oxygenation, CPAP, or other mechanical respiratory or cardiac support at the time of randomization
6 Anticipated cardiac surgery within 2 weeks after randomization
7 Anticipated survival of < 6 months after randomization
8 Receipt of any investigational drug
9 Known renal impairment
10 Known hepatic dysfunction including known or suspected active or chronic hepatitis infection
11 Clinically significant congenital anomaly of the respiratory tract
12 Chronic seizure, or evolving or unstable neurologic disorder
13 Prior history of a suspected or actual acute life-threatening event
14 Known immunodeficiency, including human immunodeficiency virus (HIV)
15 Mother with HIV infection (unless the child has been proven to be not infected)
16 Any known allergy, including to immunoglobulin products, or history of allergic reaction
17 Receipt of palivizumab or other RSV mAb or any RSV vaccine, including maternal RSV vaccination
18 Receipt of any monoclonal or polyclonal antibody (for example, hepatitis B immune globulin, intravenous immunoglobulin) or anticipated use during the study
19 Any condition that, in the opinion of the investigator, would interfere with evaluation of the study drug or interpretation of subject safety or study results
20 Concurrent enrollment in another interventional study
21 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 study drug. 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

An individual subject will not receive additional doses of study drug, including continued dosing in Season 2 for subjects with CLD/CHD, if any of the following occur in the subject in question:

1 Withdrawal of consent
2 Hypersensitivity reaction assessed as related to study drug

Subjects who have received any study drug will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn specifically from further study participation (Section 4.1.5) or the subject is lost to follow-up. Subjects who have not received study drug, regardless of reason, will not be followed.

4.1.7 Replacement of Subjects

Subjects will not be replaced.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

MedImmune ensures that biological samples are 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 visits 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

All procedures to be conducted during the treatment and follow-up periods are presented in Table 5 for Season 1, preterm and CLD/CHD cohorts and Table 6 for Season 2, CLD/CHD cohort only.

Table 5 Schedule of Treatment Period and Follow-up Period Study Procedures: Season 1, Preterm and CLD/CHD Cohorts

Study Period	**Treatment Period**							**Follow-up Period**					
Visit Number	**V2** [a]	**TC**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9** [b]	**TC**		**LRTI**	**Skin Reaction**
Procedure / Study Day	**D1**	**D8 (± 2 days)**	**D15 (± 2 days)**	**D31 (± 2 days)**	**D61 (± 2 days)**	**D91 (± 2 days)**	**D121 (± 2 days)**	**D151 (± 7 days)**	**D361 (± 7 days)**	**D1-151 Q2W (± 5 days)**	**D152-361 monthly (± 5 days)**	**D1-361 as needed**	**D1-361 as needed**
Medical history update	X		X	X	X	X	X	X	X				
Physical examination	X		X	X	X	X	X	X	X				
Weight	X		X	X	X	X	X	X	X				
Vital signs	X [c]		X	X [c]	X [c]	X [c]	X [c]	X	X				
Blood sample for PK, ADA, RSV neut Ab, and RSV serology [d]	X [e]			X (pre-dose)				X	X			X [f]	
Assessment of AEs/SAEs, AESIs, NOCDs	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Verify eligibility criteria	X												
Randomization [g]	X												
Study drug administration [h]	**X**			**X**	**X**	**X**	**X**						
Assessment of LRTI or any respiratory infection that requires hospitalization												X [f]	
Nasal swab collection												X [f]	
Assessment of skin reaction													X [i]

Table 5 Schedule of Treatment Period and Follow-up Period Study Procedures: Season 1, Preterm and CLD/CHD Cohorts

Study Period	Treatment Period							Follow-up Period					
Visit Number	**V2** [a]	**TC**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9** [b]	**TC**		**LRTI**	**Skin Reaction**
Procedure / Study Day	**D1**	**D8 (± 2 days)**	**D15 (± 2 days)**	**D31 (± 2 days)**	**D61 (± 2 days)**	**D91 (± 2 days)**	**D121 (± 2 days)**	**D151 (± 7 days)**	**D361 (± 7 days)**	**D1-151 Q2W (± 5 days)**	**D152-361 monthly (± 5 days)**	**D1-361 as needed**	**D1-361 as needed**
Telephone contact [j]		X								X	X		
HRU and caregiver burden [k]												X	

ADA = anti-drug antibody; AEs = adverse events; AESIs = adverse events of special interest; CHD = congenital heart disease; CLD = chronic lung disease; D = study day; ER = emergency room; HRU = healthcare resource utilization; ICU = intensive care unit; IM=intramuscular; LRTI = lower respiratory tract infection; neut Ab = neutralizing antibody; NOCDs = new onset chronic diseases; OTC = over-the-counter; PK = pharmacokinetic; Q2W = once every 2 weeks; RSV = respiratory syncytial virus; SAEs = serious adverse events; SID = subject identification; TC = telephone call; V = visit.

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

[b] For subjects in the CLD/CHD cohort, the Season 1 Visit 9/Day 361 may be the same as the Season 2 Visit 10/Day 1 (Dose 1).

[c] 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.

[d] Subjects requiring a replacement dose of study drug due to cardiac surgery with cardiopulmonary bypass will have a blood sample collected before and after surgery (prior to administering replacement dose) for PK evaluation.

[e] 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.

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

[g] Subjects in each cohort (preterm and CLD/CHD cohorts) will be randomized 2:1 to receive either MEDI8897 administered as a stratified dose by weight band, which includes a single fixed 50-mg IM dose for infants weighing < 5 kg or 100-mg IM dose for infants weighing ≥ 5 kg, followed by 4 once-monthly IM doses of placebo; or 5 once-monthly IM doses of 15 mg/kg palivizumab.

[h] Subjects who undergo cardiac surgery with cardiopulmonary bypass after receipt of Dose 1 but prior to receipt of Dose 5 will receive a replacement dose of the study drug that they received for Dose 1 immediately following the surgery when determined by the physician to be medically stable for an IM injection. Any subsequent doses of study drug will continue to be given according to the protocol-specified dosing schedule. See Section 3.1.2.3 for details.

[i] 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 study drug.

Table 5 Schedule of Treatment Period and Follow-up Period Study Procedures: Season 1, Preterm and CLD/CHD Cohorts

Study Period	Treatment Period							Follow-up Period					
Visit Number	V2 [a]	TC	V3	V4	V5	V6	V7	V8	V9 [b]	TC		LRTI	Skin Reaction
Procedure / Study Day	D1	D8 (± 2 days)	D15 (± 2 days)	D31 (± 2 days)	D61 (± 2 days)	D91 (± 2 days)	D121 (± 2 days)	D151 (± 7 days)	D361 (± 7 days)	D1-151 Q2W (± 5 days)	D152-361 monthly (± 5 days)	D1-361 as needed	D1-361 as needed

[j] Telephone contact must be verbal communication. Written communication via text, email, or other written form is not acceptable.

[k] 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 daycare/babysitting missed by the subject as a result of illness.

Table 6 Schedule of Treatment Period and Follow-up Period Study Procedures: Season 2, CLD/CHD Cohort Only

Study Period	**Treatment Period**							**Follow-up Period**						
Visit Number	**V10** [a]	**TC**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**TC**		**LRTI**	**Skin Reaction**	**Replacement Dose Follow-up** [b]
Procedure / Study Day	**D1**	**D8 (± 2 days)**	**D15 (± 2 days)**	**D31 (± 2 days)**	**D61 (± 2 days)**	**D91 (± 2 days)**	**D121 (± 2 days)**	**D151 (± 7 days)**	**D361 (± 7 days)**	**D1-151 Q2W (± 5 days)**	**D152–361 monthly (± 5 days)**	**D1-361 as needed**	**D1-361 as needed**	**360 days post last replacement dose (± 7 days)**
Medical history update	X		X	X	X	X	X	X	X					X
Physical examination	X		X	X	X	X	X	X	X					X
Weight	X		X	X	X	X	X	X	X					X
Vital signs	X [c]		X	X [c]	X [c]	X [c]	X [c]	X	X					X
Blood sample for PK, ADA, RSV neut Ab, and RSV serology [d]				X (pre-dose)				X	X			X [e]		X
Assessment of AEs/SAEs, AESIs, NOCDs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization [f]	X													
Study drug administration [g]	**X**			**X**	**X**	**X**	**X**							

Table 6 Schedule of Treatment Period and Follow-up Period Study Procedures: Season 2, CLD/CHD Cohort Only

Study Period	Treatment Period							Follow-up Period						
Visit Number	**V10** [a]	**TC**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**TC**		**LRTI**	**Skin Reaction**	**Replacement Dose Follow-up** [b]
Procedure / Study Day	**D1**	**D8 (± 2 days)**	**D15 (± 2 days)**	**D31 (± 2 days)**	**D61 (± 2 days)**	**D91 (± 2 days)**	**D121 (± 2 days)**	**D151 (± 7 days)**	**D361 (± 7 days)**	**D1-151 Q2W (± 5 days)**	**D152–361 monthly (± 5 days)**	**D1-361 as needed**	**D1-361 as needed**	**360 days post last replacement dose (± 7 days)**
Assessment of LRTI or any respiratory infection that requires hospitalization												X [e]		
Nasal swab collection												X [e]		
Assessment of skin reaction													X [h]	
Telephone contact [i]		X								X	X			
HRU and caregiver burden [j]												X		

ADA = anti-drug antibody; AEs = adverse events; AESIs = adverse events of special interest; CHD = congenital heart disease; CLD = chronic lung disease; D = study day; ER = emergency room; HRU = healthcare resource utilization; ICU = intensive care unit; IM=intramuscular; LRTI = lower respiratory tract infection; neut Ab = neutralizing antibody; NOCDs = new onset chronic diseases; OTC = over-the-counter; PK = pharmacokinetic; Q2W = once every 2 weeks; RSV = respiratory syncytial virus; SAEs = serious adverse events; SID = subject identification; TC = telephone call; V = visit.

[a] The Season 2 Visit 10/Day 1 (Dose 1) may be the same as the Season 1 Visit 9/Day 361.

[b] Subjects who receive a replacement dose of study drug due to cardiac surgery with cardiopulmonary bypass will be followed for 360 days after the last replacement dose with the same schedule for telephone calls and a final visit 360 days post the last replacement dose.

[c] 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.

Table 6 Schedule of Treatment Period and Follow-up Period Study Procedures: Season 2, CLD/CHD Cohort Only

Study Period	Treatment Period							Follow-up Period						
Visit Number	V10 [a]	TC	V11	V12	V13	V14	V15	V16	V17	TC		LRTI	Skin Reaction	Replacement Dose Follow-up [b]
Procedure / Study Day	D1	D8 (± 2 days)	D15 (± 2 days)	D31 (± 2 days)	D61 (± 2 days)	D91 (± 2 days)	D121 (± 2 days)	D151 (± 7 days)	D361 (± 7 days)	D1-151 Q2W (± 5 days)	D152–361 monthly (± 5 days)	D1-361 as needed	D1-361 as needed	360 days post last replacement dose (± 7 days)

[d] Subjects requiring a replacement dose of study drug due to cardiac surgery with cardiopulmonary bypass will have a blood sample collected before and after surgery (prior to administering replacement dose) for PK evaluation.

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

[f] Subjects who were randomized to receive MEDI8897 for Season 1 will receive a single 200-mg IM dose of MEDI8897 followed by 4 once-monthly IM doses of placebo for Season 2. Subjects who were randomized to receive palivizumab for Season 1 will be re-randomized 1:1 to receive a single 200-mg IM dose of MEDI8897 followed by 4 once-monthly IM doses of placebo, or 5 once-monthly IM doses of 15 mg/kg palivizumab for Season 2.

[g] Subjects who undergo cardiac surgery with cardiopulmonary bypass after receipt of Dose 1 but prior to receipt of Dose 5 will receive a replacement dose of the study drug that they received for Dose 1 immediately following the surgery when determined by the physician to be medically stable for an IM injection. Any subsequent doses of study drug will continue to be given according to the protocol-specified dosing schedule. See Section 3.1.2.3 for details.

[h] 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 study drug.

[i] Telephone contact must be verbal communication. Written communication via text, email, or other written form is not acceptable.

[j] 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 daycare/babysitting missed by the subject as a result of illness.

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 and Table 6). All subjects seeking medical attention for a respiratory illness (in either the inpatient or outpatient setting) will be evaluated for 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 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 + human metapneumovirus [hMPV] assay; Quidel Corporation, San Diego, CA, www.quidel.com; see Section 4.3.1.2). 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 LRTI.

For subjects with no underlying lung disease:

To meet the protocol-defined endpoint of medically attended RSV LRTI, subjects with signs of LRTI must have documented at least one physical examination finding of rhonchi, rales, crackles, or wheeze AND at least one of the following clinical signs (see Table 7):

- 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 intravenous fluid).

Table 7 Criteria for Meeting the Protocol-defined Endpoint of Medically Attended RSV LRTI - Subjects Without Underlying Lung Disease

RSV	Lower Respiratory Tract	Medical Significance
RSV Confirmed: • Positive by central laboratory real-time RT-PCR assay	**Documented physical examination 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; 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 medically attended RSV LRTI.

For subjects with underlying lung disease (CLD or CHD):

To meet the protocol-defined endpoint of medically attended RSV LRTI, subjects with signs of LRTI must have documented at least one new or worsened physical examination finding of rhonchi, rales, crackles, or wheeze AND at least one of the following clinical signs (see Table 8):

- Increase in baseline respiratory rate by ≥ 20% at rest and that rate is greater than the age-based criteria established for children with no underlying lung disease (age: < 2 months, ≥ 60 breaths/min; 2 to 6 months, ≥ 50 breaths/min; > 6 months, ≥ 40 breaths/min), OR
- Hypoxemia (O_2 saturation < 95% in room air or O_2 saturation drop of 5 percentage points from baseline in children with baseline O_2 saturation < 95% in room air, or acute documented need for supplemental O_2 or increased O_2 requirement compared with baseline), 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), OR
- Prescription of new or increased (from baseline) dose of medications including bronchodilators, steroids, diuretics, cardiac medications

Table 8 Criteria for Meeting the Protocol-defined Endpoint of Medically Attended RSV LRTI – Subjects With Underlying Lung Disease (CLD or CHD)

RSV	Lower Respiratory Tract	Medical Significance
RSV Confirmed: • Positive by central laboratory real-time RT-PCR assay	**Documented new or worsened physical examination findings localizing to lower respiratory tract**: • Rhonchi • Rales • Crackles • Wheeze	**Objective measures of clinical severity**: • Increased respiratory rate (from baseline) • Hypoxemia • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration due to respiratory distress • Prescription of new or increased (from baseline) dose of medications including bronchodilators, steroids, diuretics, cardiac medication

CHD = congenital heart disease; CLD = chronic lung disease; 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 medically attended 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 any 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.

4.3.1.2 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 may include other respiratory pathogens.

4.3.1.3 Monitoring for RSV Resistance

As an exploratory endpoint, novel RSV F variants identified in RSV-positive nasal specimens (based on the RSV diagnostic test results; Section 4.3.1.2) from all subjects will be evaluated

by genotypic and phenotypic methods to monitor potential susceptibility changes to MEDI8897 and palivizumab 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) 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 or by cloning the F gene from the isolate into a laboratory-adapted RSV strain such as A2 or B9320.

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 during the treatment and 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, genitourinary, drug and surgical history, or any other diseases or disorders.

A physical examination, including weight, will be performed at screening and during the treatment and follow-up period as defined in Section 4.2.

Vital signs (temperature, blood pressure, heart rate, and respiratory rate) will be collected at screening and during the treatment and follow-up period as defined in Section 4.2. On days when study drug is administered, vital signs will be obtained within 60 minutes prior to dosing, and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post dose.

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

4.3.3 Pharmacokinetic Evaluation and Methods

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.

Blood samples will be collected to evaluate PK of MEDI8897 and palivizumab in serum (see Section 4.2.2 for collection time points). Subjects in the CLD/CHD cohort requiring a

replacement dose of study drug due to cardiac surgery with cardiopulmonary bypass will have a blood sample collected before and after surgery (prior to administering replacement dose) to evaluate serum concentration of MEDI8897 or palivizumab. The PK of MEDI8897 and palivizumab will be measured utilizing validated assays.

4.3.4 Anti-drug Antibody Evaluation and Methods

Blood samples will be collected to evaluate ADA responses to MEDI8897 and palivizumab in serum (see Section 4.2.2 for collection time points). Evaluation will be performed using validated immunoassays. Tiered analyses will be performed to include screening, confirmatory, and titer assay components, and the positive-negative cut points will be statistically determined from drug-naive validation samples. Samples will be utilized for further characterization of the ADA response, including ADA to the YTE domain on MEDI8897 and the assessment of neutralizing antibody to MEDI8897 or palivizumab.

4.3.5 RSV-neutralizing Antibody and RSV Serology Evaluations and Methods

4.3.5.1 RSV Neutralizing Antibody

Blood samples will be collected to evaluate anti-RSV neutralizing antibody levels in serum (see Section 4.2.2 for collection time points). Analyses will be performed using an RSV neutralizing antibody assay previously described by Shambaugh et al (Shambaugh et al, 2017).

4.3.5.2 RSV Serology

Blood samples will be collected to measure RSV antigen-specific antibody levels in serum (see Section 4.2.2 for collection time points). Evaluations will be performed using a validated immunoassay similar to the assay described by Maifeld et al (Maifeld et al, 2016).

4.3.6 Healthcare Resource Utilization and Caregiver Burden

Information on HRU and caregiver burden will be collected for all events of medically attended LRTI (see Table 5 and Table 6). This will include admission to and duration of hospital and intensive care unit (ICU) stay, number of subjects who require respiratory support and supplemental oxygen use, duration of respiratory support and supplemental oxygen use, number and type of outpatient visits (eg, ER, urgent care, outpatient clinic), and the number of prescription and over-the-counter (OTC) medications and their duration of use. Caregiver burden will be assessed through, for example, caregiver missed work days and the subject's absence from day care.

4.3.7 Skin Reactions

Skin reaction assessment will be done for any post-dosing skin or skin-related reaction to assist in determination of the etiology of the reaction (see Table 5 and Table 6). 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 child will be brought to the study site as soon as possible for evaluation.

4.3.8 Estimate of Volume of Blood to be Collected

Blood volume estimates are provided by visit/study day for Season 1 (Table 9) and Season 2 (Table 10).

Table 9 Volume of Blood to be Collected, Season 1

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 8/Day 151	1.5 mL
Visit 9/Day 361	1.5 mL
Total	6.0 mL

Table 10 Volume of Blood to be Collected, Season 2

Visit/Study Day	Estimated Blood Volume (mL)
Visit 12/Day 31	1.5 mL
Visit 16/Day 151	1.5 mL
Visit 17/Day 361	1.5 mL
Total	4.5 mL

4.4 Study or Study Component Suspension or Termination

MedImmune reserves the right to temporarily suspend or permanently terminate this study or component of the 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 sponsor 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 sponsor 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 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 sponsor safety review committee
6 Subject enrollment is unsatisfactory
7 Sponsor decision to terminate development

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

If the study or component of 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 or component of the study is suspended for safety reasons and it is deemed appropriate by MedImmune to resume the study or component of 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 investigators with MEDI8897 and palivizumab (Table 11) using designated distribution centers.

Table 11 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	Various (sourced by sites)	Commercially available 0.9% (w/v) saline (sterile for human use)

Table 11 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Palivizumab	AstraZeneca	Supplied as 50 mg (nominal) per vial solution. The solution contains 100 mg/mL palivizumab, 25 mM Histidine, 1.6 mM glycine, 12.5 mM chloride, pH 6.0. The nominal fill volume is 0.5 mL.

HCl = hydrochloride; w/v = weight/volume.

MEDI8897 and palivizumab 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).

4.5.1.1 Investigational Product Inspection

Each vial selected for dose administration should be inspected. Refer to Table 11 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 4.5.1.4) for further instructions.

4.5.1.2 Dose Preparation Steps and Treatment Administration

The first day of dosing is considered Day 1.

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

No incompatibilities between MEDI8897 or palivizumab and polycarbonate or polypropylene syringes have been observed.

MEDI8897 and palivizumab do not contain preservatives and any unused portion must be discarded. Total in-use storage time from needle puncture of the study drug vial to administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used.

MEDI8897 group: Season 1 and Season 2, including replacement dose(s) after cardiopulmonary bypass

Subjects will receive MEDI8897 for Dose 1 and placebo for Doses 2 through 5:

1 **Season 1**

(a) Infants < 5 kg body weight at time of dosing:

- Dose 1: A dose of 50 mg (ie, 0.5 mL) MEDI8897 will be obtained by withdrawing the entire contents of 1 investigational vial with an appropriately sized syringe, and administered as one single (ie, 0.5 mL) injection
- Doses 2 through 5: A corresponding volume (0.5 mL) of saline will be obtained, and administered as one single (ie, 0.5 mL) injection

(b) Infants ≥ 5 kg body weight at time of dosing:

- Dose 1: A dose of 100 mg (ie, 1.0 mL) MEDI8897 will be obtained by withdrawing the entire contents of 2 investigational vials
- Doses 2 through 5: A corresponding volume (1.0 mL) of saline will be administered
- To maintain the blind:
  - If the weight is ≥ 5 kg to < 6.7 kg then the dose should be administered as one single (ie, 1.0 mL) injection
  - If the weight is ≥ 6.7 kg, then the volume of MEDI8897 or saline should be divided equally into 2 syringes

2 **Season 2**

- Dose 1: A dose of 200 mg (ie, 2.0 mL) MEDI8897 will be obtained by withdrawing the entire contents of 4 investigational vials
- Doses 2 through 5: A corresponding volume (2.0 mL) of saline will be administered
- To maintain the blind:
  - If the weight is < 13.4 kg, then the dose should be administered as two 1.0 mL injections (ie, 1.0 mL per injection)
  - If the weight is ≥ 13.4 kg, then the volume of MEDI8897 or saline should be divided equally into 3 syringes

3 **Replacement dose(s) after cardiopulmonary bypass**

Season 1

(a) Cardiopulmonary bypass < 90 days post first dose of MEDI8897 (or most recent replacement dose if previous cardiopulmonary bypass) for infants < 5 kg:

- Replacement dose: A dose of 50 mg (ie, 0.5 mL) MEDI8897 will be obtained by withdrawing the entire contents of 1 investigational vial with an appropriately sized syringe, and administered as one single (ie, 0.5 mL) injection

(b) Cardiopulmonary bypass < 90 days post first dose of MEDI8897 (or most recent replacement dose if previous cardiopulmonary bypass) for infants ≥ 5 kg:
- Replacement dose: A dose of 100 mg (ie, 1.0 mL) MEDI8897 will be obtained by withdrawing the entire contents of 2 investigational vials
- To maintain the blind:
  - If the weight is ≥ 5 kg to < 6.7 kg then the dose should be administered as one single (ie, 1.0 mL) injection
  - If the weight is ≥ 6.7 kg, then the volume of MEDI8897 should be divided equally into 2 syringes

(c) Cardiopulmonary bypass ≥ 90 days post first dose (or most recent replacement dose if previous cardiopulmonary bypass) for all weights:
- Replacement dose: A dose of 50 mg (ie, 0.5 mL) MEDI8897 will be obtained by withdrawing the entire contents of 1 investigational vial with an appropriately sized syringe, and administered as one single (ie, 0.5 mL) injection

Season 2

(a) Cardiopulmonary bypass < 90 days post first dose:
- Replacement dose: A dose of 200 mg (ie, 2.0 mL) MEDI8897 will be obtained by withdrawing the entire contents of 4 investigational vials
- To maintain the blind:
  - If the weight is < 13.4 kg, then the dose should be administered as two 1.0 mL injections (ie, 1.0 mL per injection)
  - If the weight is ≥ 13.4 kg, then the volume of MEDI8897 should be divided equally into 3 syringes

(b) Cardiopulmonary bypass ≥ 90 days post first dose (or most recent replacement dose if previous cardiopulmonary bypass):
- Replacement dose: A dose of 100 mg (ie, 1.0 mL) MEDI8897 will be obtained by withdrawing the entire contents of 2 investigational vials
- To maintain the blind:
  - If the weight is ≥ 5 kg to < 6.7 kg then the dose should be administered as one single (ie, 1.0 mL) injection
  - If the weight is ≥ 6.7 kg, then the volume of MEDI8897 should be divided equally into 2 syringes

4 Switch the needle prior to administration

5 MEDI8897 or placebo (saline) should be administered in the anterolateral aspect of the thigh according to standard practice procedures for IM injections. The injection should be given using standard aseptic technique. When possible, injection sites for subsequent injections should use alternating sites (eg, right then left thigh). The maximum volume to be administered with each injection is 1.0 mL

6 MEDI8897 or placebo (saline) should be administered 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

Palivizumab group: Season 1 and Season 2, including replacement dose(s) after cardiopulmonary bypass

1 A dose of 15 mg/kg palivizumab will be obtained by withdrawing the calculated volume of drug to the nearest 0.01 mL as described below:

The dose of palivizumab will be calculated based on the subject's weight (to the nearest 0.01 kg) using the following formula:

$$\text{Dose (mL)} = [\text{subject weight (kg)} \times \text{dose level (15 mg/kg)}] \div \text{palivizumab concentration (100 mg/mL)}$$

The corresponding volume of palivizumab should be rounded to the nearest 0.01 mL.

Examples:

A patient who weighs 4.90 kg at the time of injection receives 0.74 mL of study drug (4.90 kg x 15 mg/kg) ÷ 100 mg/mL = 0.735 mL (rounded to 0.74 mL)

A patient who weighs 3.70 kg at the time of injection receives 0.56 mL of study drug (3.70 kg x 15 mg/kg) ÷ 100 mg/mL = 0.555 mL (rounded to 0.56 mL)

2 Switch the needle prior to administration

3 Palivizumab should be administered in the anterolateral aspect of the thigh according to standard practice procedures for IM injections. The injection should be given using standard aseptic technique. When possible, injection sites for subsequent injections should use alternating sites (eg, right then left thigh). The maximum volume to be administered with each injection is 1 mL

4 Palivizumab should be administered 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 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 60 minutes (± 5 minutes) post dose.

As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

4.5.1.4 Reporting Product Complaints

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

MedImmune contact information for reporting product complaints:

Email: [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 MEDI8897 and palivizumab at 2°C to 8°C. Placebo (saline) should be stored according to the manufacturer instructions.

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 MEDI8897 and palivizumab 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.

In Season 1, subjects in the preterm and CLD/CHD cohorts will be randomized using a 2:1 ratio to either the MEDI8897 group or palivizumab group. Within each cohort, the randomization will be stratified by hemisphere (northern, southern) and subject age at the time of Season 1 randomization (≤ 3 months, > 3 to ≤ 6 months, > 6 months).

In Season 2, subjects in the CLD/CHD cohort only will be randomized. Subjects who were randomized to the MEDI8897 group in Season 1 will remain in the MEDI8897 group. Subjects who were randomized to the CLD/CHD group in Season 1 will be re-randomized using a 1:1 ratio to either the MEDI8897 or palivizumab group.

Study drug (MEDI8897, placebo, or palivizumab) must be administered the same day the study drug is assigned. If there is a delay in the administration of study drug such that it will not be administered within the specified timeframe, the unblinded investigational product monitor must be notified immediately.

4.6.2 Methods to Ensure Blinding

This is a double-blind study in which MedImmune will provide sites with MEDI8897 and palivizumab. Sites will use commercially available saline as the placebo. Syringe barrels will be covered by the unblinded investigational product manager. 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.

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 study drug 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 study drug. In the majority of cases, the management of a medical emergency would be the same whether or not study drug was received by the subject. If this was the case, the study drug allocation should not be unblinded. In the event there is unblinding, the investigator should promptly document and explain to MedImmune the reason for any premature unblinding.

MedImmune retains the right to unblind the treatment allocation for SAEs that are unexpected and are suspected to be causally related to a study drug and that potentially require expedited reporting to regulatory authorities.

If a subject's study drug allocation is unblinded to the blinded staff or blinded MedImmune/contract research organization study team, the subject should be discontinued from study drug.

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 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. Specifically, subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

4.7.2 Prohibited Concomitant Medications

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

4.8 Statistical Evaluation

4.8.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be

summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan.

The Intent-to-treat (ITT) Population is defined as all randomized subjects, analyzed according to randomized treatment assignment. All efficacy analyses will be performed on the ITT Population.

The As-treated Population (ATP) is defined as all subjects who receive any investigational product, analyzed according to treatment received. All analyses, with the exception of efficacy, will be performed on the ATP unless otherwise specified.

A primary analysis, Season 2 analysis, and final analysis are planned for the study. The primary analysis will be conducted after all randomized subjects have completed follow-up through the first 5-month RSV season (ie, Season 1 Day 151 visit) and include all available Season 1 safety, efficacy, PK, and ADA data at the time of the data cutoff. Season 2 analysis will be conducted after all the CLD/CHD subjects have completed follow-up through the second 5-month RSV season (ie, Season 2 Day 151 visit) and include all available Season 1 data and Season 2 safety, efficacy, PK, and ADA data at the time of the data cutoff. The final analysis will be conducted when all subjects have completed the last visit of the study and include all data collected in the study.

At the time of the primary analysis, the Season 1 data will be unblinded to the Sponsor/designated clinical research organization associated with the analysis, write-up, and regulatory submission.

To ensure the blinding of Season 2 treatment assignment for CLD/CHD subjects who were randomized to the palivizumab arm in Season 1, any data with potential unblinding risk will be split by Season 1 and Season 2 by the corresponding third party data vendors and when the primary database lock occurs, only unblinding data from Season 1 will be transferred to the Sponsor for analysis.

The site personnel, participants, and the study team members who participate in the advice or decisions involving study subjects and/or day-to-day interactions with the site, will remain blinded until the end of the study to ensure the trial integrity is maintained. Further details will be specified in the unblinding plan prior to database lock for the primary analysis.

4.8.2 Sample Size

With respect to safety, 600 subjects exposed to MEDI8897 in Season 1 will provide a 95% probability of observing at least one AE if the true event rate is 0.5%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.5%. The sample size is for safety consideration.

With respect to efficacy, approximately 600 subjects will be exposed to MEDI8897 and 300 subjects will be exposed to palivizumab in Season 1 to observe numerically similar efficacy for both mAbs. Because of the reduced incidence of RSV disease in this population following the introduction of palivizumab, a superiority or non-inferiority design is not practical. A valid non-inferiority margin cannot be established due to the lack of historical efficacy data for the medically attended RSV LRTI endpoint for palivizumab. Therefore, there is no hypothesis testing for efficacy. Using an assumption of a 6% RSV LRTI rate in palivizumab recipients, approximately 18 events will be observed in that group. The 6% RSV LRTI rate (1.9% RSV hospitalizations and 3.9% outpatient RSV illness) was based on a prior study in preterm infants with and without CLD who received palivizumab (Carbonell-Estrany et al, 2010). Assuming a 6% rate of RSV LRTI in MEDI8897 recipients, 600 MEDI8897 subjects in Season 1 will provide approximately 36 events in that group. However, because of the largely reduced RSV circulation due to COVID-19 pandemic-related measures, the observed event rates could be much lower. Only summaries will be provided for efficacy unless specified otherwise.

4.8.3 Safety

4.8.3.1 Analysis of Adverse Events

AEs will be graded according to the current version of the NCI CTCAE where applicable for pediatric assessments. AEs will be coded by the Medical Dictionary for Regulatory Activities and the type, incidence, severity, and relationship to study drug will be summarized by treatment group. Other safety assessments will include the occurrence of AESIs defined as AEs of hypersensitivity to study drug (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis) following study drug administration, and the occurrence of NOCDs following study drug administration.

Safety of MEDI8897 will be summarized by treatment group based on the ATP. The safety summary will be provided for each season, as well as for the 2 consecutive RSV seasons (ie, Season 1 and Season 2). For the Season 1 summary, the analysis dataset will include subjects from the preterm cohort and CLD/CHD cohort, presented by the treatment received in Season 1; for the Season 2 summary and the 2 consecutive-season summary, the analysis dataset will include subjects from the CLD/CHD cohort, presented by the treatment received through the 2 seasons.

4.8.4 Efficacy

The primary efficacy endpoint is the incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post Dose 1 (ie, during a typical 5-month RSV season) in Season 1. The determination of the primary efficacy endpoint will be based on RSV test results (performed centrally using real-time RT-PCR; see Section 4.3.1.2) and objective protocol-defined LRTI criteria (see Table 7 and Table 8), and will be summarized by Season 1

treatment group for all 900 subjects. The 95% CI of the percentage of subjects meeting the primary efficacy endpoint 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 efficacy summary.

In addition, the summary of incidence of RSV LRTI through 150 days post Dose 1 in Season 2 will be provided for the 300 subjects in the CLD/CHD cohort based on the treatment assignments through Season 1 and Season 2: ie, (a) 50 mg MEDI8897 for infants with body weight < 5 kg and 100 mg MEDI8897 for infants with body weight ≥ 5 kg (Season 1)/200 mg MEDI8897 (Season 2), (b) palivizumab (Season 1)/200 mg MEDI8897 (Season 2), and (c) palivizumab (Season 1)/palivizumab (Season 2).

The incidence of RSV hospitalization through 150 days after dosing (ie, during the 5-month RSV season) will be summarized by treatment group using a similar strategy as described above for RSV LRTI.

Additional analyses will include summarizing RSV-positive LRTI endpoints using results from either the central laboratory or local laboratory.

All efficacy summaries will be based on the ITT Population.

4.8.5 Analysis of Pharmacokinetics and Anti-drug Antibody

4.8.5.1 Pharmacokinetic Analysis

Individual MEDI8897 and palivizumab serum concentration data will be tabulated by treatment group along with descriptive statistics. PK parameters, eg, maximum observed concentration (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 and to palivizumab will be assessed and summarized by number and percentage of subjects who are ADA positive by treatment group. The impact of ADA on PK, and association with TEAEs and TESAEs, will be assessed.

4.8.6 Exploratory Analyses

4.8.6.1 RSV Neutralizing Antibody

Individual MEDI8897 and palivizumab serum anti-RSV neutralizing antibody levels will be tabulated by treatment group along with descriptive statistics. Anti-RSV neutralizing antibody levels in serum will be summarized by geometric mean titer and geometric mean-fold rise and corresponding 95% CI for each treatment group at each visit. Anti-RSV neutralizing antibody level $t_{1/2}$ will be estimated using non-compartmental analysis, if data permit.

4.8.6.2 RSV Serology

Analysis of anti-RSV antigens antibody levels in serum in MEDI8897 and palivizumab recipients will be summarized by geometric mean titer and geometric mean-fold rise and corresponding 95% CI for each treatment group at each visit. Seroresponses in MEDI8897 and palivizumab recipients will be determined by examining the fold-rise in antibodies to Ga, Gb, and N antigens.

4.8.6.3 Healthcare Resource Utilization 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 OTC medications and duration of use) will be summarized overall by treatment group and for subjects with at least one medically attended LRTI (protocol defined) caused by RT-PCR-confirmed RSV.

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

The HRU and caregiver burden summaries will be performed on the ITT Population.

4.8.6.4 RSV Resistance Monitoring

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 and palivizumab will be tested and compared to control viruses.

4.8.6.5 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 for Season 1 and Season 2 will be based on RSV test results (performed centrally via RT-PCR) and objective clinical LRTI criteria and will be summarized by treatment group.

4.8.7 Independent Data Monitoring Committee

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

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

An adverse event 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
- 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, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to MedImmune (see Section 5.6). See Section 5.2 for the definition of SAEs and Appendix A for guidelines for assessment of severity and relationship.

If an AE evolves into a condition that meets the regulatory definition of “serious,” it will be reported on the SAE Report Form.

5.5.1 Time Period for Collection of Adverse Events

AEs and SAEs will be recorded from the time of signature of informed consent through the follow-up period (Day 361).

All AESIs and NOCDs will be recorded from the time of dosing with study drug through the follow-up period (Day 361).

5.5.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit in the study 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. 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).

5.5.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the care provider or reported in response to the open question from the study site staff: *'Has the child had any health problems since the previous visit?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

5.5.5 Adverse Events Based on Examination and Tests

An abnormal laboratory finding that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased)

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

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 representative(s) within 1 day, ie, immediately but **no later than 24 hours** after becoming aware of the event.

The designated study representative works with the investigator to ensure that all the necessary information is provided to the sponsor's 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 inform sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** after becoming aware of the event.

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 representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports an SAE to the appropriate sponsor representative by telephone. The sponsor 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 IB, unless otherwise specified in this protocol.

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

If an overdose on a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel should inform appropriate sponsor representatives immediately, but **no later than 24 hours** after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.6. For other overdoses (ie, those not associated with an AE or SAE), reporting must occur within 30 days.

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 study site 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 electronic data capture 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 enrolment 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 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 Principal 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 intravenous 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

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