A PHASE I, RANDOMIZED, DOUBLE-BLIND, SINGLE-DOSE, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MEDI-557, A HUMANIZED MONOCLONAL ANTIBODY WITH AN EXTENDED HALF-LIFE AGAINST RESPIRATORY SYNCYTIAL VIRUS (RSV), IN HEALTHY ADULTS

Study Agent: MEDI-557

MedImmune Protocol Number: MI-CP144

IND Number: BB-IND 100,655

Manufacturer: MedImmune
[redacted]

Sponsor: MedImmune

Medical Monitor: [redacted]
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MedImmune
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Study Monitor: MedImmune

Principal Investigator Agreement:
I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with Good Clinical Practice, the ethical principles set forth in the Declaration of Helsinki and with the U.S. Code of Federal Regulations governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR 56) and the obligations of clinical investigators (21 CFR 312).

Signature_____ Date_____

Printed Name_____

LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the serum concentration-time curve from time zero to last measurable time point
$AUC_{0-\infty}$	Area under the serum concentration-time curve from time zero to infinity
BAL	Bronchoalveolar lavage
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CHD	Congenital heart disease
CL	Total body serum clearance
CLD	Chronic lung disease
C_{max}	Maximum serum concentration
CV	Coefficient of variation
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GLP	Good laboratory practice
h	Hour
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular
IND	Investigational new drug application
IRB	Institutional Review Board
ITP	Idiopathic thrombocytopenic purpura
IV	Intravenous
IVIG	Intravenous immunoglobulin
IVRS	Interactive voice response system
K_d	Dissociation constant
kg	Kilogram
L	Liter
LRI	Lower respiratory tract infection
µg	Microgram
µm	Micrometer
Mab	Monoclonal antibody
MEDI-524	Motavizumab

meq	Milliequivalent
mg	Milligram
MHC	Major histocompatibility complex
mL	Milliliter
mm^3	Cubic millimeter
mmol	Millimole
PFT	Pulmonary function test
PID	Participant identification number
PK	Pharmacokinetic
RSV	Respiratory syncytial virus
RSV-IGIV	RespiGam®
SAE	Serious adverse event
SMC	Safety monitoring committee
$t_{1/2}$	Terminal phase elimination half-life
T_{max}	Time to maximum serum concentration
ULN	Upper limit of normal
Vd_z	Terminal phase volume of distribution
WBC	White blood cell count
YTE	Triple substitution (M252Y/S254T/T256E) in the CH2 domain of the Fc region

TABLE OF CONTENTS

STUDY ABSTRACT

TITLE:

A Phase 1, Randomized, Double-blind, Single-dose, Dose-escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI-557, a Humanized Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus (RSV), in Healthy Adults

RATIONALE:

Respiratory syncytial virus (RSV) is an important respiratory pathogen of infants and young children, causing annual epidemics of bronchiolitis and pneumonia worldwide.[1,2] The greatest morbidity and mortality occur among children at high risk for severe RSV disease, including premature infants, infants with bronchopulmonary dysplasia (BPD), and infants with complicated congenital heart disease (CHD). Lower respiratory tract disease due to RSV accounts for more than 125,000 pediatric hospitalizations and approximately 6.3 deaths per 100,000 person years among children up to 4 years of age in the United States.[3,4,5] Overall, the hospitalization rate due to RSV in infants less than 1 year of age is approximately 1% to 2%. Premature infants, infants with BPD, and infants with complicated CHD are admitted 4 to 5 times more frequently than non-high-risk children and have increased morbidity and mortality.[6,7,8,9] Prevention of serious RSV disease has been a high priority for the pediatric medical community. Despite several decades of attempts, no vaccine is yet licensed for active immunization to prevent RSV infection.[10,11] However, methods for passive immunization have been developed and are currently available. Synagis® is a licensed product indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.

MEDI-557 is a recombinant humanized IgG1κ monoclonal antibody (Mab) derived from motavizumab (MEDI-524) with three amino acid changes in the Fc region. Modification of the Fc region of IgG antibodies that results in increased affinity to the FcRn receptor has been shown to prolong the time period of sustained serum concentration of the antibody. The change in the Fc region in MEDI-557 from motavizumab increases the serum half-life of MEDI-557 in cynomolgus monkeys 4-fold compared with motavizumab. Thus, MEDI-557 has the potential to reduce the frequency of administration required for motavizumab, which is given as 5 monthly intramuscular (IM) injections, while retaining the anti-RSV activity of motavizumab, the parent molecule.

Motavizumab is a recombinant humanized, RSV-specific, IgG1κ Mab [redacted] Synagis® (palivizumab) is a marketed Mab that effectively reduces hospitalizations due to RSV by approximately 50% in high-risk infants when it is given as a monthly immunoprophylaxis. In vitro and in vivo preclinical studies have demonstrated the enhanced activity of motavizumab in RSV neutralization in tissue culture and RSV titer reduction in the lungs and upper respiratory tract in the RSV cotton rat model compared with palivizumab. In a recently unblinded, multinational Phase 3 study, motavizumab showed a 26% reduction in RSV hospitalizations of high-risk infants compared to Synagis, and a 50% reduction in RSV-specific, medically attended lower respiratory tract infections compared to Synagis.

Motavizumab is being studied in four additional ongoing Phase 2/3 clinical trials of RSV infections in high-risk children.

Motavizumab is given as a monthly IM injection for five doses. Considering the anticipated superior efficacy of motavizumab against RSV in children, an important initiative is to develop a candidate drug product with comparable anti-RSV activity and clinical benefit, with the additional benefit of a prolonged half-life in vivo. Increasing systemic exposure of this molecule as a result of the prolonged half-life offers the potential advantages of sustained, higher drug concentrations, a decreased frequency of dosing, improved convenience, and improved patient compliance.

This is a Phase 1, first-in-human, randomized, double-blind, single-dose, dose-escalation study to investigate the safety, tolerability, pharmacokinetics, and immunogenicity of MEDI-557, administered as a single intravenous (IV) dose, in healthy adults. The starting dose of 0.3 mg/kg is >300-fold lower than the no-observable-adverse-effect-level of 100 mg/kg in cynomolgus monkeys.

OBJECTIVES:

The primary objective of this study is to evaluate the safety and tolerability of a single IV dose of MEDI-557 administered to healthy adult subjects in the following dose cohorts:

- Cohort 1: 0.3 mg/kg
- Cohort 2: 3 mg/kg
- Cohort 3: 15 mg/kg
- Cohort 4: 30 mg/kg

The secondary objectives of this study are to:

1. Evaluate the serum pharmacokinetics of MEDI-557 and motavizumab;
2. Determine the immunogenicity of MEDI-557 and motavizumab; and
3. Quantitate the concentration of MEDI-557 and motavizumab in the upper respiratory tract.

DESIGN:

This is a Phase 1, first-in-human, randomized, double-blind, single-dose, dose-escalation study. A maximum of 36 healthy adult subjects will participate in this study comprising four dose cohorts: Cohort 1 (0.3 mg/kg), Cohort 2 (3 mg/kg), Cohort 3 (15 mg/kg), and Cohort 4 (30 mg/kg). Within each dose cohort, subjects will be randomized in a 1:1 ratio to receive a single IV dose of either MEDI-557 or motavizumab on Study Day 0 and will be followed 240 days for safety as follows:

- In Cohort 1, 2 subjects will receive 0.3 mg/kg MEDI-557 (n=1) or motavizumab (n=1) and will be followed for 60 days before additional subjects are dosed. If no safety concerns are observed in these 2 subjects through Study Day 60, an additional 4 subjects will receive a single IV dose of 0.3 mg/kg MEDI-557 (n=2) or motavizumab (n=2) and will be followed for 60 days before additional subjects are dosed. If no safety concerns are observed in these 4 subjects through Study Day 60, enrollment into the next higher dose cohort (Cohort 2 [3 mg/kg]) will commence. Before escalation to the next dose level, 2 subjects will have been followed for 120 days and 4 subjects for 60 days. Because of the low dose with resultant

predicted low serum levels (less than the limit of quantification) at 60 days, this length of follow-up should provide adequate safety information for dose escalation. If there is an occurrence of 1 serious adverse event (SAE) deemed possibly, probably, or definitely related to study drug in Cohort 1, 6 additional subjects will receive a single IV dose of 0.3 mg/kg MEDI-557 (n=3) or motavizumab (n=3) and will be followed for 60 days before additional subjects are dosed. If there is a recurrence of a similar related SAE in ≥ 2 subjects in Cohort 1, the trial will be terminated. All subjects will be followed 240 days for safety.

- In Cohort 2, 2 subjects will receive 3 mg/kg MEDI-557 (n=1) or motavizumab (n=1) and will be followed for 90 days before additional subjects are dosed. If no safety concerns are observed through Study Day 90, an additional 4 subjects will receive a single IV dose of 3 mg/kg MEDI-557 (n=2) or motavizumab (n=2) and will be followed for 90 days before additional subjects are dosed. On Study Day 90, blood samples will be drawn from all 6 subjects to measure serum drug levels. If pharmacokinetic data indicate a <2-fold increase in MEDI-557 serum half-life and area under the concentration-time curve (AUC) compared to motavizumab, it will be concluded that additional data at that dose level will not be useful and further enrollment into Cohort 2 and higher dose cohorts will not occur. If no safety concerns are observed and the pharmacokinetic results are favorable in these 6 subjects through Study Day 90, an additional 6 subjects will receive a single IV dose of 3 mg/kg MEDI-557 (n=3) or motavizumab (n=3) and be followed for 30 days before additional subjects are dosed. On Study Day 30, if no safety concerns are observed in any subject in Cohort 2, enrollment into the next higher dose cohort (Cohort 3 [15 mg/kg]) will commence. Before escalation to the next dose level, 2 subjects will be ~200 days post dose, 4 subjects ~120 days post dose, and 6 subjects will be 30 days post dose. It is expected that any acute reactions to MEDI-557 would occur within the 30 days after dosing. All subjects will be followed 240 days for safety.

- In Cohort 3, 2 subjects will receive 15 mg/kg MEDI-557 (n=1) or motavizumab (n=1) and will be followed for 30 days before additional subjects are dosed. If no safety concerns are observed through Study Day 30, an additional 4 subjects will receive a single IV dose of 15 mg/kg MEDI-557 (n=2) or motavizumab (n=2) and will be followed for 60 days before additional subjects are dosed. On Study Day 60, blood samples will be drawn from all 6 subjects to measure serum drug levels. If pharmacokinetic data indicate a <3-fold increase in MEDI-557 serum half-life and AUC compared to motavizumab, it will be concluded that additional data at this and higher dose levels will not be useful and enrollment into the higher dose level (Cohort 4 [30 mg/kg]) will not occur. If no safety concerns are observed and the pharmacokinetic results are favorable in these 6 subjects through Study Day 60, enrollment into the next higher dose cohort (Cohort 4 [30 mg/kg]) will commence. With the long follow-up period for the subjects in Cohort 2, adequate safety information should be available for this proposed dose escalation. All subjects will be followed 240 days for safety.

- In Cohort 4, 2 subjects will receive 30 mg/kg MEDI-557 (n=1) or motavizumab (n=1) and will be followed for 30 days before additional subjects are dosed. If no safety concerns are observed through Study Day 30, an additional 4 subjects will receive a single IV dose of 30 mg/kg MEDI-557 (n=2) or motavizumab (n=2). All 6 subjects will be followed 240 days for safety.

Decisions regarding dose escalation will be made by the Medical Monitor based on review of cumulative safety data and pharmacokinetic results. The blinded safety data will also be independently reviewed after each dose escalation by the Safety Monitoring Committee, which can recommend interrupting or stopping study entry or modification of the dose level. In the event that a subject does not complete the designated safety follow-up for assessment for dosing of additional subjects in a given cohort, a decision to provide a replacement subject, to enroll additional subjects, or to escalate to a new dosing cohort will occur after safety review by the medical monitor and recommendations are made by the SMC.

Unless consent for follow-up is withdrawn, subjects discontinued after receiving a partial study drug dose will be followed for the full study period (240 days post study drug administration) with all laboratory and clinical evaluations collected as defined in the protocol.

SUBJECT POPULATION:

The subjects in this study will be healthy male or female adults.

Inclusion criteria:

Subjects must meet all of the following criteria:

1. Age 18 through 45 years at the time of study entry;
2. Weight ≤ 90 kg;
3. Healthy by medical history and physical examination;
4. Normotensive (systolic blood pressure [BP] < 150 mmHg and diastolic BP < 90 mmHg);
5. Normal electrocardiogram at screening (must occur within 21 days before entry into the study);
6. Normal spirometry at screening (must occur within 21 days before entry into the study). Normal spirometry is defined as FEV1 (forced expiratory volume in 1 second) and FVC (forced vital capacity) ≥ 80% predicted and an FEV1/FVC > 70%.
7. Written informed consent obtained from the subject;
8. Sexually active females, unless surgically sterile, must have used an effective method of avoiding pregnancy (including oral or implanted contraceptives, intrauterine device, female condom with spermicide, diaphragm with spermicide, cervical cap, abstinence, use of a condom with spermicide by the sexual partner or sterile sexual partner) for 14 days prior to study drug dosing, must agree to continue using such precautions for 1 year after administration of study drug, and must have a negative serum pregnancy test within 3 days prior to study drug dosing and a negative urine pregnancy test on the day of study drug administration; and
9. Ability to complete follow-up period of 240 days as required by the protocol.

Exclusion criteria:

Subjects must have none of the following:

1. Acute illness at study entry;
2. Fever ≥ 99.5°F at study entry;
3. Any drug therapy within 7 days prior to Study Day 0 (except contraceptives);
4. Blood donation in excess of 400 mL within 6 months prior to study entry;
5. Receipt of immunoglobulin or blood products within 60 days prior to study entry;

6. Receipt of any investigational drug therapy or standard vaccine within 120 days prior to study drug dosing through 240 days after study drug dosing;
7. Previous receipt of palivizumab or motavizumab;
8. History of immunodeficiency;
9. History of allergic disease or reactions likely to be exacerbated by any component of either study drug;
10. Previous medical history or evidence of an intercurrent illness that may compromise the safety of the subject in the study;
11. Evidence of any systemic disease on physical examination;
12. Evidence of infection (ie, positive laboratory test result) with hepatitis A, B, or C virus or human immunodeficiency virus-1;
13. At screening (must be within 21 days before entry into the study) any of the following: hemoglobin < 12.0 gm/dL, white blood cell count < 4,000/mm^3, platelet count < 120,000/mm^3 (or laboratory normal values); aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, serum creatinine > upper limit of normal; other abnormal laboratory values in the screening panel which, in the opinion of the principal investigator, are judged to be clinically significant; other abnormal laboratory values in the screening panel which, in the opinion of the principal investigator, are judged to potentially confound analysis of study results;
14. Pregnancy, or nursing mother;
15. History of alcohol or drug abuse within the past 2 years; or
16. History of asthma, seasonal allergies, or exercise-induced wheezing.

TREATMENT:

Subjects will be enrolled in one of four dose cohorts in a stepwise escalation. In each dose cohort, subjects will be randomized to receive a single IV dose of either MEDI-557 or motavizumab as follows:

Cohort 1:	N= 6* or 12	Single IV dose of 0.3 mg/kg MEDI-557 or motavizumab
Cohort 2:	N= 12	Single IV dose of 3 mg/kg MEDI-557 or motavizumab
Cohort 3:	N= 6	Single IV dose of 15 mg/kg MEDI-557 or motavizumab
Cohort 4:	N= 6	Single IV dose of 30 mg/kg MEDI-557 or motavizumab

* If a related SAE occurs in the first 6 subjects, an additional 6 subjects will be added to the cohort.

SUBJECT EVALUATION AND FOLLOW-UP:

Subjects will be followed for safety and tolerability of the study drug including the assessment of adverse events (AEs), SAEs, and hematologic and blood chemistry abnormalities. Blood will be drawn to determine serum MEDI-557 and motavizumab concentrations and to measure anti-MEDI-557 and anti-motavizumab antibodies. Serum samples will also be used to perform functional assays such as microneutralization assays to test the activity of the antibody. Nasal wash samples will be assessed for the presence of MEDI-557 and motavizumab. A schedule of subject evaluations is presented in Table 1.

ASSESSMENT OF ENDPOINTS:

The primary endpoint is the safety and tolerability of MEDI-557 as measured by:

- The occurrence of AEs from the period immediately following study drug administration through 28 days after dosing and the occurrence of targeted AEs of immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), wheezing, abnormal pulmonary function tests (PFTs), and hypersensitivity reactions from the period immediately following study drug administration through 240 days after dosing.
- The occurrence of laboratory AEs from the period immediately following study drug administration through 90 days after dosing. Increased toxicity grades for laboratory evaluations will be noted through the 90-day period following administration of study drug. On Study Day 90, a medical history update and complete physical examination will be performed.
- The occurrence of SAEs from the period immediately following study drug administration through 240 days after dosing.

The secondary endpoints are the single-dose pharmacokinetic parameters of MEDI-557 and motavizumab such as:

- C_{max}: Maximum serum concentration
- T_{max}: Time to maximum serum concentration
- $t_{½}$: Terminal phase elimination half-life
- AUC_{0-t}: Area under the serum concentration-time curve from time zero to last measurable time point
- $AUC_{0-\infty}$: Area under the serum concentration-time curve from time zero to infinity
- Vd_z: Terminal phase volume of distribution
- CL: Total body serum clearance

Pharmacokinetic parameters will be estimated using noncompartmental analysis. Relative increase in MEDI-557 half-life and AUC will be compared to motavizumab. Dose proportionality and linearity of pharmacokinetic parameters will also be assessed.

The occurrence of serum anti-MEDI-557 and anti-motavizumab antibodies will be determined.

MEDI-557 and motavizumab levels in nasal wash aspirates will be summarized.

1 INTRODUCTION

1.1 Background

Respiratory syncytial virus (RSV) is an important respiratory pathogen of infants and young children, causing annual epidemics of bronchiolitis and pneumonia worldwide.[1,2] Severe RSV illness commonly occurs among infants with primary infection in the first year of life. By 2 years of age, almost all infants have experienced a primary RSV infection.[12] Respiratory syncytial virus is estimated to cause as much as 75% of all childhood bronchiolitis and up to 40% of all pediatric pneumonias.[13] Lower respiratory tract disease due to RSV accounts for more than 125,000 pediatric hospitalizations and approximately 6.3 deaths per 100,000 person years among children up to 4 years of age in the United States.[3,4,5] Infants with chronic lung disease (CLD) of prematurity and hemodynamically significant congenital heart disease (CHD) are hospitalized 4-5 times more frequently than non-high-risk children and experience increased morbidity and mortality.[6,7,8,9] Despite improvements in treatment, there is a 3% to 4% case fatality rate in infants with heart and/or lung disease who are hospitalized with RSV infection, whereas the overall infant case fatality rate due to RSV has been documented as 1%.[5] Long-term complications of RSV infection, and bronchiolitis in general, include recurrent wheezing, pulmonary function abnormalities and airway hyperreactivity.[14] In some studies, RSV lower respiratory tract infection (LRI) has been linked to chronic reactive airway disease.[15,16,17]

One product, namely, palivizumab, a humanized monoclonal antibody directed against a neutralizing epitope on the RSV F protein, is currently approved and marketed worldwide for passive immunoprophylaxis of RSV in infants at risk for serious RSV disease. Two placebo-controlled Phase 3 studies of palivizumab were conducted, ie, MI-CP018 (in premature children and children with CLD of prematurity) and MI-CP048 (in children with CHD). In both of these studies, monthly intramuscular (IM) administration of 15 mg/kg palivizumab was highly effective compared to placebo in reduction of RSV hospitalization.[18,19,20] For both populations studied, the overall reduction in RSV hospitalization rates was approximately 50%, and palivizumab was shown to be well-tolerated.

The impetus for the development of a second-generation enhanced potency RSV-specific Mab product is the challenge to further impact on the RSV hospitalization rate reductions afforded by palivizumab, and possibly provide additional clinical benefits. Prior to initiation of the clinical program for motavizumab, preclinical studies demonstrated that motavizumab has enhanced activity against RSV. Using the cotton rat model of RSV infection as an important correlate for the clinical efficacy of palivizumab, motavizumab at equivalent serum levels reduces viral titers in the lower respiratory tract by 50- to 100-fold over palivizumab. At equivalent serum concentrations, motavizumab reduces RSV in the upper respiratory tract of cotton rats by 2 to 3 logs, whereas palivizumab has minimal effect. In a pivotal Phase 3 study in high-risk children, 5 monthly intramuscular (IM) doses of 15 mg/kg motavizumab were given for RSV prophylaxis over an RSV season with palivizumab as the comparator (n=3306, palivizumab; n=3329, motavizumab). Motavizumab met the primary endpoint of demonstrating non-inferiority to palivizumab with a 26% overall reduction [RR: 0.740, 95% CI: (0.503, 1.083)] in RSV hospitalizations, $p<0.01$. In addition, motavizumab demonstrated superior efficacy compared to

palivizumab with approximately a 50% reduction of RSV-specific LRI requiring medical outpatient treatment, $p<0.01$.

Motavizumab is given as a monthly IM injection for five doses. Considering the anticipated superior efficacy of motavizumab against RSV in children, an important initiative is to develop a candidate drug product with comparable anti-RSV activity and clinical benefit, with the additional benefit of a prolonged half-life in vivo. Increasing systemic exposure of this molecule as a result of the prolonged half-life offers the potential advantages of sustained, higher drug concentrations, a decreased frequency of dosing, improved convenience, and improved patient compliance.

1.2 Description of MEDI-557

Persuasive evidence indicates that the major histocompatibility complex (MHC) class I-related neonatal Fc receptor (FcRn) plays a central role in the control of the homeostasis of serum γ-globulins in mammals.[21] The Fc-binding FcRn is a heterodimer formed by the association of a light (β2-microglobulin) and membrane-anchored heavy (α) chain. The most notable feature of this interaction is its pH-dependency, as the binding affinity of the Fc portion of IgGs to FcRn is strongest at slightly acidic pH but marginal under neutral pH. Previous work carried out in mice and nonhuman primates has suggested that engineering IgGs for better binding to FcRn at pH 6.0 is a viable strategy to extend their serum half-life in humans.[22,23,24] Thus, the Fc-FcRn interaction has been engineered in an effort to improve the stability of this complex.[25] More precisely, using phage display, libraries were screened in which specific Fc residues in contact with (or in close proximity of) FcRn were randomized.[25] This allowed the identification of several substitutions in the Fc region, some of which resulted in an increase in the human IgG-human FcRn binding affinity. Among these changes, a triple substitution in the CH2 domain (M252Y/S254T/T256E; EU numbering, referred to as "YTE") increased the binding of various human IgG1s to human FcRn by about 10-fold at pH 6.0 while allowing their efficient release at pH 7.4.

MEDI-557 differs from motavizumab in the YTE variation described above. MedImmune anticipates that MEDI-557 will have a prolonged pharmacokinetic half-life because of the triple mutation on the Fc region. Both antibodies bind to the F-protein of RSV and have no internal targets in man. Motavizumab was studied in healthy adult subjects at intravenous (IV) doses of 3, 15, and 30 mg/kg in a Phase 1 clinical trial (MI-CP101) and was found to be safe and was well tolerated. In addition, a sizeable body of clinical evidence exists on the safety and tolerability of multiple IM doses of motavizumab over 5 months in approximately 5000 children. Because of the YTE variation present in MEDI-557, MEDI-557 has the potential to reduce the frequency of administration required for motavizumab, which is given as five monthly IM injections, while retaining the anti-RSV activity of the parent molecule.

1.3 Nonclinical Experience With MEDI-557

Nonclinical investigations of MEDI-557 include comparative in vitro binding studies of MEDI-557 and motavizumab for human and cynomolgus monkey FcRn receptor, investigations of MEDI-557's RSV microneutralization activity, tissue cross-reactivity studies, and pharmaco-

and toxicokinetic studies in cynomolgus monkeys administered a single IV dose. A complete description of these investigations is provided in the Investigator's Brochure.

Binding of MEDI-557 and motavizumab to human and cynomolgus monkey FcRn was analyzed by surface plasmon resonance detection using a BIAcore 3000 instrument (BIAcore International AB, Uppsala, Sweden). MEDI-557 and motavizumab were coupled to the dextran matrix of a CM5 sensor chip at a surface density of approximately 1000 resonance units. For equilibrium binding experiments, human and cynomolgus monkey FcRn were buffer-exchanged against 50 mM phosphate-buffered saline (PBS) pH 6.0 containing 0.05% Tween 20. Measurements were performed at 25°C with FcRn concentrations typically ranging from 2.86 μM to 6 nM at a flow rate of 5 μL/minute. The dissociation constant (K_d) for the interaction of motavizumab with human FcRn (~2.2 μM) concurs with previous values determined for other human IgG1s.[26,27] Similarly, the affinity constant determined for the binding of MEDI-557 to human FcRn (~0.2 μM) agreed with that measured for the same triple mutation in a different humanized IgG1 (palivizumab).[26] Interestingly, the observed affinities for the binding of motavizumab and MEDI-557 to cynomolgus monkey FcRn (~1.2 and 0.1 μM, respectively) were approximately 2-fold higher than seen for human FcRn. However, the affinity increase of IgG1 binding to cynomolgus monkey and human FcRn at pH 6.0 (9- and 11-fold, respectively) was similar between motavizumab and MEDI-557. No such increase was observed at pH 7.4. At pH 7.4, neither motavizumab nor MEDI-557 exhibited significant binding to either monkey or human FcRn.

To investigate the effect of the triple mutation (YTE) on antibody function, an RSV microneutralization assay was conducted. The assay was carried out as previously described.[18] MEDI-557 and motavizumab exhibited indistinguishable RSV microneutralization properties, indicating that the triple Fc mutation did not result in major structural changes in the IgG molecule or in significant alteration of its functional activity. These results agree with data that show that the affinity of MEDI-557 for its cognate antigen (RSV F protein) is not significantly different from that of motavizumab.

An in vivo study was designed to examine the effect of the triple mutation (YTE) on serum IgG half-life. In this non-Good Laboratory Practice (non-GLP) study conducted by [redacted] (Gaithersburg, MD), 20 male cynomolgus monkeys were randomized using computer-generated random numbers and assigned to one of two study groups. Each animal received a single IV dose of motavizumab or MEDI-557 at 30 mg/kg. Blood samples were drawn prior to dosing on Day 0, at 1 and 4 hours after dosing, and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 31, 41 and 55 days after dosing. Serum concentrations of motavizumab and MEDI-557 were determined using an anti-motavizumab enzyme-linked immunosorbent assay (ELISA). In summary, MEDI-557 exhibited a significantly increased serum persistence compared to motavizumab. Although the mean serum concentration of MEDI-557 and motavizumab were similar during the first day post dose, the serum levels of motavizumab decreased rapidly from approximately 300 μg/mL on Day 2 to below the limit of detection on Day 55 (end of study). In contrast, the serum levels of MEDI-557 gradually decreased from approximately 380 μg/mL on Day 2 to approximately 60 μg/mL on Day 55. The corresponding pharmacokinetic parameters from this study were also determined. The serum half-life of MEDI-557 was nearly 4-fold greater than that of motavizumab (21.2 ± 9.1 vs. 5.7 ±1.4 days, respectively). Likewise, the area

under the concentration-time curve (AUC; a measure of drug exposure) for MEDI-557 was nearly 5 times greater than for motavizumab (29.4 ± 0.5 and 6.1 ± 1.5 h μg/mL x 10^4, respectively). Application of a statistical test (Wilcoxon test[28]) suggested the differences in half-lives and AUCs were statistically significant ($p<0.001$). The mean maximum serum antibody concentration was similar for MEDI-557 and motavizumab and was achieved by 1 hour post infusion in most of the animals (639 ± 248 and 644 ± 211 μg/mL, respectively).

The results of a second, similar pharmacokinetic study in which blood samples were drawn at intervals up to and including 24 days post infusion showed the same trends in serum pharmacokinetic profiles and in the corresponding pharmacokinetic parameters (data not shown). The serum half-life and AUC of MEDI-557 were more than 3 and 8 times, respectively, greater than that of motavizumab. Also in this study, bronchoalveolar lavage (BAL) samples were collected at two time points for both MEDI-557 and motavizumab and the corresponding human IgG levels were quantitated.[25] MEDI-557 levels in BALs were significantly increased on Days 4 (2.6-fold) and 24 (4.1-fold) post infusion when compared to motavizumab.

A GLP-compliant study designed to assess the toxicokinetic and safety profile of MEDI-557 administered as a single IV dose was conducted in cynomolgus monkeys. The study was performed by [redacted] (Vienna, VA). Twenty-four male and 24 female cynomolgus monkeys were administered MEDI-557 (3, 30, or 100 mg/kg) or control vehicle as a single IV infusion over 30 minutes on Day 1. After dosing, animals were observed for 14 days (Day 15 interim sacrifice) and 84 days (Day 85 terminal necropsy) to assess the reversibility, persistence, or delayed occurrence of effects. Toxicity evaluations included mortality, clinical, body weight, dermal irritation, ophthalmologic, electrocardiographic, heart rate, blood pressure, clinical pathology, organ weight, macroscopic, and microscopic data. Blood samples were drawn once predose, immediately post infusion, and at 1, 4, 12, and 24 hours post dose, and at intervals up to and including Day 85. Three monkeys/sex/dose group were sacrificed on Day 15, and the remaining monkeys in each dose group were sacrificed on Day 85. There were no treatment-related findings following dosing in the GLP toxicology study, and the no-observed-adverse-effect level was determined to be at least 100 mg/kg (the highest dose tested.)

Toxicokinetic results showed that the mean maximum concentration (C_{max}) of MEDI-557 in serum increased approximately dose proportionately. At doses of 3, 30, and 100 mg/kg, C_{max} was equal to 73, 1159, and 4088 μg/mL for animals sacrificed on Day 15, respectively, and 79, 1044, and 3274 μg/mL for animals sacrificed on Day 85, respectively. Mean C_{max} was similar in male and female animals at each dose level. Mean serum half-life was 26, 23, and 21 days in the 3, 30, and 100 mg/kg dose groups, respectively. For males, the mean serum half-life was 29, 27, and 25 days for the 3, 30, and 100 mg/kg groups, respectively, while mean serum half-life for females was shorter (23, 19, and 16 days, respectively). The mean observed AUC from time 0 to 84 hours after the last dose ($AUC_{(0-84)}$) for males was 30680, 389367, and 710630 μg•h/mL for the low-, mid-, and high-dose groups, respectively. The mean observed $AUC_{(0-84)}$ for females was 24993, 286766, and 795340 μg•h/mL for the low-, mid-, and high-dose groups, respectively. The mean AUC from time zero to infinity ($AUC_{(0-\infty)}$) for males was 35257, 435775, and 787819 μg•h/mL for the 3, 30, and 100 mg/kg groups, respectively. The mean $AUC_{(0-\infty)}$ for females was 26848, 300410, 819139 μg•h/mL for the 3, 30, and 100 mg/kg group respectively. Both observed $AUC_{(0-84)}$ and $AUC_{(0-\infty)}$ demonstrated approximate dose proportionality across the dose

range of 3, 30, and 100 mg/kg. Consistent with differences in serum half-life, MEDI-557 clearance was lower in males compared to females (2.2 vs. 2.7 mL/day/kg for the 3 mg/kg group and 1.7 vs. 2.5 mL/day/kg for the 30 mg/kg group), and similar for the 100 mg/kg group (ie, 3.2 vs. 3.3 mL/day/kg).

Further details of preclinical experiments with MEDI-557, including but not limited to tissue cross-reactivity and immunogenicity results, and studies comparing the binding of MEDI-557 and motavizumab to monkey or human serum, are presented in the Investigator's Brochure.

1.4 Clinical Experience

1.4.1 Clinical Experience With MEDI-557

No clinical studies of MEDI-557 have yet been conducted. Clinical experience with MEDI-557 is updated annually in the Investigator Brochure (IB). Please see the current IB for the most current information.

1.4.2 Clinical Experience With Motavizumab

Motavizumab, from which MEDI-557 is derived, has been investigated in approximately 5000 adults and children in clinical trials.

The Phase 1/2 program for motavizumab consists of four completed studies, one in healthy adults (MI-CP101) and three in pediatric patients (MI-CP104, MI-CP106, MI-CP118). A pivotal Phase 3 palivizumab-controlled study in high-risk children (MI-CP110) has also been completed. A clinical study report for MI-CP110 is in preparation. A second Phase 3 placebo-controlled study in otherwise healthy Native American infants (MI-CP117) has completed the third season of enrollment. Two additional Phase 2 prophylaxis studies were initiated: a study of motavizumab in children with hemodynamically significant CHD, with palivizumab as a control, which has completed the first season of enrollment and patient visits (MI-CP124); and a study in high-risk children in which motavizumab and palivizumab are administered in the same season in two groups and motavizumab alone in a third group (MI-CP127). MI-CP124 is an ongoing trial. The MI-CP127 study has been completed and a clinical study report is in preparation. Two Phase 2 treatment studies have also been initiated: a study in children hospitalized with RSV illness (MI-CP141), and a study for the outpatient treatment of children with RSV illness (MI-CP146). Enrollment and patient visits for MI-CP141 and MI-CP146 are ongoing.

In MI-CP101, 30 healthy adults received motavizumab as a single IV dose at 3, 15, or 30 mg/kg, a single IM dose at 3 mg/kg, or two IM doses at 3 mg/kg (n=6 per group). In MI-CP104, 217 high-risk non-infected infants received between 1 and 5 IM doses of motavizumab at 3 (n=6) or 15 (n=211) mg/kg. Of the 217 children who participated in MI-CP104, 136 children received 15 mg/kg IM motavizumab or palivizumab for a second RSV season (MI-CP118). In MI-CP106, 30 children hospitalized with RSV infection received a single IV dose of motavizumab (3, 15, or 30 mg/kg) or placebo (n=5 at each dose level, and n=15 placebo). Over 3300 children received 15 mg/kg IM motavizumab in MI-CP110. In addition, more than 1200 children have received motavizumab in the 1 recently completed and 2 ongoing Phase 2/3 studies (MI-CP127, MI-CP117, and MI-CP124).

Safety data from the completed Phase 1, 2, and 3 trials in adults and children indicate that motavizumab is well tolerated. Adverse events (AEs) were typically Level 1 (mild) or Level 2 (moderate) in severity, and consistent with the underlying conditions in the high-risk pediatric population (MI-CP104 and MI-CP118) or hospitalized children (MI-CP106). No dose-limiting toxicities were observed in adults or children up to the 30 mg/kg dose tested. In MI-CP104, one serious adverse event (SAE; idiopathic thrombocytopenic purpura [ITP]) was considered to be possibly related to study drug by the Medical Monitor and dosing was discontinued after Dose 4. The child's platelet count normalized within 11 days after the onset of the event. In MI-CP118, there was one SAE (acute hypersensitivity reaction) that resulted in permanent discontinuation of study drug.

In MI-CP110 (A Pivotal Phase 3 Study of MEDI-524 [Numax], an Enhanced Potency Humanized Respiratory Syncytial Virus [RSV] Monoclonal Antibody, for the Prophylaxis of Serious RSV Disease in High-Risk Children), 5 monthly IM doses of 15 mg/kg motavizumab were given for RSV prophylaxis over an RSV season with palivizumab as the comparator (n=3306, palivizumab; n=3329, motavizumab). Motavizumab met the primary endpoint of demonstrating non-inferiority to palivizumab with a 26% overall reduction [RR: 0.740, 95% CI: (0.503, 1.083)] in RSV hospitalizations, $p<0.01$. In addition, motavizumab demonstrated superior efficacy compared to palivizumab with approximately a 50% reduction of RSV-specific LRI requiring medical outpatient treatment, $p<0.01$.

In MI-CP110, monthly IM injections of motavizumab were well tolerated in this high-risk pediatric study population. The 2 monoclonal antibodies had comparable rates of adverse events, SAEs overall, and AEs leading to drug discontinuations. Skin events consistent with hypersensitivity occurring within 2 days of dosing were infrequent with a higher incidence in patients receiving motavizumab (0.7% motavizumab vs 0.2% palivizumab); for 0.3% of patients in the motavizumab group these events were reported as Level 3 or SAEs. All skin events resolved (most within 3 days) without recurrence. No significant differences in fatalities were observed between groups, and rates of sudden death or sudden infant death syndrome were consistent with reported rates.

At all dosages evaluated in adults, motavizumab had a serum half-life similar to palivizumab and other IgG1 antibodies, and had serum concentrations similar to palivizumab. Trough serum concentrations in children receiving repeat doses of 15 mg/kg IM in MI-CP104 and MI-CP110 increased with repeat dosing, as expected. The predicted serum half-life of motavizumab in children is consistent with that of an IgG1 monoclonal antibody and is similar to that seen in children dosed with palivizumab.

Anti-idiotype immune responses to motavizumab were demonstrated in 4 adult subjects; these responses occurred in the absence of any systemic clinical findings. In 3 of these subjects with detectable immune reactivity who were available for follow-up, responses decreased (to <1:40 or by more than 4-fold) through 8 to 10 months post final dose. This rate is similar to that seen in adults dosed with palivizumab. In MI-CP104, anti-motavizumab immune responses were seen in approximately 3% of children receiving repeat IM doses of 3 or 15 mg/kg motavizumab and only after the completion of dosing (first detected at 30 days post Dose 5 or 90 days after final dose).

Anti-motavizumab antibody in the 3 children who developed an immune response 30 days after Dose 5 was associated with no detectable serum motavizumab at that time point. One child with transient ITP subsequently had a motavizumab immune response detected 90 days after the last dose (Dose 4). There have been no other individual or group SAEs or other safety signals associated with the children having shown immune reactivity to motavizumab. In the IMpact-RSV trial in high-risk children, the incidence of anti-palivizumab antibody 30 days following the fourth injection was 1.1% in the placebo group and 0.7% in the palivizumab group. In MI-CP118, following 4 to 5 doses of motavizumab, no immune reactivity to motavizumab was detected at 90 to 120 days post last dose. In MI-CP110, the incidence of anti-motavizumab antibody in the motavizumab group was low, <1%, and comparable to the historical anti-palivizumab antibody rate, ie, 0.7% in MI-CP018.

Clinical experience with motavizumab is updated annually in the Investigator Brochure (IB). Please see the current IB for the most current information.

1.5 Rationale

Respiratory syncytial virus (RSV) is an important respiratory pathogen of infants and young children, causing annual epidemics of bronchiolitis and pneumonia worldwide.[1,2] The greatest morbidity and mortality occur among children at high risk for severe RSV disease, including premature infants, infants with BPD, and infants with complicated CHD. Lower respiratory tract disease due to RSV accounts for more than 125,000 pediatric hospitalizations and approximately 6.3 deaths per 100,000 person years among children up to 4 years of age in the United States.[3,4,5] Overall, the hospitalization rate due to RSV in infants less than 1 year of age is approximately 2%. Premature infants, infants with BPD, and infants with complicated CHD are admitted 4 to 5 times more frequently than non-high-risk children and have increased morbidity and mortality.[6,7,8,9] Prevention of serious RSV disease has been a high priority for the pediatric medical community. Despite several decades of attempts, no vaccine is yet licensed for active immunization to prevent RSV infection.[10,11] However, methods for passive immunization have been developed and are currently available.

MEDI-557 is a recombinant humanized IgG1κ Mab derived from motavizumab with three amino acid changes in the Fc region. Modification of the Fc region of IgG antibodies that results in increased affinity to the FcRn receptor has been shown to prolong the time period of sustained serum concentration of the antibody. The change from motavizumab in the Fc region in MEDI-557 increases the serum half-life of MEDI-557 in cynomolgus monkeys by 4-fold compared with motavizumab. Thus, MEDI-557 has the potential to reduce the frequency of administration required for motavizumab, which is given as five monthly IM injections, while retaining the anti-RSV activity of the parent molecule.

Motavizumab is a recombinant humanized, RSV-specific, IgG1 Mab derived by in vitro affinity maturation of the murine complementarity determining regions of the heavy and light chains of palivizumab. Synagis® (palivizumab) is a marketed Mab that effectively reduces hospitalizations due to RSV by approximately 50% in high-risk infants when it is given as a monthly immunoprophylaxis. In vitro and in vivo preclinical studies have demonstrated the enhanced potency of motavizumab in RSV neutralization in tissue culture and RSV titer

reduction in the lungs and upper respiratory tract in the RSV cotton rat model compared with palivizumab. In a recently unblinded, multi-national Phase 3 study (MI-CP110), motavizumab showed a 26% reduction in RSV hospitalizations of high-risk infants compared to Synagis, and a 50% reduction in RSV-specific, medically attended LRIs compared to Synagis. Motavizumab is being studied in four additional ongoing Phase 2/3 clinical trials of RSV infections in high-risk children.

This is a Phase 1, first-in-human, randomized, double-blind, single-dose, dose-escalation trial to investigate the safety, tolerability, pharmacokinetics, and immunogenicity of MEDI-557, administered as a single IV dose, in healthy adults. The starting dose of 0.3 mg/kg is >300-fold lower than the no-observable-adverse-effect-level of 100 mg/kg in cynomolgus monkeys.

2 STUDY OBJECTIVES AND OVERVIEW

2.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of a single IV dose of MEDI-557 administered to healthy adult subjects in the following dose cohorts:

- Cohort 1: 0.3 mg/kg
- Cohort 2: 3 mg/kg
- Cohort 3: 15 mg/kg
- Cohort 4: 30 mg/kg

2.2 Secondary Objectives

The secondary objectives of this study are to:

1. Evaluate the serum pharmacokinetics of MEDI-557 and motavizumab;
2. Determine the immunogenicity of MEDI-557 and motavizumab; and
3. Quantitate the concentration of MEDI-557 and motavizumab in the upper respiratory tract.

2.3 Overview

This is a Phase 1, first-in-human, randomized, double-blind, single-dose, dose-escalation study. A maximum of 36 healthy adult subjects will participate in this study comprising four dose cohorts: Cohort 1 (0.3 mg/kg), Cohort 2 (3 mg/kg), Cohort 3 (15 mg/kg), and Cohort 4 (30 mg/kg). Within each dose cohort, subjects will be randomized in a 1:1 ratio to receive a single IV dose of either MEDI-557 or motavizumab on Study Day 0 and will be followed 240 days for safety as follows:

- In Cohort 1, 2 subjects will receive 0.3 mg/kg MEDI-557 (n=1) or motavizumab (n=1) and will be followed for 60 days before additional subjects are dosed. If no safety concerns are observed in these 2 subjects through Study Day 60, an additional 4 subjects will receive a single IV dose of 0.3 mg/kg MEDI-557 (n=2) or motavizumab (n=2) and will be followed for 60 days before additional subjects are dosed. If no safety concerns are observed in these 4 subjects through Study Day 60, enrollment into the next higher dose cohort (Cohort 2 [3 mg/kg]) will commence. Before escalation to the next dose level, 2 subjects will have been followed for 120 days and 4 subjects for 60 days. Because of the low dose with resultant

predicted low serum levels (less than the limit of quantification) at 60 days, this length of follow-up should provide adequate safety information for dose escalation. If there is an occurrence of 1 SAE deemed possibly, probably, or definitely related to study drug in Cohort 1, 6 additional subjects will receive a single IV dose of 0.3 mg/kg MEDI-557 (n=3) or motavizumab (n=3) and will be followed for 60 days before additional subjects are dosed. If there is a recurrence of a similar related SAE in ≥ 2 subjects in Cohort 1, the trial will be terminated. All subjects will be followed 240 days for safety.

- In Cohort 2, 2 subjects will receive 3 mg/kg MEDI-557 (n=1) or motavizumab (n=1) and will be followed for 90 days before additional subjects are dosed. If no safety concerns are observed through Study Day 90, an additional 4 subjects will receive a single IV dose of 3 mg/kg MEDI-557 (n=2) or motavizumab (n=2) and will be followed for 90 days before additional subjects are dosed. On Study Day 90, blood samples will be drawn from all 6 subjects to measure serum drug levels. If pharmacokinetic data indicate a <2-fold increase in MEDI-557 serum half-life and AUC compared to motavizumab, it will be concluded that additional data at that dose level will not be useful and further enrollment into Cohort 2 and higher dose cohorts will not occur. If no safety concerns are observed and the pharmacokinetic results are favorable in these 6 subjects through Study Day 90, an additional 6 subjects will receive a single IV dose of 3 mg/kg MEDI-557 (n=3) or motavizumab (n=3) and be followed for 30 days before additional subjects are dosed. On Study Day 30, if no safety concerns are observed in any subject in Cohort 2, enrollment into the next higher dose cohort (Cohort 3 [15 mg/kg]) will commence. Before escalation to the next dose level, 2 subjects will be ~200 days post dose, 4 subjects ~120 days post dose, and 6 subjects 30 days post dose. It is expected that any acute reactions to MEDI-557 would occur within the 30 days after dosing. All subjects will be followed 240 days for safety.

- In Cohort 3, 2 subjects will receive 15 mg/kg MEDI-557 (n=1) or motavizumab (n=1) and will be followed for 30 days before additional subjects are dosed. If no safety concerns are observed through Study Day 30, an additional 4 subjects will receive a single IV dose of 15 mg/kg MEDI-557 (n=2) or motavizumab (n=2) and will be followed for 60 days before additional subjects are dosed. On Study Day 60, blood samples will be drawn from all 6 subjects to measure serum drug levels. If pharmacokinetic data indicate a <3-fold increase in MEDI-557 serum half-life and AUC compared to motavizumab, it will be concluded that additional data at this and higher dose levels will not be useful and enrollment into the higher dose level (Cohort 4 [30 mg/kg]) will not occur. If no safety concerns are observed and the pharmacokinetic results are favorable in these 6 subjects through Study Day 60, enrollment into the next higher dose cohort (Cohort 4 [30 mg/kg]) will commence. With the long follow-up period for the subjects in Cohort 2, adequate safety information should be available for this proposed dose escalation. All subjects will be followed 240 days for safety.

- In Cohort 4, 2 subjects will receive 30 mg/kg MEDI-557 (n=1) or motavizumab (n=1) and will be followed for 30 days before additional subjects are dosed. If no safety concerns are observed through Study Day 30, an additional 4 subjects will receive a single IV dose of 30 mg/kg MEDI-557 (n=2) or motavizumab (n=2). All 6 subjects will be followed 240 days for safety.

Decisions regarding dose escalation will be made by the Medical Monitor based on review of cumulative safety data and pharmacokinetic results. The blinded safety data will also be independently reviewed after each dose escalation by the Safety Monitoring Committee (SMC), which can recommend interrupting or stopping study entry or modification of the dose level. In the event that a subject does not complete the designated safety follow-up for assessment for dosing of additional subjects in a given cohort, a decision to provide a replacement subject, to enroll additional subjects, or to escalate to a new dosing cohort will occur after safety review by the medical monitor and recommendations are made by the SMC.

Unless consent for follow-up is withdrawn, subjects discontinued after receiving a partial study drug dose will be followed for the full study period (240 days post study drug administration) with all laboratory and clinical evaluations collected as defined in the protocol.

A study schematic is presented in Figure 1.

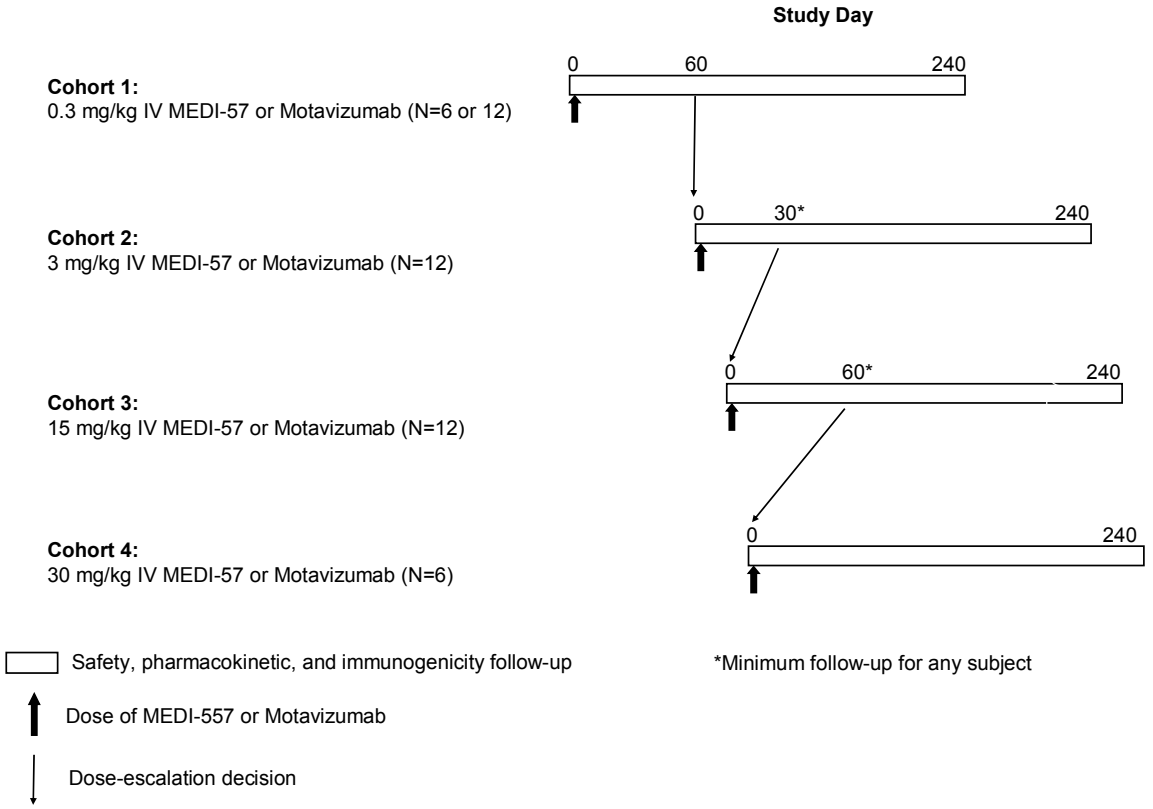

Figure 1 Study schematic of the Phase 1, dose-escalation study of MEDI-557 and motavizumab in healthy adult subjects

3 STUDY PROCEDURES

3.1 Subject Selection

The subjects in this study will be healthy male or female adults.

Each subject will be counseled by an investigator or qualified designee who will address the questions and concerns of the subject and secure written informed consent for participation in the study. Written informed consent will be obtained prior to conducting study procedures or administration of study drug.

3.1.1 Inclusion Criteria

Subjects in this study must meet all of the following criteria:

1. Age 18 through 45 years at the time of study entry;
2. Weight ≤ 90 kg;
3. Healthy by medical history and physical examination;
4. Normotensive (systolic blood pressure [BP] < 150 mmHg and diastolic BP <90 mmHg);

5. Normal electrocardiogram (ECG) at screening (must occur within 21 days before entry into the study);
6. Normal spirometry at screening (must occur within 21 days before entry into the study). Normal spirometry is defined as FEV1 (forced expiratory volume in 1 second) and FVC (forced vital capacity) ≥ 80% predicted and an FEV1/FVC > 70%.
7. Written informed consent obtained from the subject;
8. Sexually active females, unless surgically sterile, must have used an effective method of avoiding pregnancy (including oral or implanted contraceptives, intrauterine device, female condom with spermicide, diaphragm with spermicide, cervical cap, abstinence, use of a condom with spermicide by the sexual partner or sterile sexual partner) for 14 days prior to study drug dosing, must agree to continue using such precautions for 1 year after administration of study drug, and must have a negative serum pregnancy test within 3 days prior to study drug dosing and a negative urine pregnancy test on the day of study drug administration; and
9. Ability to complete follow-up period of 240 days as required by the protocol.

3.1.2 Exclusion Criteria

Subjects in this study must have none of the following:

1. Acute illness at study entry;
2. Fever ≥ 99.5°F at study entry;
3. Any drug therapy within 7 days prior to Study Day 0 (except contraceptives);
4. Blood donation in excess of 400 mL within 6 months prior to study entry;
5. Receipt of immunoglobulin or blood products within 60 days prior to study entry;
6. Receipt of any investigational drug therapy or standard vaccine within 120 days prior to study drug dosing through 240 days after study drug dosing;
7. Previous receipt of palivizumab or motavizumab;
8. History of immunodeficiency;
9. History of allergic disease or reactions likely to be exacerbated by any component of either study drug;
10. Previous medical history or evidence of an intercurrent illness that may compromise the safety of the subject in the study;
11. Evidence of any systemic disease on physical examination;
12. Evidence of infection (ie, positive laboratory test result) with hepatitis A, B, or C virus or human immunodeficiency virus-1 (HIV-1);
13. At screening (must be within 21 days before entry into the study) any of the following: hemoglobin < 12.0 gm/dL, white blood cell count (WBC) < 4,000/mm^3, platelet count < 120,000/mm^3 (or laboratory normal values); aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), serum creatinine > upper limit of normal (ULN); other abnormal laboratory values in the screening panel which, in the opinion of the principal investigator, are judged to be clinically significant; other abnormal laboratory values in the screening panel which, in the opinion of the principal investigator, are judged to potentially confound analysis of study results;
14. Pregnancy, or nursing mother;
15. History of alcohol or drug abuse within the past 2 years; or
16. History of asthma, seasonal allergies, or exercise-induced wheezing.

3.2 Randomization

3.2.1 Randomization Procedures and Treatment Allocation

Subjects will be screened by the investigator or qualified designees to assess eligibility for entry into the study. A master log will be maintained of all screened subjects. When a subject arrives in the clinic for the Study Day 0 visit, the investigator or qualified designee will confirm that the subject meets all eligibility criteria. Subjects who have signed an informed consent and who meet eligibility criteria will be randomized into the study.

An Interactive Voice Response System (IVRS) will be used for assignment of the participant identification number (PID), randomization to a treatment arm, and assignment of blinded study drug kits. A subject is considered to be randomized into the study upon receipt from the IVRS of the PID and assignment of a blinded study drug kit from the site supply.

Study drug (MEDI-557 or motavizumab) must be administered as soon as possible on the day of randomization. If the subject is entered into IVRS and then there is a delay in the administration of study drug such that it will not be administered on the day of randomization, MedImmune must be notified immediately.

Additional subjects, up to 3 per dose cohort, can be entered into the study at the discretion of the sponsor in the case of any subject who:

- Is assigned a PID but does not receive any study drug;
- Does not complete at least 50% of the study visits for reasons other than an adverse event; or
- Withdraws consent for participation in the study for reasons other than an AE

3.2.2 Blinding

This is a double-blind study. All protocol-associated MedImmune personnel or designees including the Medical Monitor, biostatistician, project manager, site monitors, and data management personnel will be blinded to treatment assignments, except for partial unblinding of personnel to treatment codes (blinding retained for subject PID, demographic, and safety data) for pharmacokinetic analyses, and MedImmune Quality Assurance. In addition, the subject and the clinical site staff (ie, the investigators, study nurses and coordinators) will be blinded except for the clinical trial material manager, who will be unblinded. MedImmune Clinical Research Pharmacy Services personnel will be unblinded to the kit randomization.

The independent clinical trial material manager will be unblinded and will prepare study drug according to the treatment group assigned by the IVRS. The clinical trial material manager will not be involved in any other aspects of the study. For this study, an independent monitor, who will only review the pharmacy records, and the study pharmacy personnel at the study site are the only individuals who will have access to information that identifies a patient's treatment allocation; these individuals will not reveal randomization/treatment code information to anyone. In the event that treatment allocation for a patient becomes known to the investigator, the investigator must notify MedImmune immediately. The clinical site staff will order study drug in a blinded fashion from the pharmacy using prescription forms provided by MedImmune and

the site's normal ordering procedures. The clinical trial material manager or designated pharmacy personnel will prepare the study drug from one or more of the appropriate vials (determined by the patient's weight and randomization assignment).

Detailed instructions for study drug ordering, preparation, IV dosing, and blinding are provided in the Clinical Trial Material Manual supplied by MedImmune (see Section 3.3.3).

3.3 Study Drug

3.3.1 Study Drug Supplies and Accountability

The sponsor will provide the investigator with adequate quantities of MEDI-557 and motavizumab for IV infusion.

MEDI-557: MEDI-557 is provided in sterile vials containing 100 mg of MEDI-557 in 1 mL of a sterile preservative-free liquid product [redacted]

Motavizumab: Motavizumab is provided in sterile vials containing 100 mg of motavizumab in 1 mL of a sterile preservative-free liquid product [redacted]

MEDI-557 and motavizumab are identical in appearance.

The Clinical Trial Material Manager is required to maintain accurate drug accountability records. Upon completion of the study, copies of all study drug accountability records as well as unused study drug will be returned to the sponsor.

3.3.2 Treatment Regimen

Subjects will be enrolled in one of four dose cohorts in a stepwise escalation. In each dose cohort, subjects will be randomized to receive a single IV dose of either MEDI-557 or motavizumab as follows:

Cohort 1:	N= 6* or 12	Single IV dose of 0.3 mg/kg MEDI-557 or motavizumab
Cohort 2:	N= 12	Single IV dose of 3 mg/kg MEDI-557 or motavizumab
Cohort 3:	N= 6	Single IV dose of 15 mg/kg MEDI-557 or motavizumab
Cohort 4:	N= 6	Single IV dose of 30 mg/kg MEDI-557 or motavizumab

* If a related SAE occurs in the first 6 subjects, an additional 6 subjects will be added to the cohort.

3.3.3 Study Drug Ordering and Preparation

The dose of study drug for administration must be prepared by the Clinical Trial Material Manager, as outlined in the Clinical Trial Material Manual. The Clinical Trial Material Manager will prepare the study drug using the PID and the subject's body weight provided by the

investigator (or designee) on the study drug order form and the confirmatory fax sent by the IVRS indicating the PID, the kit number(s), and treatment dose. To prepare study drug for administration, the Clinical Trial Material Manager should remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent. *To avoid foaming, the vial should not be shaken.*

The dose for each subject will be calculated by the Clinical Trial Material Manager (as described below) based on the subject's weight (to the nearest 0.1 kg) on the day study drug is administered. The dose should be rounded to the nearest 0.1 mL. After preparing the correct dose, the Clinical Trial Material Manager will affix one portion of the completed label to the study dose and another to the pharmacy dose preparation log along with his/her signature.

The required dose (volume) of study drug (MEDI-557 or motavizumab) will be calculated using the subject's weight in kg measured on the day of administration multiplied by the dose level in mg/kg according to the subject's assigned treatment dose. The required volume (in mL) of study drug to be given is then determined by taking the mg dose level required divided by the concentration of MEDI-557 or motavizumab (100 mg/mL). The final calculated required volume of MEDI-557 or motavizumab will be obtained by pooling the contents of as many vials as necessary within an appropriately sized syringe.

> **Dose (mL) = [subject weight]** ***(kg) x*** **[dose level]** ***mg/kg ÷ MEDI-557 or motavizumab concentration (100 mg/mL)***
>
> ***For example: For a 60.0 kg subject, at the 30 mg/kg dose level, the volume of study drug required would be 60.0 kg x 30 mg/kg ÷ 100 mg/mL = 18.0 mL***

This required volume of liquid (MEDI-557 or motavizumab) will then be mixed with a volume of normal saline to produce an infusion solution that is near isomolar. The total volume (study drug + normal saline) of the infusion for each dose level will be as follows:

- 0.3 mg/kg dose level: each subject will receive 10 cc over 15 minutes
- 3 mg/kg dose level: each subject will receive 25 cc over 15 minutes
- 15 mg/kg dose level: each subject will receive 100 cc over 70 minutes
- 30 mg/kg dose level: each subject will receive 150 cc over 140 minutes

3.3.4 Administration of Study Drug

Study drug (MEDI-557 or motavizumab) will be supplied by the Clinical Trial Material Manager in identical appearing syringes. All preparations of MEDI-557 or motavizumab must be administered within 6 hours after entering the vial of study drug. If study drug is not administered within 6 hours, a new dose must be prepared.

MEDI-557 or motavizumab **must be infused through a low protein binding 0.22 μm filter** using an IV infusion pump. After study drug has been administered, the IV tubing should be flushed with 3 to 5 mL 0.9% NaCl over 2 minutes to clear the tubing. A full description of IV dosing procedures is presented in the Clinical Trial Material Manual.

3.3.5 Concomitant Medications

All concomitant medications used by the subject from Study Day 0 through Study Day 28 will be recorded. Additionally, all concomitant medications used to treat any targeted AEs or SAEs will be recorded through Study Day 240.

Receipt of the following during the study should be immediately reported:

- Chronic immunosuppressive medication (topical or inhaled corticosteroids and short-course systemic steroids for ≤ 7 days are permitted).
- Immunoglobulin products (such as intravenous immunoglobulin [IVIG] or any investigational agents through 240 days after dosing.
- Vaccines

The sponsor or designee must be notified if any subject receives the immediately reportable concomitant medications. Subjects may receive medications to treat AEs as deemed necessary by the investigator or the subject's physician.

3.4 Schedule of Evaluations

All subjects who are assigned a PID and receive any study drug will be followed according to the protocol, unless consent for follow-up is withdrawn. It is very important to collect blood for pharmacokinetic analysis on time. The sponsor must be notified of all deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule.

Subjects will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator.

A schedule of screening and on-study visit procedures is presented in Table 1, followed by a detailed description of each visit.

Table 1 Schedule of Subject Evaluations

		Study Day																		
	Scrn[a]	0	1	3	5	7	14	21	28[k]	35	42	49	60	70	90[l]	120	150	180	210	240[m]
ELIGIBILITY																				
Written Informed Consent	X																			
Verify Eligibility Criteria	X	X																		
Assignment of PID		X																		
Medical History	X														X[b]					
Physical Examination	X														X[b]					
Height and Body Weight	X	X																		
Hepatitis A, B, C, HIV-1	X																			
Serum βHCG[c]	X																			
Urine βHCG[c]		X											X				X			X
STUDY DRUG ADMINISTRATION																				
MEDI-557 or Motavizumab		X																		
SAFETY ASSESSMENTS																				
Notation of Concomitant Medications		X	X	X	X	X	X	X	X											
Vital Signs[e]		X																		
Serum Chemistry[f]	X	X				X			X						X					
CBC With Differential, Platelets	X	X				X			X						X					
Urinalysis	X	X				X			X						X					
ECG	X																			
Spirometry	X[g]	X	X	X	X	X	X		X				X		X					X
Assessment of AEs		X	X	X	X	X	X	X	X											
Assessment of Laboratory AEs[h]						X			X						X					
Assessment of SAEs/Targeted AEs[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK/IM/OTHER																				
MEDI-557 or Motavizumab Serum Level		X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-MEDI-557 or Anti-Motavizumab Antibody Level		X					X		X				X		X		X		X	X
MEDI-557 or Motavizumab Nasal Wash Level		X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum IgG Level		X							X				X		X		X	X		X
Tetanus Antibody Level		X							X				X		X		X	X		X

Table 1 Footnotes

a. All tests to be performed within 21 days prior to Study Day 0 except for serum pregnancy which must be performed within 3 days prior to Study Day 0.
b. A medical history update and complete physical examination (PE) will be performed on Study Day 90.
c. Female subjects only.
d. Blood will be sampled for study drug serum concentration before dosing, at the end of infusion and at 0.5, 1, 4, 8, and 12 hours after end of infusion.
e. Vital signs obtained before and 30 minutes after dosing, and then at 2, 6, 12, and 24 hours after dosing.
f. ALT, AST, BUN, and creatinine.
g. Must be normal in order to be eligible for the study.
h. Scheduled labs collected on Study Days 7, 28, and 90 and additional unscheduled labs collected through Study Day 90 with increased toxicity grades will be recorded as AEs.
i. Baseline nasal wash to be performed within 12 hours prior to dosing.
j. AEs of special interest, eg, immune complex disease, wheezing, abnormal PFTs, hypersensitivity reactions.
k. Subjects who discontinue prior to Study Day 28 will undergo Study Day 28 assessments for the discontinuation visit.
l. Subjects who discontinue on Study Day 29-90 will undergo Study Day 90 assessments for the discontinuation visit.
m. Subjects who discontinue on Study Day 91-239 will undergo Study Day 240 assessments for the discontinuation visit.

Screening

Note: All screening laboratory assessments must be performed within 21 days prior to Study Day 0, except for serum pregnancy which must be performed within 3 days prior to Study Day 0. The screening evaluations may be carried out over more than one visit.

1. Written informed consent
2. Verify eligibility criteria
3. Medical history
4. Physical examination, including height and body weight
5. Urinalysis
6. ECG
7. Spirometry (must be normal in order to be eligible for the study)
8. Blood collection for screening
   - AST, ALT, BUN, creatinine
   - CBC with differential and platelet count
   - Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody and HIV-1 antibody
   - Serum βHCG (female subjects only)

Study Day 0: Study Drug Infusion

1. Verify eligibility criteria
2. Assignment of PID
3. Update body weight and height
4. Urine βHCG (female subjects only)
5. Baseline blood collection
   - AST, ALT, BUN, creatinine
   - CBC with differential and platelet count
   - Anti-MEDI-557 or anti-motavizumab antibodies
   - MEDI-557 or motavizumab serum concentration
   - Serum IgG concentration
   - Serum tetanus antibody level
6. Urinalysis
7. Spirometry
8. Baseline nasal wash aspirate (within 12 hours prior to dosing)
   - MEDI-557 or motavizumab concentration
9. Vital signs (temperature, blood pressure, pulse rate, respiratory rate) obtained before dosing, 30 minutes after dosing, and 2, 6, 12, and 24 hours after dosing
10. Administration of study drug
11. Post-infusion blood collection
    - MEDI-557 or motavizumab serum concentration (at the end of infusion, and 0.5, 1, 4, 8, and 12 hours post infusion)
12. Notation of concomitant medications
13. AE assessment
14. SAEs/targeted AEs assessment

Study Days 1, 3, and 5

1. Blood collection
   - MEDI-557 or motavizumab serum concentration
2. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
3. Spirometry
4. Notation of concomitant medications
5. AE assessment
6. SAEs/targeted AEs assessment

Study Day 7

1. Urinalysis
2. Blood collection
   - AST, ALT, BUN, creatinine
   - CBC with differential and platelet count
   - MEDI-557 or motavizumab serum concentration
   - Laboratory AE assessment
3. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
4. Spirometry
5. Notation of concomitant medications
6. AE assessment
7. SAEs/targeted AEs assessment

Study Day 14

1. Blood collection
   - MEDI-557 or motavizumab serum concentration
   - Anti-MEDI-557 or anti-motavizumab antibodies
2. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
3. Spirometry
4. Notation of concomitant medications
5. AE assessment
6. SAEs/targeted AEs assessment

Study Day 21

1. Blood collection
   - MEDI-557 or motavizumab serum concentration
2. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
3. Notation of concomitant medications
4. AE assessment
5. SAEs/targeted AEs assessment

Study Day 28 (or Study Discontinuation Visit if Discontinuation Occurs Study Day 0-28)

1. Urinalysis
2. Blood collection
   - AST, ALT, BUN, creatinine
   - CBC with differential and platelet count
   - MEDI-557 or motavizumab serum concentration
   - Anti-MEDI-557 or anti-motavizumab antibodies
   - Serum IgG
   - Serum tetanus antibody level
   - Laboratory AE assessment
3. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
4. Spirometry
5. Notation of concomitant medications
6. AE assessment
7. SAEs/targeted AEs assessment

Study Days 35, 42, 49, 70, and 120

1. Blood collection
   - MEDI-557 or motavizumab serum concentration
2. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
3. SAEs/targeted AEs assessment

Study Day 60

1. Urine βHCG (female subjects only)
2. Blood collection
   - MEDI-557 or motavizumab serum concentration
   - Anti-MEDI-557 anti-motavizumab antibodies
   - Serum IgG
   - Serum tetanus antibody level
3. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
4. Spirometry
5. SAEs/targeted AEs assessment

Study Day 90 (or Study Discontinuation Visit if Discontinuation Occurs Study Day 29-90)

1. Update medical history
2. Update physical examination
3. Urinalysis
4. Blood collection
   - AST, ALT, BUN, creatinine
   - CBC with differential and platelet count

- MEDI-557 or motavizumab serum concentration
- Anti-MEDI-557 or anti-motavizumab antibodies
- Serum IgG
- Serum tetanus antibody level
- Laboratory AE assessment

5. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
6. Spirometry
7. SAEs/targeted AEs assessment

Study Day 150

1. Urine βHCG (female subjects only)
2. Blood collection
   - MEDI-557 or motavizumab serum concentration
   - Anti-MEDI-557 or anti-motavizumab antibodies
   - Serum IgG
   - Serum tetanus antibody level
3. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
4. SAEs/targeted AEs assessment

Study Day 180

1. Blood collection
   - MEDI-557 or motavizumab serum concentration
   - Serum IgG
   - Serum tetanus antibody level
2. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
3. SAEs/targeted AEs assessment

Study Day 210

1. Blood collection
   - MEDI-557 or motavizumab serum concentration
   - Anti-MEDI-557 or anti-motavizumab antibodies
2. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
3. SAEs/targeted AEs assessment

Study Day 240 (or Study Discontinuation Visit if Discontinuation Occurs Study Day 91-239)

1. Urine βHCG (female subjects only)
2. Blood collection
   - MEDI-557 or motavizumab serum concentration
   - Anti-MEDI-557 or anti-motavizumab antibodies
   - Serum IgG

- Serum tetanus antibody level

3. Nasal wash aspirate
   - MEDI-557 or motavizumab concentration
4. Spirometry
5. SAEs/targeted AEs assessment

3.5 Subject Evaluation Methods

3.5.1 Routine Laboratory Evaluations

Routine laboratory tests during screening and during the study will be performed at the study site's local accredited clinical laboratory. Urine pregnancy tests during the study will be performed in the clinic using a licensed test. Abnormal laboratory results should be repeated as soon as possible (preferably within 24 hours). Appendix A summarizes toxicity ranges for clinical laboratory tests.

3.5.2 Nasal Wash Aspirates

Nasal wash aspirates will be collected as described in the laboratory manual. Specimens will be transported on ice, aliquoted, processed, and tested for the presence of MEDI-557 and motavizumab as indicated in the laboratory manual.

3.5.3 Pharmacokinetic and Immunogenicity Evaluations

Details for collection, aliquoting, storage, and shipment of serum samples for evaluation of serum levels of MEDI-557 and motavizumab and anti-MEDI-557 and anti-motavizumab antibodies are presented in a separate laboratory manual. All pharmacokinetic and immunologic laboratory evaluations will be performed by MedImmune. MEDI-557 and motavizumab serum concentrations and MEDI-557 and motavizumab immunogenicity will be measured by immunoassays. Unused sera will be stored and used for additional pharmacokinetic analyses (MEDI-557 characterization) and anti-MEDI-557 immunogenicity analyses as needed. Serum samples will also be used to perform functional assays such as microneutralization assays to test the activity of the antibody.

3.6 Completion of Study and Loss to Follow-up

Subjects will be considered to have completed the study if they were followed up through Study Day 240. It should be specified whether or not the subjects have completed the study follow-up procedures through Study Day 240.

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status at Study Day 240. Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, follow-up should resume according to the protocol.

4 SAFETY ASSESSMENT

4.1 Adverse Events

4.1.1 Definition of Adverse Events

As defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) an AE is:

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

An AE includes but is not limited to:

- Any clinically significant worsening of a pre-existing condition;
- An AE occurring from overdose (ie, a dose higher than that prescribed by a healthcare professional for clinical reasons, or a dose higher than that described on the marketed product label) of an investigational or marketed product, whether accidental or intentional;
- An AE occurring from abuse (eg, use for non-clinical reasons) of an investigational or marketed product;
- An AE that has been associated with the discontinuation of the use of an investigational or marketed product; and
- Adverse changes from baseline are listed on the toxicity table in Appendix A.

A protocol-related AE is an AE occurring during a clinical trial that is not related to the investigational product, but is considered by the Investigator or Medical Monitor (or designee) to be related to the research conditions, ie, related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

4.1.2 Study Reporting Period for Adverse Events

The reporting period for all AEs is the period immediately following the first administration of study drug through Study Day 28, except for 1) laboratory AEs and 2) targeted AEs of immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), wheezing, abnormal PFTs, and hypersensitivity reactions. Laboratory AEs will be collected through Study Day 90. Targeted AEs will be monitored through Study Day 240.

4.1.3 Recording of Adverse Events

Adverse events will be reported using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational study product, possible etiologies, and whether the event meets criteria as a

SAE and therefore requires immediate notification of the Sponsor. See Sections 4.3 and 4.4 regarding guidelines for assessment of severity and relationship, respectively, and Section 4.2.1 for the definition of SAEs. If the event has not resolved at the end of the study reporting period it will be documented as ongoing. If an AE evolves into a condition which becomes "serious" the investigator will additionally report to the Sponsor on the ***SERIOUS ADVERSE EVENT (SAE) REPORT FORM***.

4.2 Serious Adverse Events

4.2.1 Definition of Serious Adverse Events

A Serious Adverse Event (SAE) is any AE that:

- Results in death;
- Is life-threatening;
  - This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires in-subject hospitalization or prolongation of existing hospitalization;
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in a physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity; or
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Medically important events.
  - Medical or scientific judgment should be exercised in deciding whether (expedited) reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should also be considered serious. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm: blood dyscrasias or convulsions that not result in hospitalizations; or development of drug dependency or drug abuse.

4.2.2 Study Reporting Period for Serious Adverse Events

The reporting period for serious adverse events is the period immediately following the start of the subject's study product administration through Study Day 240. Serious adverse events must be followed until resolution by the investigator, even if this extends beyond the study-reporting period. Resolution of a serious adverse event is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

At any time after the 240-day safety follow-up period, if an investigator becomes aware of a serious adverse event that is suspected by the investigator to be related to study product, the event should be reported to MedImmune Product Safety.

4.2.3 Notification of Sponsor of Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the Study Drug, the investigator must complete the *SERIOUS ADVERSE EVENT (SAE) REPORT FORM* and fax to MedImmune Product Safety.

Note: Provide all available information at the time of form completion. When additional information becomes available, submit a follow-up ***SERIOUS ADVERSE EVENT (SAE) REPORT FORM*** with the new information. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune, Inc. of an SAE.

MedImmune contact information:

Product Safety
MedImmune
[redacted]
Fax: [redacted]

MedImmune, as sponsor of the study being conducted under an Investigational New Drug Application (IND), is responsible for reporting certain serious adverse events as IND safety reports to the FDA, other applicable regulatory authorities, and participating investigators, in accordance with the U.S. Code of Federal Regulations (21 CFR 312.32 and 312.33), ICH Guidelines, and/or local regulatory requirements. MedImmune may be required to report certain serious adverse events to regulatory authorities within 7 or 15 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by MedImmune as soon as it becomes available.

4.2.4 Notification of Institutional Review Board or Independent Ethics Committee of Serious Adverse Events

The investigator must comply with the applicable regulatory requirements related to the reporting of serious adverse events to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB or IEC must be informed in a timely manner by the principal investigator of serious adverse events occurring at their site during the study. Investigators must

also submit safety information provided by MedImmune to the IRB or IEC as detailed in Section 7.2.

4.2.5 Recording of Serious Adverse Events

Serious adverse events will be recorded on the ***SERIOUS ADVERSE EVENT (SAE) REPORT FORM*** using a recognized medical term or diagnosis that accurately reflects the event. Serious adverse events will be assessed by the investigator for severity, relationship to the study product and possible etiologies. See Sections 4.3 and 4.4 regarding guidelines for assessment of severity and relationship, respectively. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period it will be documented as ongoing. For purposes of regulatory safety monitoring the investigator is required to follow the event to resolution and report to the Sponsor the outcome of the event using the ***SERIOUS ADVERSE EVENT (SAE) REPORT FORM.***

4.3 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of adverse events and serious adverse events. The determination of severity should be made by a health care professional, one who is qualified to review adverse event information, provide a medical evaluation of adverse events, and classify adverse events based upon medical judgment and the severity categories of mild, moderate, severe, and life-threatening as provided in the toxicity table in Appendix A.

4.4 Assessment of Relationship

An SAE is considered "product-related" for the purposes of regulatory reporting if the Investigator, the Medical Monitor, or the Product Safety Physician assesses the SAE as possibly, probably, or definitely related. This is not a conclusive determination of causal association between the product and the event. Whenever the Investigator's assessment is unknown or unclear, the SAE is treated as product-related for the purposes of reporting to regulatory authorities. An SAE may be deemed to be not related to the product for purposes of regulatory reporting only if the Investigator, Medical Monitor, and Product Safety Physician, if applicable, agree that the SAE is not product-related.

The investigator is required to provide an assessment of relationship of AEs and SAEs to the study product. A number of factors should be considered in making this assessment including: 1) the temporal relationship of the event to the administration of study product; 2) whether an alternative etiology has been identified; and 3) biological plausibility. The following guidelines should be used by investigators to assess the relationship of an adverse event to study product administration.

Relationship assessments that indicate an **"Unlikely Relationship"** to study product:

None: The event is related to an etiology other than the study product (the alternative etiology must be documented in the study subject's medical record and on the SAE report form).

Remote: The event is unlikely to be related to the study product and likely to be related to factors other than study product.

Relationship assessments that indicate a **"Likely Relationship"** to study product:

Possible: There is an association between the event and the administration of the study product and there is a plausible mechanism for the event to be related to study product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

Probable: There is an association between the event and the administration of study product, a plausible mechanism for the event to be related to the study product and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.

Definite: There is an association between the event and the administration of study product, a plausible mechanism for the event to be related to the study product and causes other than the study product have been ruled out and/or the event re-appeared on re-exposure to the study product.

4.5 Other Events Requiring Immediate Reporting

The following events must be reported ***within 24 hours*** via fax to MedImmune Product Safety:

1. Any withdrawal of consent during the study
2. Moderate or severe adverse events that occur during study drug administration or during the 30-minute observation period after dosing
3. Any anaphylactic event (the occurrence of generalized urticaria, wheezing, hypotension, dyspnea, cyanosis, respiratory failure, pruritus, angioedema, hypotonia, and/or unresponsiveness) or any adverse events that are thought to be allergic reactions
4. Any medically severe adverse event (as judged by the clinical investigator)
5. Events that, in the opinion of the clinical investigator, contraindicate further dosing of additional subjects
6. Immune complex disease related to study drug

4.6 Safety Management During the Study

The MedImmune Medical Monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes immediate review of serious adverse events and timely review of other adverse events reported during the study. The MedImmune Product Safety Monitor has responsibility for the receipt, review, investigation, and follow-up of serious adverse events reported by the clinical study sites.

A Safety Monitoring Committee (SMC) will independently review safety data and make recommendations regarding further conduct of the study as requested by the Medical Monitor. Cumulative review of available safety data for all subjects will be performed by the Medical Monitor. The SMC will review safety data in response to adverse events felt to be medically significant by the Medical Monitor. The SMC is composed of at least two MedImmune physicians who are not directly involved in the day-to-day operations of the study, and two physicians who are not employees of MedImmune.

The SMC will review blinded safety surveillance data reported to MedImmune but may request to have data unblinded, if necessary, to make safety assessments and study recommendations.

4.7 Interruption or Discontinuation of Study Dosing in Individual Subjects

An individual subject will have study drug discontinued if any of the following occur in the subject in question:

1. Withdrawal of consent by the subject
2. A severe or potentially life-threatening serious systemic, allergic, or local reaction during study drug administration thought to be related to study drug

Subjects who are permanently discontinued from study drug will be followed for the full study period (through Study Day 240), including the collection of any protocol-mandated blood specimens unless consent for follow-up is withdrawn.

4.8 Interruption or Discontinuation of Study Group Dosing

If any of the following occur, no further subjects will be entered into the study until review of the event in question by the Medical Monitor and Safety Monitoring Committee (SMC):

1. Death from any cause in any subject during the 240-day period following dosing with study drug
2. Any anaphylactic event (the occurrence of generalized urticaria, wheezing, hypotension, dyspnea, cyanosis, respiratory failure, pruritus, angioedema, hypotonia, and/or unresponsiveness) or any serious allergic event
3. Any serious adverse event judged to be related (as determined by the clinical investigator and/or Medical Monitor) to study drug
4. Occurrence of 2 or more similar laboratory adverse events at severity Level 3 or 4
5. Events that, in the opinion of the Principal Investigator and/or Medical Monitor, contraindicate further dosing of additional subjects

If one of the above events occurs, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted by the Medical Monitor and the SMC to determine whether study entry should be discontinued permanently or resumed, or limited to a specific dose of study drug. SMC approval is required for resumption of the study in the event study entry was stopped due to one of the above events.

4.9 Dose-Limiting Toxicities

The following events will be considered dose-limiting toxicities and will result in no further administration of study drug to any subject until the Medical Monitor and SMC approve continuance of dosing:

1. The occurrence of immune complex disease related to study drug
2. The occurrence of two similar serious adverse events (with the exception of events associated with RSV) judged to be related to study drug, as determined by the Principal Investigator and/or Medical Monitor

4.10 Dose Escalation

Dose escalation from 0.3 mg/kg (Cohort 1) to 3 mg/kg (Cohort 2) will commence when the first 6 subjects in Cohort 1 have been followed for at least 60 days after dosing and cumulative safety data from all 6 subjects reveal no safety concerns or when all 12 subjects in Cohort 1 have been followed for at least 60 days after dosing and cumulative safety data from all subjects reveal only one related SAE. If there is a recurrence of a similar related SAE in ≥ 2 subjects in Cohort 1, the trial will be terminated.

Dose escalation from 3 mg/kg (Cohort 2) to 15 mg/kg (Cohort 3) will commence when 6 subjects in Cohort 2 have been followed for ~120 days after dosing and cumulative safety data from all subjects reveal no safety concerns and there is at least a 2-fold increase in serum half-life and AUC compared to motavizumab.

Dose escalation from 15 mg/kg (Cohort 3) to 30 mg/kg (Cohort 4) will commence when all 6 subjects in Cohort 3 have been followed for at least 60 days after dosing and cumulative safety data from all subjects reveal no safety concerns and there is at least a 3-fold increase in serum half-life and AUC in the MEDI-557 arm compared to motavizumab.

All subjects will be followed for 240 days after study drug administration.

5 STATISTICAL CONSIDERATIONS

5.1 General Considerations

All data will be provided in data listings sorted by dose cohort and PID. All tabular summaries will be by dose cohort. Categorical data will be summarized by the number and percent of subjects in each category. Continuous variables will be summarized by descriptive statistics including mean, standard deviation, minimum, and maximum. No statistical tests are planned.

5.2 Sample Size

In the Phase 1 study of motavizumab (MI-CP101), the coefficient of variation (CV) for motavizumab AUC ranged between 10% and 22% across the dose range of 3 to 30 mg/kg. Based on the assumption of a 22% CV for MEDI-557, a sample size of 6 subjects per arm in each dose cohort will be sufficient to detect a 2-fold increase in AUC with ≥ 95% power.

5.3 Subject Populations

All subjects who receive study drug and experience any safety follow-up will be included in safety summaries. Subjects who receive a full dose of study drug will be included in pharmacokinetics and immunogenicity summaries. Missing data will be treated as missing. No data will be imputed.

5.4 Primary Endpoints

The safety and tolerability of MEDI-557 will be measured by:

- The occurrence of AEs from the period immediately following study drug administration through 28 days after dosing and the occurrence of targeted AEs of immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), wheezing, abnormal PFTs, and hypersensitivity reactions from the period immediately following study drug administration through 240 days after dosing.
- The occurrence of laboratory AEs from the period immediately following study drug administration through 90 days after dosing.
- The occurrence of SAEs from the period immediately following study drug administration through 240 days after dosing.

5.5 Secondary Endpoints

The single-dose pharmacokinetic parameters of IV MEDI-557 and motavizumab such as

- C_{max}: Maximum serum concentration after infusion
- T_{max}: Time to maximum serum concentration after infusion
- $t_{½}$: Terminal phase elimination half-life
- AUC_{0-t}: Area under the serum concentration-time curve from time zero to last measurable time point
- $AUC_{0-\infty}$: Area under the serum concentration-time curve from time zero to infinity
- Vd_z: Terminal phase volume of distribution
- CL: Total body clearance

will be monitored using noncompartmental analysis. Relative increase in MEDI-557 half-life and AUC will be compared to motavizumab. Dose proportionality and linearity of pharmacokinetic parameters of MEDI-557 and motavizumab will also be assessed.

The occurrence of serum anti-MEDI-557 and anti-motavizumab antibodies will be determined.

MEDI-557 or motavizumab levels in nasal wash aspirates will be summarized.

5.6 Interim Analyses

Four separate interim analyses of pharmacokinetic parameters which may include evaluations of anti-drug antibodies are planned, one to include the first 6 subjects in Cohort 1 (0.3 mg/kg) after Study Day 90 has been completed, the second to include the first 6 subjects in Cohort 2 (3 mg/kg) after Study Day 90 has been completed, the third to include all subjects in Cohort 2 after Study Day 90 has been completed in addition to all available data from the first 6 subjects in Cohort 2, and the fourth to include all subjects in Cohort 3 (15 mg/kg) after Study Day 60 has been completed.

To ensure the blinding of each subject's treatment assignment throughout the study, the personnel who will perform the pharmacokinetic assessments will be partially unblinded to treatment codes (blinding retained for subject PID, demographic, and safety data). Independent programmers who are not involved in the conduct of the trial will be fully unblinded to prepare

the partially unblinded data for the pharmacokinetic assessments. No further unblinding will occur until the end of study.

Pharmacokinetic results will be reviewed by the Medical Monitor in consideration of the decision to continue enrollment and dose-escalate.

6 DATA COLLECTION AND MONITORING

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the investigator(s), both the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Data recorded on source documents will be transcribed onto case report forms provided by MedImmune or designee. Completed original case report forms will be retrieved by MedImmune or designee. A copy of each completed case report form will be retained by the investigator.

The study will be monitored by MedImmune or its designee on a regular basis throughout the study period. All study documents (subject's files, signed informed consent forms, copies of case report forms, Study File Notebook, etc) must be kept secured for a period of 2 years following marketing of MEDI-557 or for 2 years after centers have been notified that the IND has been discontinued. There may be other circumstances for which MedImmune is required to maintain study records and, therefore, MedImmune should be contacted prior to removing study records for any reason.

7 HUMAN SUBJECTS

7.1 Ethics and Regulatory Considerations

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

The protocol and Informed Consent Form will be reviewed and approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to MedImmune and to the IRB/IEC, and the investigator will keep the IRB/IEC informed as to the progress of the study.

The investigator will explain the nature of the study and will inform the subject that participation is voluntary and that they can withdraw at any time. Written informed consent will be obtained from each subject prior to entry into the study. A copy of the signed consent form will be given to every participant and the original will be maintained with the subject's records.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a participant identification number will

be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA or MedImmune of the clinical trial. The principal investigator must also comply with all applicable privacy regulations (eg, Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

7.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

A list of IRB/IEC members should be obtained by the investigator and provided to MedImmune.

Any documents that the IRB/IEC may need to fulfill its responsibilities, such as protocol amendments, any information concerning subject recruitment, payment or compensation procedures, or information from MedImmune will be submitted to the IRB/IEC by the investigator. The IRB/IEC's written unconditional approval of the study protocol and the informed consent form will be in the possession of the investigator and MedImmune before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to MedImmune prior to shipment of study drug supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted should be obtained.

The IRB/IEC must be informed by the principal investigator of informed consent changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

7.3 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki should be implemented before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 CFR 50.25.

Information should be given in both oral and written form, and subjects or their legal representatives must be given ample opportunity to inquire about details of the study.
The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Subjects must be informed about the aims, expected benefits, possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or the fetus, if the subject should become pregnant) which are currently unforeseeable. They must also be informed of alternative procedures. Subjects must receive an explanation as to whether any

compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. They must be informed whom to contact for answers to any questions relating to the research project. The participants must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time, without penalty or loss of benefits to which they are otherwise entitled. The extent of the confidentiality of individuals' records must be defined, and subjects must be informed that applicable data protection legislation will be complied with. Subjects must be informed that the monitor(s), auditor(s), IRB/IEC members, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

The consent form generated by the investigator must be approved by the IRB/IEC and be acceptable to MedImmune. Consent forms must be written so as to be understood by the prospective subject. Informed consent will be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or MedImmune professional and Regulatory Compliance persons. The subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

8 STUDY COMPLETION

All materials or supplies provided by MedImmune will be returned to MedImmune upon study completion. The investigator will notify the IRB/IEC when the study has been completed. Procedures for returning materials and supplies to the sponsor are provided in the Clinical Trial Materials Manual.

9 PUBLICATIONS

Publication by the site of any data from this study must be carried out in accordance with the clinical study agreement.

10 CHANGES IN THE PROTOCOL

The protocol may not be modified without written approval of MedImmune. All changes to the protocol must be submitted to the FDA and IRB/IEC, and must be approved by the IRB/IEC prior to their implementation. Documentation of IRB/IEC approval must be sent to MedImmune immediately upon receipt.

Version 4.0 of the protocol (27Mar2008) was revised on 02Apr2009. Changes to the protocol are described in APPENDIX B and are incorporated in the body of Version 5.0 of the protocol.

APPENDIX A Toxicity Table Adverse Events

Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Emergency room (ER) visit or hospitalization
Tenderness	Mild pain to touch	Pain with movement	Significant pain at rest	ER visit or hospitalization
Erythema/Redness *	2.5 - 5 cm	5.1 - 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Swelling **	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F)	38.0 - 38.4 100.4 - 101.1	38.5 - 38.9 101.2 - 102.0	39.0 - 40 102.1 - 104	> 40 > 104
Tachycardia - beats per minute	101 - 115	116 - 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute	50 - 54	45 - 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 - 150	151 - 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 - 95	96 - 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) - mm Hg	85 - 89	80 - 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate - breaths per minute	17 - 20	21 - 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 gms/ 24 hours	4 - 5 stools or 400 - 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Some interference with activity or repeated use of non-narcotic pain reliever	Significant, prevents daily activity or repeated use of narcotic pain reliever	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization

Systemic illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulation)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Sodium - Hyponatremia mEq/L	132 - 134	130 - 131	125 - 129	< 125 or abnormal sodium with clinical signs #
Sodium - Hypernatremia mEq/L	144 - 145	146 - 147	148 - 150	> 150
Potassium - Hyperkalemia mEq/L	5.1 - 5.2	5.3 - 5.4	5.5 - 5.6	> 5.6
Potassium - Hypokalemia mEq/L	3.5 - 3.6	3.3 - 3.4	3.1 - 3.2	< 3.1
Glucose - Hypoglycemia mg/dL	65 - 69	55 - 64	45 - 54	< 45
Glucose - Hyperglycemia Fasting - mg/dL Random - mg/dL	 100 - 110 110 - 125	 111 - 125 126 - 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 - 26	27 - 31	> 31	Requires dialysis
Creatinine - mg/dL	1.1 - 1.5	1.6 - 2.0	2.1 - 2.5	> 2.5 or requires dialysis
Calcium - hypocalcemia mg/dL	8.0 - 8.4	7.5 - 7.9	7.0 - 7.4	< 7.0
Calcium - hypercalcemia mg/dL	10.5 - 11.0	11.1 - 11.5	11.6 - 12.0	> 12.0
Magnesium - hypomagnesemia mg/dL	1.3 - 1.5	1.1 - 1.2	0.9 - 1.0	< 0.9
Phosphorous - hypophosphatemia mg/dL	2.3 - 2.5	2.0 - 2.2	1.6 - 1.9	< 1.6
CPK - mg/dL	1.25 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 10 x ULN	> 10 x ULN
Albumin - Hypoalbuminemia g/dL	2.8 - 3.1	2.5 - 2.7	< 2.5	--
Total Protein - Hypoproteinemia g/dL	5.5 - 6.0	5.0 - 5.4	< 5.0	--
Alkaline phosphate - increase by factor	1.1 - 2.0 x ULN	2.1 - 3.0 x ULN	3.0 - 10 x ULN	> 10 x ULN
Liver Function Tests - ALT, AST increase by factor	1.1 - 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 10 x ULN	> 10 x ULN
Bilirubin - when accompanied by any increase in Liver Function Test increase by factor	1.1 - 1.25 x ULN	1.26 - 1.5 x ULN	1.51 - 1.75 x ULN	> 1.75 x ULN

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Bilirubin - when Liver Function Test is normal; increase by factor	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.0 - 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 - 210	211 - 225	> 226	---
Pancreatic enzymes - amylase, lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
# The clinical signs of an abnormal elevation or decline should be described for each laboratory parameter to be monitored in the study.
** "ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	12.0 - 13.0	10.0 - 11.9	8.0 - 9.9	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease - 1.5	1.6 - 2.0	2.1 - 5.0	> 5.0
Hemoglobin (Male) - gm/dl	12.5 - 14.5	10.5 - 12.4	8.5 - 10.4	< 8.5
Hemoglobin (Male) change from baseline value - gm/dL	Any decrease - 1.5	1.6 - 2.0	2.1 - 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 - 15,000	15,001 - 20,000	20,001 - 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 - 3,500	1,500 - 2,499	1,000 - 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 - 1,000	500 - 749	250 - 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 - 2,000	1,000 - 1,499	500 - 999	< 500
Eosinophils - cell/mm^3	650 - 1500	1501 - 5000	> 5000	Hypereosinophilic syndrome
Platelets Decreased - cell/mm^3	125,000 - 140,000	100,000 - 124,000	25,000 - 99,000	< 25,000
PT - increase by factor (prothrombin time)	1.0 - 1.10 x ULN	1.11 - 1.20 x ULN	1.21 - 1.25 x ULN	> 1.25 ULN
PTT - increase by factor (partial thromboplastin time)	1.0 - 1.2 x ULN	1.21 - 1.4 x ULN	1.41 - 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 - 500	501 - 600	> 600	--
Fibrinogen decrease - mg/dL	150 - 200	125 - 149	100 - 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	>2+
Glucose	Trace	1+	2+	>2+
Blood (microscopic) - red blood cells per high power field (rbc/hpf)	1 - 10	11 - 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

APPENDIX B Summary of Changes to the Protocol

Version 4.0 ([redacted])

All text revisions resulting from this amendment are incorporated in the body of the protocol in Version 4.0. Major changes to the protocol are described below.

Study Abstract, Assessment of Endpoints: For consistency purposes with the body of the protocol, the time period for which AEs will be summarized was changed from 30 days to 28 days after dosing.

Section 2.3 (Overview): Text was added to clarify that for a subject who does not complete the designated safety follow-up for assessment for dosing of additional subjects in a given cohort, a decision to provide a replacement subject, to enroll additional subjects, or to escalate to a new dosing cohort will occur after safety review by the medical monitor and recommendations are made by the SMC.

Section 5.6 (Interim Analyses): Two interim analyses for PK parameters were added (the first 6 subjects in Cohort 1 after Study Day 90, and all subjects in Cohort 2 after Study Day 90 and the first 6 subjects in Cohort 2 for all available data) because it was thought that useful information could be gained by analyzing the PK data from these cohorts.

Version 5.0 ([redacted])

All text revisions resulting from this amendment are incorporated in the body of the protocol in Version 5.0. Major changes to the protocol are described below.

Study Abstract: For consistency purposes with the body of the protocol, the abstract was updated to reflect the changes described below.

Section 1.3, Non-Clinical Experience with MEDI-557: Section was updated to include results from a GLP-compliant study.

Section 1.4.2, Clinical Experience With Motavizumab: The following sentence was added: "Clinical experience with motavizumab is updated annually in the Investigator Brochure (IB). Please see the current IB for the most current information."

Section 2.3, Overview: There have been no safety concerns in this study of MEDI-557, and there have been no serious adverse events reported in this study. A total of 13 subjects (6 in Cohort 1; 7 in Cohort 2) have been enrolled into this study. Of these 13 subjects, 6 subjects (5 subjects Cohort 1; 1 subject Cohort 2) have completed the study through Day 240, 1 subject (Cohort 2) has completed through Day 180, and 4 subjects in Cohort 2 have completed through Day 90 with no safety concerns. One subject (Cohort 1) was lost to follow-up after Day 42, and one subject in Cohort 2 was lost to follow-up after Day 7 and was replaced. As there have been no safety concerns with MEDI-557, the safety observation periods for adding subjects within cohorts and to dose escalate to the next cohort have been decreased for the remaining cohorts although the entire safety surveillance period for each subject remains unchanged. Specifically,

the observation period between dosing for the second half of Cohort 2 (6 subjects) and escalation to the next dose level in Cohort 3 has been decreased from 60 days to 7 days. Any acute reactions to the administration of MEDI-557 would be expected to occur within the 7-day timeframe. For Cohorts 3 and 4, the time between dosing the 2 sentinel subjects and dosing the remaining subjects has been decreased from 60 days to 7 days. The observation period between Cohort 3 and dose escalation to Cohort 4 has been decreased from 120 days to 60 days. The total safety observation period (240 days) remains unchanged.

Section 3.5.3 (Pharmacokinetic and Immunogenicity Evaluations): Text was edited regarding immunogenicity. In addition, the following sentence was added to allow for additional evaluation of serum samples: "Serum samples will also be used to perform functional assays such as microneutralization assays to test the activity of the antibody."

Section 4.10 (Dose Escalation): The timing of the dose escalation was changed to reflect the changes in Section 2.3.

Section 5.6 (Interim Analysis): Text was edited to included possible analysis for anti-drug antibody at the interim analyses. The interim analysis for Cohort 3 was changed to 60 days instead of 120 days.

Version 6.0 ([redacted])

All text revisions resulting from this amendment are incorporated in the body of the protocol in Version 6.0. Major changes to the protocol are described below.

Study Abstract: For consistency purposes with the body of the protocol, the abstract was updated to reflect the changes described below.

Section 2.3, Overview: To response to comments from the FDA on [redacted] regarding Version 5.0, the observation period between dosing for the second half of Cohort 2 (6 subjects) and escalation to the next dose level in Cohort 3 has been increased from 7 days to 30 days. For Cohorts 3 and 4, the time between dosing the 2 sentinel subjects and dosing the remaining subjects has been increased from 7 days to 30 days. The total safety observation period (240 days) remains unchanged.

Section 4.10 (Dose Escalation): The timing of the dose escalation was changed to reflect the changes in Section 2.3.

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