A Phase 1 Multicenter, Open-label Study to Evaluate the Safety and Tolerability of Single and Multiple Intravenous Doses of MEDI-546, a Fully Human Monoclonal Antibody Directed Against Subunit 1 of the Type I Interferon Receptor, in Adult Subjects with Scleroderma

Investigational Product: MEDI-546

MedImmune Protocol Number: MI-CP180

IND Number: IND 101849

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Amendment 1, [redacted]
Amendment 2, [redacted]
Amendment 3, [redacted]
Amendment 4, [redacted]

Principal Investigator Agreement:

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), 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), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56) and the obligations of clinical investigators (21 CFR 312).

Signature_____ Date_____

Printed Name_____

List of Abbreviations

List of Abbreviations and Definition of Terms

Abbreviation or specialist term	Explanation
α	Alpha
β	Beta
τ	Tau
κ	Kappa
ω	Omega
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Antinuclear antigen autoantibodies
AST	Aspartate aminotransferase
GCP	Good Clinical Practice
ATS/ERS	American Thoracic Society/European Respiratory Society
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 to infinity
AUC_{0-t}	Area under the serum concentration-time curve from time zero to the last measurable time point
AUC_{0-7d}	Area under the serum concentration-time curve from time zero to 7 days post dose
βHCG	β human chorionic gonadotropin
CBC	Complete blood count
CDC	Complete dependent cytotoxicity
CL	Systemic clearance
C_{max}	Maximum observed serum concentration
CMV	Cytomegalovirus
CpG	Cytosine followed by a guanine (Cytosine-phosphate-guanine)
CPK	Creatine phosphokinase
CRP	Cross-reactive protein
DAI	Disease Activity Index
DC	Dendritic cell
DL_{CO}	Diffusing capacity for carbon monoxide

List of Abbreviations and Definition of Terms

Abbreviation or specialist term	Explanation
DNA	Deoxyribonucleic acid
EBV	Epstein Barr virus
ECG	Electrocardiogram
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FcγR	Fc gamma receptor
FcRn	Neonatal Fc receptor
FVC	Forced vital capacity
GCP	Good clinical practice
GLP	Good laboratory practice
GVH-SSc	Graft vs host-induced systemic sclerosis
HAQ-DI	Health assessment questionnaire-disability index
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HSV	Herpes simplex virus
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IFN	Interferon
IFNAR	Type I interferon receptor
IFNAR1	Subunit 1 of the type I interferon receptor
IFNAR2	Subunit 2 of the type I interferon receptor
Ig	Immunoglobulin
IgG1κ	Immunoglobulin G_1 kappa
IM	Immunogenicity
IND	Investigational New Drug
IRB	Institutional Review Board
ISGF3	IFN-stimulated gene factor 3
ISRE	IFN-stimulated response element
IV	Intravenous

List of Abbreviations and Definition of Terms

Abbreviation or specialist term	Explanation
IVRS	Interactive voice response system
JAK-STAT	Janus kinases-signal transducers and activation of transcription
LLQ	Lower limit of quantitation
MAD	Multiple ascending dose
MHC	Major histocompatibility complex
miHag	Minor histocompatibility antigen
mRTSS	Modified Rodnan Total Skin Score
NCI CTCAE V4.0	National Cancer Institute's Common Terminology for Adverse Events Version 4.0
NK	Natural killer
NOAEL	No observed adverse effect level
NRS	Numeric rating scales
NSAIDs	Nonsteroidal anti-inflammatory drugs
PD	Pharmacodynamics
pDC	Plasmacytoid dendritic cells
PK	Pharmacokinetics
PPD	Purified protein derivative
SAD	Single ascending dose
SAE	Serious adverse event
SID	Subject identification number
SLE	Systemic lupus erythematosus
SMC	Safety monitoring committee
SNP	Single nucleotide polymorphism
ssRNA	Single-stranded ribonucleic acid
STAT	Signal transducer and activation of transcription
TB	Tuberculosis
TK	Toxicokinetics
TLR	Toll-like receptor
T_{max}	The time of the observed C_{max}
t½	Terminal elimination half life
ULN	Upper limit of normal
USP	Unites States Pharmacopeia

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Study Abstract

Title:

A Phase 1 Multicenter, Open-label Study to Evaluate the Safety and Tolerability of Single and Multiple Intravenous Doses of MEDI-546, a Fully Human Monoclonal Antibody Directed Against Subunit 1 of the Type I Interferon Receptor, in Adult Subjects with Scleroderma

Objectives:

The primary objective of this study is to evaluate the safety and tolerability of single and multiple intravenous (IV) doses of MEDI-546 in adult subjects with scleroderma who have skin thickening in an area suitable for repeat biopsy.

The secondary objectives of this study are:

1) To evaluate the pharmacokinetics (PK) of MEDI-546;
2) To evaluate the immunogenicity (IM) of MEDI-546; and
3) To evaluate the pharmacodynamics (PD) of MEDI-546. Type I interferon (IFN) gene signature in whole blood and involved skin, and subunit 1 of the type I interferon receptor (IFNAR1) receptor occupancy in whole blood will be used as the PD markers.

The exploratory objectives of the study are:

1) To evaluate the effect of MEDI-546 on measures of disease activity and patient-reported outcomes;
2) To evaluate the effect of MEDI-546 on the expression of other genes and/or proteins in whole blood, serum, and skin and on immunohistopathology of the skin; and
3) To evaluate whether DNA polymorphisms in type I IFN-related genes are associated with safety of MEDI-546.

Study Design:

This is a Phase 1, multicenter, open-label, dose-escalation study to evaluate the safety and tolerability of single and multiple IV doses of MEDI-546 in adult subjects with scleroderma who have skin thickening in an area suitable for repeat biopsy. Approximately 10 to 20 sites in North America will participate in the study. A minimum of 33 evaluable subjects are planned for the study, with cohorts of subjects receiving 1 of 6 single IV doses (0.1, 0.3, 1.0,

3.0, 10.0, or 20.0 mg/kg) followed by 3 cohorts of subjects receiving 1 of 3 multiple IV doses (0.3, 1.0, or 5.0 mg/kg weekly × 4) of MEDI-546; an additional singe-dose cohort (Cohort 9, 20 mg/kg) has been included to evaluate safety and tolerability at this dose. The single dose Cohort 9 will enroll simultaneously to the multiple ascending dose cohorts (Cohorts 6, 7, and 8). Simultaneous dosing of Cohort 9 to Cohorts 6, 7 and 8 may occur as cumulative safety data of the lower single ascending dose cohorts (Cohorts 1-5) were evaluated for safety and progression to higher doses approved; the multiple ascending dose cohorts 6, 7, and 8 (0.3, 1.0, 5.0 mg/kg respectively) are lower doses than Cohort 9. Cohort 9 was added to the protocol to test a higher dose of MEDI-546 for safety and tolerability to enable greater flexibility in dosing regimens during later phases of clinical development. The non-clinical toxicology studies in primates did not reveal any adverse events for single doses up to 100 mg/kg and for weekly doses up to 30 mg/kg. The starting dose level will be 0.1 mg/kg administered as a single IV dose. Rules for dose escalation are provided in Section 4.9. Subjects are considered evaluable for safety if they receive MEDI-546 and complete the required evaluations through Study Day 7 or if they discontinue MEDI-546 for safety reasons. In addition, subjects are considered evaluable for the exploratory endpoints if they receive MEDI-546 and complete the required evaluations through Study Day 28. Nonevaluable subjects may be replaced for reasons other than safety to maintain the stipulated cohort sizes in each dose cohort.

If there is a possible safety signal from the analysis of safety information for a particular dose cohort (Dose Cohorts 2-9 only) that does not warrant discontinuation but does warrant further investigation (prior to dose escalation for Dose Cohorts 2-8), then the sponsor may add 4 subjects to the dose cohort for a maximum of 8 subjects in the dose cohort. A maximum of 2 dose cohorts may be expanded to a total of 8 subjects each. If a possible safety signal occurs subsequent to expansion of 2 dose cohorts to a maximum of 8 subjects each, then the study will be terminated. In addition, Dose Cohorts 2-9 may be expanded by up to 2 additional subjects each if eligible subjects are already in screening at the time 4 subjects have been entered into the dose cohort and there is no possible safety signal to warrant expansion of the dose cohort to a maximum of 8 subjects. Therefore, the maximum number of subjects allowed in the study is 53 (33 + 8 [4×2]+ 12 [2×6]).

Subject Population:

The subjects in this study will be adult male or female subjects with scleroderma who have skin thickening in an area suitable for repeat biopsy.

Treatment:

A minimum of 33 evaluable subjects are planned for the study, with cohorts of subjects receiving 1 of 6 single IV doses followed by 3 cohorts of subjects receiving 1 of 3 multiple IV doses of MEDI-546, the additional single dose cohort 9 (20 mg/kg) will enroll simultaneously to Cohorts 6, 7 and 8 as shown below.

- Dose Cohort 1 (N=1): 0.1 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 2 (N=4): 0.3 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 3 (N=4): 1.0 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 4 (N=4): 3.0 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 5 (N=4): 10.0 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 6 (N=4): 0.3 mg/kg MEDI-546 as a weekly IV dose × 4 doses
- Dose Cohort 7 (N=4): 1.0 mg/kg MEDI-546 as a weekly IV dose × 4 doses
- Dose Cohort 8 (N=4): 5.0 mg/kg MEDI-546 as a weekly IV dose × 4 doses
- Dose Cohort 9 (N=4): 20 mg/kg MEDI-546 as a single IV dose

MEDI-546 will be administered as an IV infusion over at least 60 minutes for IV doses of ≤ 10 mg/kg or at least 120 minutes for doses of > 10 mg/kg. For doses > 10 mg/kg and for subjects weighing > 250 lbs. or 114 kg please call the medical monitor to discuss the infusion rate instructions. Single IV dose administration will occur on Study Day 0, with follow-up through Study Day 84; multiple-dose IV administration of MEDI-546 will occur on Study Days 0, 7, 14, and 21, with follow-up through Study Day 105.

On [redacted], an interim analysis of PK and type 1 IFN gene signature from all subjects through Day 14 of Cohort 4 (Dose Cohorts 1-4) was performed as described in Section 5.7 of the study protocol. Results of this analysis are summarized in Section 1.4 of the study protocol.

Subject Evaluation and Follow-up:

Screening evaluations will be performed within 28 days prior to MEDI-546 administration. Safety evaluations will be performed from the time the informed consent is signed through end of study and will include history and physical examinations, assessment of adverse events (AEs) and serious adverse events (SAEs), monitoring of laboratory tests including hematology, serum chemistry, and urinalysis, safety biomarkers in any subject who has a Grade 1 or higher infusion reaction (including serum levels of mast cell tryptase,

cytokines/chemokines, and IgE antibodies), and viral monitoring. Pharmacokinetics, IM, and receptor occupancy will be assessed throughout the study. Receptor occupancy and level of type I IFN gene signature in whole blood and skin will be determined to assess the PD effect of MEDI-546. Clinical outcomes will be evaluated.

The schedule of subject evaluations for subjects receiving single IV doses of MEDI-546 (Dose Cohorts 1-5 and 9) is presented in Table 3.5-1; the schedule of subject evaluations for subjects receiving multiple IV doses of MEDI-546 (Dose Cohorts 6-8) is presented in Table 3.5-2.

Sample Size and Power Calculations:

A minimum of 33 subjects are planned for this study, with dose cohorts of subjects receiving 1 of 6 single IV doses followed by 3 cohorts of subjects receiving 1 of 3 multiple IV doses of MEDI-546; the final single dose cohort 9 (20 mg/kg) will enroll simultaneously to Cohorts 6, 7, and 8 as follows:

- Dose Cohort 1 (N=1): 0.1 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 2 (N=4): 0.3 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 3 (N=4): 1.0 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 4 (N=4): 3.0 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 5 (N=4): 10.0 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 6 (N=4): 0.3 mg/kg MEDI-546 as a weekly IV dose × 4 doses
- Dose Cohort 7 (N=4): 1.0 mg/kg MEDI-546 as a weekly IV dose × 4 doses
- Dose Cohort 8 (N=4): 5.0 mg/kg MEDI-546 as a weekly IV dose × 4 doses
- Dose Cohort 9 (N=4): 20.0 mg/kg MEDI-546 as a single IV dose

If there is a possible safety signal from the analysis of safety information for a particular dose cohort (Dose Cohorts 2-9 only) that does not warrant discontinuation but does warrant further investigation (prior to dose escalation for Dose Cohorts 2-8), then the sponsor may add 4 subjects to the dose cohort for a maximum of 8 subjects in the dose cohort. A maximum of 2 dose cohorts may be expanded to a total of 8 subjects each. If a possible safety signal occurs subsequent to expansion of 2 dose cohorts to a maximum of 8 subjects each, then the study will be terminated. In addition, Dose Cohorts 2-9 may be expanded by up to 2 additional subjects each if eligible subjects are already in screening at the time 4 subjects have been entered into the dose cohort and there is no possible safety signal to warrant expansion of the dose cohort to a maximum of 8 subjects. Therefore, the maximum number

of subjects allowed in the study is 53 (33 + 8 [4×2] + 12 [2×6]). No formal calculation was performed to determine sample size because safety is the primary outcome and this will be assessed with descriptive analyses.

Assessment of Endpoints:

The safety and tolerability of MEDI-546 will be assessed primarily by summarizing treatment-emergent AEs and SAEs and by assessing changes in viral cultures. The occurrence of treatment-emergent AEs and SAEs will be summarized from the period immediately following the first administration of MEDI-546 through end of study (Study Day 84 for subjects receiving single IV doses and Study Day 105 for subjects receiving multiple IV doses). No formal statistical testing will be performed to compare treatment groups. Other variables used for the safety assessments include serum chemistry, CBC with differential and platelets, and urinalysis. These variables as well as their changes from baseline will be summarized descriptively.

The secondary endpoints of the study are to assess the PK, IM, and PD of single and multiple IV doses of MEDI-546 in adult subjects with scleroderma. Serum MEDI-546 concentration data will be tabulated by dose cohort together with descriptive statistics. Individual and mean serum concentration-time profiles of MEDI-546 by dose cohort will be generated and included in the report. Immunogenicity results will be analyzed by summarizing the number and percentage of scleroderma subjects who develop detectable anti-MEDI-546 antibodies by treatment and dose cohort. Pharmacodynamic endpoints will include the level of receptor occupancy (flow cytometry measurement of the binding of labeled MEDI-546 in the presence of dosed levels of MEDI-546), total type I interferon receptor (IFNAR) levels (using a separate anti-IFNAR1 antibody that binds to a distinct epitope from MEDI-546), and the level of expression of type I IFN-inducible genes in blood and skin (using Affymetrix technology). Results will be listed by dose cohort with mean and individual results at different time points. Changes from baseline will be described and PD assessed. Relationships between receptor occupancy and inhibition of type I IFN gene signature will be explored.

The exploratory endpoints of the study include measures of the effect of MEDI-546 on disease activity, patient-reported outcomes, and gene and/or protein expression, and the relationship of type I IFN-related DNA polymorphisms and safety signals. Measures of disease activity will include pulmonary function tests, the modified Rodnan Total Skin Score (mRTSS), and the European Disease Activity Index (DAI). Patient-reported outcomes will

include the health assessment questionnaire-disability index (HAQ-DI) with scleroderma numeric rating scores (NRS) and DAI with a numeric rating scale to assess changes in skin, changes in vascular manifestations, and changes in heart/lung (Appendix 4). The mRTSS, European DAI, and the HAQ-DI with scleroderma NRS will be computed. These measures of disease activity, as well as their respective changes from baseline, will be summarized descriptively at each visit by dose cohort and all cohorts combined. The effect of MEDI-546 on the expression of other genes and/or proteins in whole blood, serum, skin and on immunohistopathology of the skin will be assessed using descriptive statistics. Polymorphisms in type I IFN-related genes associated with safety signals to MEDI-546 will be assessed using descriptive statistics.

Interim Analyses

Type I IFN gene expression may be assessed cumulatively in blood and skin after each dose cohort reaches Study Day 28. On [redacted], an interim analysis of PK and type 1 IFN gene signature from all subjects through Day 14 of Cohort 4 (Dose Cohorts 1-4) was performed as specified in Section 5.7 of the study protocol. Results of this analysis are summarized in Section 1.4 of the study protocol.

1 Introduction

1.1 Background

1.1.1 Scleroderma

Systemic sclerosis (scleroderma) is an uncommon, complex systemic autoimmune disease characterized by immune system activation, autoimmunity with autoantibody production, and excessive deposition of extracellular matrix. Scleroderma strikes three to four times as many women as men, and adults more than children. Constitutional symptoms, Raynaud's phenomenon, digital ulcers, skin fibrosis, interstitial pulmonary fibrosis causing restrictive lung disease, pulmonary hypertension, inflammatory arthritis with joint contractures, systemic hypertension and renal crisis, esophageal reflux, gut hypomotility with malabsorption, and inflammatory myositis all cause morbidity and, in some cases, mortality in subjects. Scleroderma can substantially reduce patients' quality of life and has the highest mortality of any systemic autoimmune rheumatic disease. In recent years, treatments to improve symptoms in secondary pulmonary hypertension associated with scleroderma and

other connective tissue diseases have been approved. Angiotensin-converting enzyme inhibitors have been associated with reduced severity and mortality of renal crisis. Methotrexate, cyclophosphamide, azathioprine, and mycophenolate mofetil are used off-label for symptomatic relief and reduction in inflammation in target organs such as skin, lungs, and joints. There is a tremendous unmet medical need for disease-modifying therapies in scleroderma.

1.1.2 Type I Interferon and its Receptors

Type I interferons (IFNs) -α, –β, –τ, –κ, and -ω, are cytokines expressed from 13 functional IFN-α genes, one IFN-β gene, one IFN-τ gene, one IFN-κ gene, and one IFN-ω gene (Theofilopoulos, 2005). Characterization of IFN activity has focused primarily on the antiviral properties of these molecules. In recent years, the role of type I IFNs in both innate and adaptive immunity has been the subject of intense research and a greater role of type I IFNs in immune homeostasis is becoming apparent (Belardelli, 1996; Baccala, 2005). Type I IFNs induce multiple biological effects in key components of the immune system including dendritic, T, B, and natural killer (NK) cells (Biron, 2001; Pogue, 2004). For example, type I IFNs promote dendritic cell (DC) maturation, memory $CD8^+$ T cell proliferation, inhibition of $CD4^+$ T cell apoptosis, NK cell activation, and B-cell differentiation (Banchereau, 2004; Taki, 2002; Maillard, 2003; Jego, 2003).

Type I IFNs bind to the type I interferon receptor (IFNAR), a heterodimer comprising subunits 1 and 2 of IFNAR (IFNAR1 and IFNAR2) that is widely expressed on most cells at low levels (Mogensen, 1999). Both IFNAR1 and IFNAR2 belong to the class II helical cytokine receptor family, which includes the receptor for type II IFN, tissue factor, and the interleukin-10Rβ (IL10Rβ; Mogensen, 1999). The extracellular domain of IFNAR1 comprises 409 amino acids and contains 4 sub-domains, each containing one fibronectin domain. IFNAR2 binds all type I IFNs but with low affinity, which has made identification of the critical residues required for IFN binding difficult to determine. However, three-dimensional structural information suggests that IFNs have multiple interactions with IFNAR2, including hydrophobic and electrostatic bonding (Chill, 2002). This model predicts that IFN-IFNAR2 complexes bind IFNAR1 to form the extracellular receptor pocket (Cajean-Feroldi, 2004; Quadt-Akabayov, 2006). IFNAR1 is preassembled with Tyk-2 and upon IFNAR2-complex interactions, Jak and signal transducer and activator of transcription (STAT) proteins are recruited resulting in signal transduction (Mogensen, 1999). Whilst further work is required to elucidate the precise associations between type I IFNs and

IFNAR1 and IFNAR2, the current data available provide a basis for generation of antibodies against the IFNAR1 to inhibit signaling mediated by all type I IFNs.

The binding of type I IFN to IFNAR results in the activation of intracellular signal transduction pathways (Stark, 1998) initiated by the activation of Jak kinases, Jak1 and Tyk2. These kinases subsequently phosphorylate STAT proteins, STAT1 and STAT2. Phosphorylated STAT1 and STAT2 heterodimers form the transcription factor complex, IFN-stimulated gene factor 3 (ISGF3), that translocates into the nucleus. These complexes activate the IFN-stimulated response element (ISRE) that induces the expression of IFN-inducible genes. In addition, type I IFN induces the formation of STAT homodimers (STAT1, STAT3, and STAT5) and heterodimers (STAT1 and STAT3). These STAT dimers are translocated to the nucleus where they bind to specific response elements leading to gene transcription (Stark, 1998; Darnell, 1997).

1.1.3 Role of Type I Interferons in Autoimmune Diseases

Recent research data suggest a potential role of type I IFNs in disease pathogenesis of a number of autoimmune disorders that includes scleroderma, systemic lupus erythematosus (SLE), and myositis. Therefore, type I IFN inhibition may be efficacious in the treatment of these diseases. Scleroderma is an uncommon, complex systemic fibrosing autoimmune disease characterized by activation of the immune system with macrophage, T-cell, and B-cell abnormalities and autoantibodies, an obliterative proliferative small vessel vasculopathy, and excessive deposition of collagen I and III and other extracellular matrix components. Type I IFN levels are elevated in the serum of patients with scleroderma (Hooks, 1979; Ytterberg, 1982). In addition, increased expression of type I IFN-induced genes and proteins has also been observed in blood and skin of patients with scleroderma (Tan, 2006; Coelho, 2007; York, 2007; Whitfield, 2003). Finally, patients treated with type I IFNs have been reported to develop scleroderma or sclerodermatous-like disease (Tahara, 2007; Solans, 2004). In SLE, circulating antinuclear antibody (ANA) immune complexes have been shown to induce type I IFN production by plasmacytoid dendritic cells (pDCs) in vitro (Means, 2005), suggesting a role for this pathway in promoting inflammation. Further support for type I IFNs contributing to SLE pathogenesis arises from detection of type I IFN activity in SLE sera (Dall'era, 2005), IFN gene signatures in SLE peripheral blood mononuclear cells (PBMC; Baechler, 2003; Bennet, 2003) and IFN-inducible proteins in SLE skin lesions (Wenzel, 2005).

Graft-versus-host-induced systemic sclerosis (GVH-SSc) is a murine model of scleroderma where pathogenesis is driven by an anti-host response against mismatched minor histocompatibility antigens (miHag). This model was used to determine the role of IFNAR1 in an experimental murine model of scleroderma. A murine monoclonal antibody that blocks binding and signaling of all type I IFN by binding to the IFNAR1 (5A3; Sheehan, 2006) was administered prophylactically in this model (GVH-SSc). IFNAR1 blockade conferred significant protection from clinical and histological manifestations of dermal fibrosis, while having no impact on kidney pathology (ie, measurement of proteinuria) or serum autoantibody levels. The central role of type I IFNs in dermal fibrosis was further supported by depleting pDCs (via depletion of the Gr-1(+) fraction in graft donor splenocytes), which also significantly reduced skin disease but did not affect kidney endpoints (proteinuria). Kinetic studies of IFN-inducible gene expression indicated that the early expression of these IFN-inducible genes was IFNAR1-independent, but at later time points interferon-inducible gene expression was inhibited by IFNAR1 monoclonal antibody and correlated with clinical disease. Immunohistochemical staining of GVH-SSc skin demonstrated that some IFN-inducible proteins were most highly expressed in murine stromal cells. Overall, prophylactic IFNAR1 blockade had a profound impact on gene regulation in murine systemic sclerosis, with inhibition of a broad range of pro-inflammatory and pro-remodeling gene families in addition to known interferon-inducible genes. While the precise mechanism by which type I IFNs contribute to dermal fibrogenesis remain to be fully identified, these studies suggest a type I IFN-dependent activation of stromal cell populations in the dermis.

1.2 Description of MEDI-546

MEDI-546 is a fully human IgG1 kappa (IgG1κ) monoclonal antibody directed against type I IFNAR1. MEDI-546 is composed of 2 light chains and 2 heavy chains, with an overall molecular weight of approximately 148 kDa.

The biological activity of MEDI-546 is quantified relative to Reference Standard using a binding enzyme-linked immunosorbent assay (ELISA) and a bioassay. The ELISA measures the binding of MEDI-546 to IFNAR. The cell-based bioassay measures the inhibition of IFN-α- induced signaling activity resulting from the binding of MEDI-546 to cell surface IFNAR.

1.3 Nonclinical Experience with MEDI-546

MEDI-546 blocks the binding of type I IFN to IFNAR and inhibits the biologic activity of all type I IFN subtypes. MEDI-546 does not have agonistic activity and is devoid of FcγRI,

FcγRIIA, FcγRIIB FcγRIIIA, and C1q binding activity. Therefore, MEDI-546, does not induce ADCC and CDC. With the growing evidence that type I IFNs play an important role in autoimmune diseases such as scleroderma, SLE, and myositis, inhibition of the biological activity of type I IFNs with MEDI-546 may, therefore, be a novel therapy for the treatment of these diseases with significant unmet medical need

Cynomolgus monkey was selected as the pharmacologically relevant animal species for nonclinical safety assessment based on binding affinity and neutralization activity of MEDI-546 in monkey cells. MEDI-546 does not cross-react with murine IFN-α.

The preliminary non-Good Laboratory Practice (GLP) single intravenous (IV) infusion receptor occupancy study was designed to evaluate safety and receptor occupancy at toxicologically relevant MEDI-546 dose levels (5, 30, or 100 mg/kg). There was no evidence of MEDI-546 toxicity after a single 30-minute IV infusion on Day 1 up to 100 mg/kg (single dose no-observable-adverse-effect-level [NOAEL]), the highest dose tested. Anti-MEDI-546 antibodies were detected in most animals following a single dose, with the frequency inversely proportional to the dose level administered and increasing at later time points. Clinical observations consistent with a hypersensitivity reaction occurred in 1 of 3 animals that received repeat MEDI-546 doses (5 mg/kg) on Days 37 and 50, with the intensity of the clinical response greatest at the Day 50 (third) administration. This monkey's symptoms were relieved by administration of IV antihistamine (Benadryl® with no further observations through the end of the study. Investigative and exploratory analyses (cytokine analysis and isotyping and specificity characterization of the anti-MEDI-546 antibody response) were conducted in an effort to identify the underlying mechanism of the apparent hypersensitivity response. While the IgE, IgA, and IgM classes were assessed, the major isotype of anti-MEDI-546 antibody is anticipated to be IgG (IgG could not be assessed due to technical limitations in the isotyping assay). Isotyping analysis showed that only the animal with clinical symptoms following re-dose possessed a detectable IgE response against MEDI-546 on Days 22 and 29 prior to re-dosing (IgM was also detected for this animal on Day 22) and all three re-dosed animals had detectable IgE antibody by Day 70 following the 2 additional MEDI-546 doses. Results of specificity characterization and cytokine analysis did not show any clear correlation with hypersensitivity potential. This isolated case of hypersensitivity-like reaction was not reproducible in the subsequent 1-month repeated IV infusion dose toxicity study (described in more detail below).

A GLP single IV infusion dose study was conducted using MEDI-546 dose levels (0.003, 0.03, 0.3, or 1 mg/kg) chosen to evaluate safety and receptor occupancy at pharmacologically

relevant doses and to determine the minimum dose at which no receptor occupancy is detected. There were no adverse MEDI-546-related observations during the 28-day study period. Immunogenicity results showed evidence of anti-MEDI-546 antibodies in the majority of MEDI-546-dosed animals. Receptor occupancy analysis and PD analysis by in vitro genomic assay (IFN-inducible gene expression profile in whole blood samples) suggested the MEDI-546 doses administered in this study were in a pharmacologically active range.

A non-GLP single (IV)or subcutaneous (SC) dose toxicity study was conducted using a 5 mg/kg MEDI-546 dose level chosen to evaluate safety PK , PD , and IM (Study No. 7140-142, Covance Laboratories, Inc, Vienna, VA). In this study, one group of 3 male animals received a single 30-minute IV infusion of 5 mg/kg MEDI-546, while the other group received a single subcutaneous injection of 5 mg/kg MEDI-546. Animals were observed for 28 days to assess the reversibility, persistence, or delayed occurrence of effects. There was no control group comparator or necropsy in this study. Assessment of toxicity was based on mortality, clinical signs (including food consumption), dermal observation of the injection/infusion site, physical examinations, and body weight.

There were no observations of systemic or dermal toxicity or remarkable differences between the effects of the two routes of exposure. Pharmacodynamic activity was evident with the strongest target neutralization observed at Day 2 for intravenously dosed animals and Day 8 for subcutaneously dosed animals. The absolute bioavailability of MEDI-546 could not be determined, most likely due to variability influenced by the small sample size in this study. Similar titer values of anti-MEDI-546 antibody were detected by Day 29 for all animals, regardless of dose route.

A GLP 1-month repeated IV infusion dose toxicity study in cynomolgus monkeys was conducted using MEDI-546 dose levels (0.5, 5, or 30 mg/kg/dose) chosen to evaluate safety at toxicologically relevant doses when administered weekly for 4 total administrations. No adverse MEDI-546-related changes (including hypersensitivity-like reactions) in toxicological end points were noted during the 70-day study period. The NOAEL of MEDI-546 after 4 once-weekly IV infusions to cynomolgus monkeys was considered to be 30 mg/kg, the highest dose tested.

A GLP 9-month repeat dose toxicity study was conducted in cynomolgus monkeys (6/sex/dose group) where MEDI-546 was administered by IV infusion or subcutaneous (SC) injection at the dose levels (0, 5, 50, 15, 60 mg/kg/dose), once weekly for 39 weeks. The

control group received once weekly IV infusion and SC injection of formulation buffer. Necropsies were performed three days (terminal) or 13 weeks (recovery) following the final dose. Toxicity was assessed based on physical examination and clinical signs, dermal irritation, body weight, qualitative food consumption, ophthalmic exam, electrocardiographic (ECG), blood pressure, semen analysis, immunophenotyping, hematology, coagulation, clinical chemistry, urinalysis, organ weight, macroscopic and microscopic parameters.

Though all of the data for the study are not yet available at this time, there have been no unscheduled deaths and no MEDI-546-related adverse changes in clinical signs, physical examination, dermal irritation, body weight, qualitative food consumption, ophthalmic examination, electrocardiographic, blood pressure, semen analysis, hematology, coagulation, clinical chemistry, urinalysis, organ weight, or macroscopic parameters. In a total of 5 male animals (5/24, 21%) and 0 female animals (0/24, 0%) exposed to MEDI-546, microscopic examination found signs of focal arteritis in small and medium sized arteries. The severity grades of the arteritis ranged from 1 to 3 on a 5-point scale, with Grade 2 findings most frequent and reflected both the intensity of the change as well as the overall distribution in the tissue (number of vessels affected). The arteritis was manifest primarily by intramural and perivascular infiltrates of lymphocytes and macrophages, without necrosis, giant cells or granulomas. Several tissue types/organs were affected, the kidney and gut most frequently, and there were no lesions in kidney glomeruli. Findings were less pronounced and generally less widespread in recovery necropsy animals following a 13 week dose free period when compared to the terminal necropsy animals. Though a vasculitis background incidence of 1-6% has been noted in the literature for this species, no control animal tissues showed vascular pathology and there were no other significant pathology findings attributable to MEDI-546 administration.

The relevance of these findings to human treatment with MEDI-546 is not definitely known at this time. Due to the immunogenicity (high ADA titers) of MEDI-546 in primates, the current hypothesis is that the vascular findings are likely the result of a chronic immune-mediated reaction in the animals, involving antigen-antibody complexes. This will be explored with further testing of the toxicology study tissue samples. The development of ADA in animals is common and does not accurately predict responses in humans. One recent literature abstract describes similar vascular lesions in monkeys dosed with a monoclonal antibody, that were considered likely due to deposits of ADA/drug complexes.[1] While animal immune responses do not accurately predict responses in humans, the vascular findings in the present study may indicate an increased risk to patients of immune-mediated

adverse effects with MEDI-546 treatment, such as the risk of hypersensitivity reactions or immune-complex reactions, including vasculitis.

In cynomolgus monkeys, MEDI-546 showed a biphasic serum disposition profile. No appreciable gender difference was observed. In general, the maximum observed serum concentration (C_{max}) was dose proportional, while a more than dose-proportional increase in the area under the concentration-time curve (AUC) was observed. The nonlinear drug exposure (AUC) was likely the result of an antigen sink effect and an uneven frequency of anti-MEDI-546 antibody formation across dose groups. In most dose groups, the elimination half-life of MEDI-546 was less than a week.

Tissue cross reactivity studies with MEDI-546 supported the cynomolgus monkey as a relevant toxicology model. The distribution of MEDI-546 specific staining on the panel of cynomolgus tissues was similar to the staining of human tissues. MEDI-546-specific staining on both human and cynomolgus monkey tissues was present in epithelium, endothelium, mesothelium, mononuclear cells, spindloid/dendritic cells, and intravascular and leaked proteinaceous material (serum) throughout the tissue panels examined. MEDI-546 also stained myenteric plexi in the gastrointestinal tract, glomerular tuft cells in the kidney, granulosa cells in the ovary, beta cells in the pancreas, chief cells of the parathyroid, endocrine cells and pituicytes in the pituitary, decidual cells in the placenta, and spermatogenic cells in the testis in both the human and cynomolgus monkey tissue panels. The staining reported in these studies is consistent with published reports of broad expression of IFNAR in tissues.

A GLP 9-month dose toxicity study in cynomolgus monkeys (6/sex/dose group) where MEDI-546 was administered by IV infusion or SC injection at the dose levels (0, 5, 50, 15, 60 mg/kg/dose), once weekly for 39 weeks. The control group received once weekly IV infusion and SC injection of formulation buffer. Necropsies were performed three days or 13 weeks following the final dose. Toxicity was assessed based on physical examination and clinical signs, dermal irritation, body weight, qualitative food consumption, ophthalmic exam, ECG, blood pressure, semen analysis, immunophenotyping, hematology, coagulation, clinical chemistry, urinalysis, organ weight, macroscopic and microscopic organ/tissue data.

In a total of 5 male animals (5/24, 21%) and 0 female animals (0/24, 0%) exposed to MEDI-546, there were histopathology signs of focal arteritis in small and medium sized arteries. The severity grades of the arteritis ranged from 1 to 3 on a 5-point scale, with Grade 2 findings most frequent. The arteritis was characterized as focal/segmental, with both normal and

affected arteries within each tissue section. It was manifest primarily by intramural and perivascular infiltrates of lymphocytes and macrophages, without necrosis, giant cells or granulomas. Several tissue types/organs were affected, the kidney and gut most frequently, and with no lesions in glomeruli.

In three animals in the high dose 50 mg/kg IV group, effects of Grades 1, 2 and 3 were seen, with Grade 3 findings in one animal only. In one animal in the 60 mg/kg SC group, Grade 2 effects were seen, while one animal in the 5 mg/kg IV group had Grade 2 effects in the arteries of one eye only. Though a vasculitis background incidence of 1-6% has been noted in the literature for this species, no control animal tissues showed vascular pathology and there were no other significant pathology findings attributable to MEDI-546 administration.

Additional details n the nonclinical experience with MEDI-546 are provided in the Investigator's Brochure.

1.4 Clinical Experience with MEDI-546

A phase 1 clinical study (MI-CP 180) was initiated on September 1, 2009 and is presently active. As of 14July2010 a total of 17 subjects have been enrolled into the study and dose escalation has progressed through cohort 5, (10.0 mg/kg).

On 14 July 2010 an interim analysis of cumulative data on PK and type I IFN gene signatures was completed on all subjects treated through the completion of Study Day 14 of Cohort 4 to determine whether dose adjustments needed to be made in the multiple dose cohorts (Dose Cohorts 6-8). The PK and PD data from the single dose cohorts was modeled to predict PK profiles and PD response with various doses given weekly × 4 as described in the protocol. The results indicate that doses of 0.3, 1.0 and 5.0 mg/kg respectively, best target the pre-specified criteria as defined in the protocol of one dose that provides incomplete inhibition of type I IFN gene signature defined as ≥ 70% inhibition in < 3 patients per cohort, one dose that provides nearly complete inhibition of type I IFN gene signature defined as ≥ 70% inhibition in at least 3 subjects per cohort, and one dose that is approximately ½ log higher than the dose that provides nearly complete inhibition of type I IFN gene signature.

To date the safety profile is acceptable to continue further clinical testing.

1.5 Rationale for Study

Recent research data suggest a potential role of type I IFNs in disease pathogenesis of scleroderma. Therefore, type I IFN inhibition may be efficacious in the treatment of this disease. Scleroderma is an uncommon, complex, systemic fibrosing autoimmune disease characterized by activation of the immune system with macrophage, T-cell, and B-cell abnormalities and autoantibodies, an obliterative proliferative small vessel vasculopathy, and excessive deposition of collagen I and III and other extracellular matrix components. Type I IFN levels are elevated in the serum of patients with scleroderma (Hooks, 1979; Ytterberg, 1982). In addition, increased expression of type I IFN-induced genes and proteins has also been observed in blood and skin of patients with scleroderma (Tan, 2006; Coelho, 2007; York, 2007; Whitfield, 2003).

The actions of type I IFNs are mediated by specific cell surface receptors and JAK-STAT signal transduction pathways. Type I IFNs share the same receptor complex consisting of 2 chains, IFNAR1 and IFNAR2. MEDI-546 is a fully human IgG1κ monoclonal antibody directed against type I IFNAR1. Type I IFNs bind to IFNAR, which is widely expressed on most cells at low levels (Mogensen, 1999). Recent research data suggest a potential role of type I IFNs in disease pathogenesis of a number of autoimmune disorders that includes scleroderma, SLE, and myositis. Therefore, type I IFN inhibition may be efficacious in the treatment of these diseases.

The proposed study is a Phase 1, multicenter, open-label, dose-escalation trial to evaluate the safety and tolerability of single IV doses (0.1, 0.3, 1.0, 3.0,10.0 and 20 mg/kg) and multiple IV doses (0.3, 1.0, and 5.0 mg/kg) of MEDI-546 in subjects with scleroderma who have skin thickening in an area suitable for repeat biops. In addition to PK and IM evaluations, the binding of MEDI-546 to type I IFNAR1-bearing cells will be monitored by a receptor occupancy assay. This study will also test neutralization of type I IFN gene expression in whole blood and skin of subjects. The planned starting dose of 0.1 mg/kg corresponds to the human equivalence dose of the primate pharmacologically active dose of 0.3 mg/kg, which is associated with minimal receptor occupancy and target neutralization and is 100-fold lower than the highest dose (30 mg/kg/week × 4 weeks) administered in the one month repeated-dose study 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 single and multiple IV doses of MEDI-546 in adult subjects with scleroderma who have skin thickening in an area suitable for repeat biopsy.

2.2 Secondary Objectives

The secondary objectives of this study are:

1) To evaluate the pharmacokinetics of MEDI-546;
2) To evaluate the immunogenicity of MEDI-546; and
3) To evaluate the pharmacodynamics of MEDI-546. Type I interferon gene signature in whole blood and involved skin, and subunit 1 of the type I interferon receptor occupancy in whole blood will be used as the PD markers.

2.3 Exploratory Objectives

The exploratory objectives of the study are:

1) To evaluate the effect of MEDI-546 on measures of disease activity and patient-reported outcomes;
2) To evaluate the effect of MEDI-546 on the expression of other genes and/or proteins in whole blood, serum, and skin and on immunohistopathology of the skin; and
3) To evaluate whether DNA polymorphisms in type I IFN-related genes are associated with safety of MEDI-546.

2.4 Overview

Study Design

This is a Phase 1, multicenter, open-label, dose escalation study to evaluate the safety and tolerability of single and multiple IV doses of MEDI-546 in adult subjects with scleroderma who have skin thickening in an area suitable for repeat biopsy. Approximately 10 to 20 sites in North America will participate in the study. A minimum of 33 evaluable subjects are planned for the study, with cohorts of subjects receiving 1 of 6 single IV doses (0.1, 0.3, 1.0,

3.0, 10.0, or 20.0mg/kg) followed by 3 cohorts of subjects receiving 1 of 3 multiple IV doses (0.3, 1.0, or 5.0 mg/kg weekly × 4) of MEDI-546 as described in Figure 2.4-1; an additional single-dose cohort (Dose Cohort 9, 20 mg/kg) has been included to evaluate safety and tolerability at this dose. The single ascending dose Cohort 9 will enroll simultaneously to the multiple ascending dose cohorts (Cohorts 6, 7, and 8). Simultaneous dosing of Cohort 9 to Cohorts 6, 7, and 8 may occur as cumulative safety data of the lower single ascending dose cohorts (Cohorts 1-5) were evaluated for safety and progression to higher doses approved; the multiple ascending dose cohorts 6, 7, and 8 (0.3, 1.0, 5.0 mg/kg respectively) are lowr doses than Cohort 9. The starting dose level will be 0.1 mg/kg administered as a single IV dose. Rules for dose escalation are provided in Section 4.9. Subjects are considered evaluable for safety if they receive MEDI-546 and complete the required evaluations through Study Day 7 or if they discontinue MEDI-546 for safety reasons. In addition, subjects are considered evaluable for the exploratory endpoints if they receive MEDI-546 and complete the required evaluations through Study Day 28. Nonevaluable subjects may be replaced for reasons other than safety to maintain the stipulated cohort sizes in each dose cohort.

If there is a possible safety signal from the analysis of safety information for a particular dose cohort (Dose Cohorts 2-9 only) that does not warrant discontinuation but does warrant further investigation (prior to dose escalation for Dose Cohorts 2-7), then the sponsor may add 4 subjects to the dose cohort for a maximum of 8 subjects in the dose cohort. A maximum of 2 dose cohorts may be expanded to a total of 8 subjects each. If a possible safety signal occurs subsequent to expansion of 2 dose cohorts to a maximum of 8 subjects each, then the study will be terminated. In addition, Dose Cohorts 2-8 may be expanded by up to 2 additional subjects each if eligible subjects are already in screening at the time 4 subjects have been entered into the dose cohort and there is no possible safety signal to warrant expansion of the dose cohort to a maximum of 8 subjects. Therefore, the maximum number of subjects allowed in the study is 53 (33 + 8 [4×2] + 12 [2×6]).

MEDI-546 will be administered as an IV infusion over at least 60 minutes for IV doses of ≤ 10 mg/kg or over at least 120 minutes for IV doses of > 10 mg/kg. For doses > 10 mg/kg and for subjects weighing > 250 lbs. or 114 kg please call the medical monitor to discuss the infusion rate instructions. Single-dose IV administration of MEDI-546 will occur on Study Day 0, with follow-up through Study Day 84; multiple-dose IV administration of MEDI-546 will occur on Study Days 0, 7, 14, and 21, with follow-up through Study Day 105.

Subject Evaluation/Follow-up

Screening evaluations will be performed within 28 days prior to MEDI-546 administration. Safety evaluations will be performed from the time the informed consent is signed through end of study and will include history and physical examinations, assessment of AEs and SAEs, monitoring of laboratory tests including hematology, serum chemistry, and urinalysis, safety biomarkers in any subject who has a Grade 1 or higher infusion reaction (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies), and viral monitoring. Pharmacokinetics (PK), IM, and receptor occupancy will be assessed throughout the study. Receptor occupancy and level of type I IFN gene signature in whole blood and skin will be determined to assess the PD effect of MEDI-546. Clinical outcomes will be evaluated.

The schedule of subject evaluations for subjects receiving single IV doses of MEDI-546 (Dose Cohorts 1-5 and 9) is presented in Table 3.5-1; the schedule of subject evaluations for subjects receiving multiple IV doses of MEDI-546 (Dose Cohorts 6-8) is presented in Table 3.5-2.

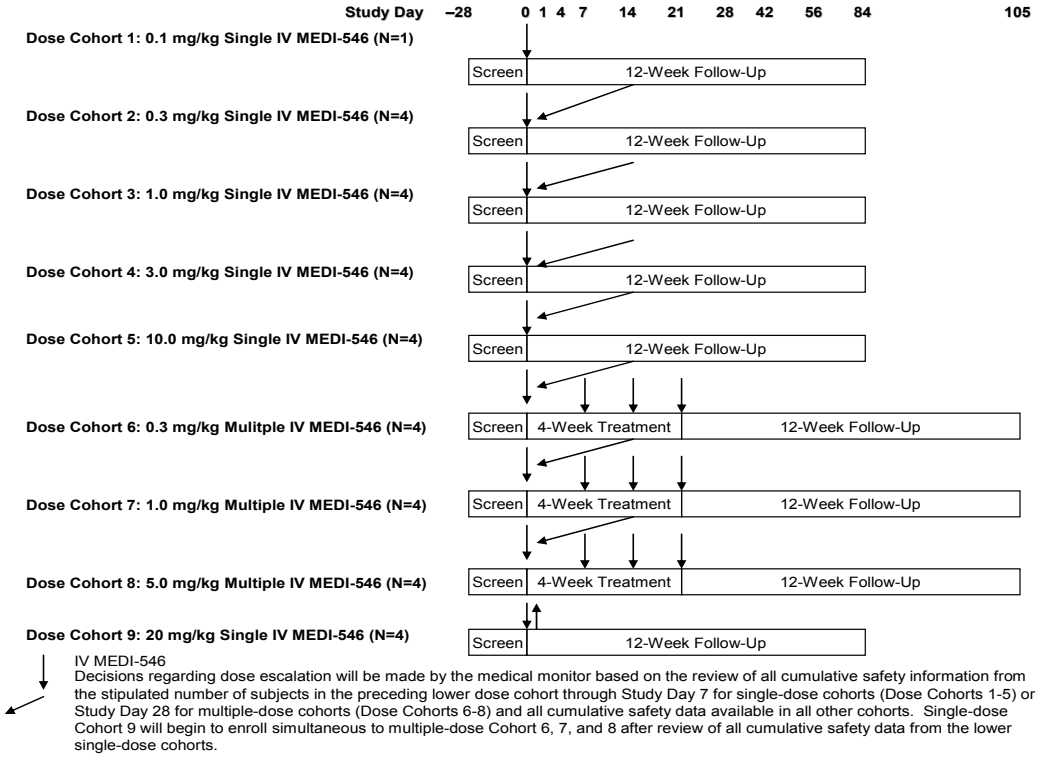

Figure 2.4-1 Study Flow Diagram

3 Study Procedures

3.1 Subject Selection

The subjects in this study will be adult male or female subjects with scleroderma who have skin thickening in an area suitable for repeat biopsy.

The investigator (physician) or qualified designee will discuss the study with a subject/the legal representative of a subject who is considered a potential candidate for the study. If there is interest in participating in the study, the subject/legal representative will be provided with the informed consent form. The investigator or designee will address any questions and/or concerns that the subject/legal representative may have and, if there is continued interest, will secure written informed consent for participation in the study. Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization (applies to covered entities in the US only) will be obtained prior to conducting any protocol-related procedures, including screening evaluations or medication washouts.

3.1.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) Male or female subjects ≥ 18 years of age at the time of the first dose of MEDI-546;
2) Written informed consent and HIPAA authorization (applies to covered entities in the US only) obtained from the subject or subject's legal representative;
3) Must fulfill the American Rheumatism Association (American College of Rheumatology) preliminary classification criteria for systemic sclerosis (Appendix 1);
4) Has at least moderate skin thickening (score of at least 2 by modified Rodnan Total Skin Score [mRTSS]) in at least one area suitable for repeat biopsy, such as arms, legs, or trunk;
5) Women, unless surgically sterile (including tubal ligation) or at least 2 years post-menopausal, must use an effective method of avoiding pregnancy (including oral, injectable, transdermal, or implanted contraceptives, intrauterine device, diaphragm with spermicide, cervical cap, abstinence, and sterile sexual partner) in addition to the use of condoms (male or female condoms with spermicide) from signing of the informed consent through the end of the study. Cessation of birth control after this point should be discussed with a responsible physician. Men, unless surgically sterile, must likewise practice 2 effective methods of birth control (condom with spermicide

or abstinence) and must use such precautions from Study Day 0 through the end of the study;

6) Ability to complete the study period, including follow-up period through a maximum of Study Day 105; and

7) Willing to forego other forms of experimental treatment during study.

3.1.2 Exclusion Criteria

Subjects must have *none* of the following:

1) History of allergy or reaction to any component of the MEDI-546 formulation;

2) Forced vital capacity (FVC) < 60% predicted, diffusing capacity for carbon monoxide (DL_{CO}) < 40% predicted, pulmonary hypertension requiring treatment with endothelin receptor antagonists or prostacyclin analogues, scleroderma renal crisis within the last year, or medically significant malabsorption;

3) Have received the following medications within 28 days before entry:

- Cyclophosphamide at any dose
- Systemic cyclosporine at any dose
- Thalidomide at any dose
- Hydroxychloroquine > 600 mg/day
- Mycophenolate mofetil > 3 g/day
- Methotrexate > 25 mg/week
- Azathioprine > 3 mg/kg/day;

4) Have received leflunomide > 20 mg/day within 6 months before entry;

5) Have received fluctuating doses of the following within 28 days before entry:

- Antimalarials
- Mycophenolate mofetil
- Methotrexate
- Leflunomide
- Azathioprine;

6) Have received prednisone > 20 mg/day or in fluctuating doses within 14 days before entry;

7) Have received fluctuating doses of nonsteroidal anti-inflammatory drugs (NSAIDs) within 14 days before entry;

8) Treatment with any investigational drug therapy within 28 days before entry into the study, B cell-depleting therapies within 12 months before entry, or biologic therapies within 30 days or 5 half-lives of the biologic agent, whichever is longer, before entry into the study;

9) In the investigator's opinion, evidence of clinically significant active infection, including ongoing, chronic infection, within 28 days before entry;

10) A history of severe viral infection as judged by the investigators, including severe infections of either cytomegalovirus (CMV) or the herpes family such as disseminated herpes, herpes encephalitis, ophthalmic herpes;

11) Herpes zoster infection within 3 months before entry;

12) Evidence of infection with hepatitis B or C virus, or human immunodeficiency virus (HIV)-1 or HIV-2, or active infection with hepatitis A, as determined by results of testing at screening;

13) Vaccination with live attenuated viruses within 28 days before entry;

14) Pregnancy (women, unless surgically sterile or at least 2 years post-menopausal, must have a negative serum pregnancy test within 28 days before receiving MEDI-546 and a negative urine pregnancy test on days of MEDI-546 administration before receiving MEDI-546);

15) Breastfeeding or lactating women;

16) History of primary immunodeficiency;

17) History of alcohol or drug abuse < 1 year prior to entry;

18) History of cancer except basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy > 1 year prior to entry.

19) History of active tuberculosis (TB) infection or latent TB infection without completion of an appropriate course of treatment;

20) Newly positive TB skin test (defined as a reaction ≥ 10 mm in diameter if not on systemic immunosuppressive medication or ≥ 5 mm if on systemic immunosuppressive medication) without concomitant prophylactic therapy;

21) Elective surgery planned from the time of signing of the informed consent through end of study;

22) At screening blood tests (within 28 days before entry), any of the following:

- Aspartate aminotransferase (AST) > 2.5 x upper limit of the normal range (ULN), unless due to documented myositis
- Alanine aminotransferase (ALT) > 2.5 x ULN, unless due to documented myositis.
- Creatinine > 4.0 mg/dL
- Neutrophils < 1,500/mm^3

- Platelet count < 50,000/mm^3;

23) History of any disease, evidence of any current disease (other than scleroderma), any finding upon physical examination, chest x-ray, or any laboratory abnormality that, in the opinion of the investigator or medical monitor, may compromise the safety of the subject in the study or confound the analysis of the study; or

24) Any employee of the research site who is involved with the conduct of the study.

25) History of vasculitis (vasculopathy of scleroderma is not a vasculitis)

3.2 Enrollment and Study Entry

A subject is considered enrolled into the study once written informed consent is obtained. A subject is considered entered into the study at the time of the investigational product administration (Study Day 0).

Once informed consent is obtained, a subject identification number (SID) will be assigned by a central system (eg, an interactive voice response system, IVRS) and the screening evaluations may begin. This number will be used to identify the subject during the screening process and throughout study participation.

Enrolled subjects will be screened by investigators or qualified designees to assess eligibility for entry into the study. A master log will be maintained of all enrolled subjects and will document all screening failures (ie, subjects who are consented and enrolled but not entered), including reason for screening failure.

Subjects who fail to meet all eligibility criteria, who decline further participation, or who are lost to follow-up will not proceed to entry.

The procedure for study entry is as follows:

- The subject arrives at the clinic or hospital for the Study Day 0 visit;
- The investigator or designee confirms that written informed consent has been obtained and that the subject meets eligibility criteria;
- The investigator or designee calls the IVRS and provides the SID and subject's baseline characteristic(s) used to verify that it is the same subject; and
- A confirmatory fax with this information is sent to the investigator/designee.

MEDI-546 must be administered within 8 hours after preparation. If the dose is not administered within 8 hours, a new dose must be prepared using a new vial. Subjects are considered evaluable for safety if they receive MEDI-546 and complete the required

evaluations through Study Day 7 or if they discontinue MEDI-546 for safety reasons. In addition, subjects are considered evaluable for the exploratory endpoints if they complete Study Day 28. Nonevaluable subjects may be replaced for reasons other than safety to maintain the stipulated cohort sizes in each dose cohort.

If there is a possible safety signal from the analysis of safety information for a particular dose cohort (Dose Cohorts 2-9 only) that does not warrant discontinuation but does warrant further investigation (prior to dose escalation for Dose Cohorts 2-7), then the sponsor may add 4 subjects to the dose cohort for a maximum of 8 subjects in the dose cohort. A maximum of 2 dose cohorts may be expanded to a total of 8 subjects each. If a possible safety signal occurs subsequent to expansion of 2 dose cohorts to a maximum of 8 subjects each, then the study will be terminated. In addition, Dose Cohorts 2-9 may be expanded by up to 2 additional subjects each if eligible subjects are already in screening at the time 4 subjects have been entered into the dose cohort and there is no possible safety signal to warrant expansion of the dose cohort to a maximum of 8 subjects. Therefore, the maximum number of subjects allowed in the study is 53 (29 + 8 [4×2] + 12 [2×6]).

Decisions regarding dose escalation will be made by the medical monitor based on the review of all cumulative safety information from the stipulated number of subjects in the preceding lower dose cohort through Study Day 7 for single-dose cohorts (Dose Cohorts 1-5) or Study Day 28 for multiple-dose cohorts (Dose Cohorts 6 and 7) and all cumulative safety data available in all other cohorts. The SMC, which includes physicians external to MedImmune, also will review cumulative safety surveillance data throughout the study and can make recommendations regarding the study progression. The Safety Monitoring Committee (SMC) can stop study entry and dosing as it deems necessary.

3.3 Blinding

This study is not blinded.

3.4 Investigational Product (MEDI-546)

3.4.1 Investigational Product Supplies and Accountability

The sponsor will provide the investigators with adequate quantities of investigational product. Investigational product is stored at 2°C to 8°C (36°F-46°F) and must not be frozen.

MEDI-546: MEDI-546 is supplied at a concentration of 20 mg/mL in a 3 mL type I borosilicate 13 mm clear glass vial with 13 mm stoppers and overseals containing 2 mL of MEDI-546 Drug Product. [redacted]

Specific details regarding investigational product supplies, dose preparation, and accountability will be provided in the Investigational Product Manual supplied to the sites.

The investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of all investigational product accountability records will be returned to the sponsor. All unused investigational product will be returned to assigned distribution centers as designated by MedImmune (refer to the Investigational Product Manual for contact information and specific shipping instructions).

3.4.2 Treatment Regimens

A minimum of 33 evaluable subjects are planned for the study, with cohorts of subjects receiving 1 of 5 single IV doses followed by 3 cohorts of subjects receiving 1 of 3 multiple IV doses of MEDI-546 as shown in Table 3.4.2-1; an additional single-dose cohort (Dose Cohort 9, 20 mg/kg) will enroll simultaneous to Cohort 6, 7, and 8. MEDI-546 will be administered as an IV infusion over at least 60 minutes for IV doses of ≤ 10 mg/kg or at least 120 minutes for IV doses of > 10 mg/kg For doses > 10 mg/kg and for subjects weighing > 250 lbs. or 114 kg please call the medical monitor to discuss the infusion rate instructions.. Single-dose IV administration of MEDI-546 will occur on Study Day 0, with follow-up through Study Day 84; multiple-dose IV administration of MEDI-546 will occur on Study Days 0, 7, 14, and 21, with follow-up through Study Day 105.

Table 3.4.2-1 Treatment Regimens

Dose Cohort	Number of Subjects [a]	MEDI-546 Treatment [b]
1	1	0.1 mg/kg MEDI-546 as a single IV dose
2	4	0.3 mg/kg MEDI-546 as a single IV dose
3	4	1.0 mg/kg MEDI-546 as a single IV dose
4	4	3.0 mg/kg MEDI-546 as a single IV dose
5	4	10.0 mg/kg MEDI-546 as a single IV dose
6	4	0.3 mg/kg MEDI-546 as a weekly IV dose x 4 doses
7	4	1.0 mg/kg MEDI-546 as a weekly IV dose x 4 doses
8	4	5.0 mg/kg MEDI-546 as a weekly IV dose x 4 doses
9	4	20 mg/kg MEDI-546 as a single IV dose

[a] Each dose cohort may be expanded by 2 additional subjects if the eligible subjects are already in screening at the time that enrollment into that cohort has been completed and there is no possible safety signal to warrant expansion of the dose cohort to a maximum of 8 subjects.

[b] Dose levels for Dose Cohorts 6-8 may be modified based on possible interim analyses.

If there is a possible safety signal from the analysis of safety information for a particular dose cohort (Dose Cohorts 2-9 only) that does not warrant discontinuation but does warrant further investigation (prior to dose escalation for Dose Cohorts 2-7), then the sponsor may add 4 subjects to the dose cohort for a maximum of 8 subjects in the dose cohort. A maximum of 2 dose cohorts may be expanded to a total of 8 subjects each. If a possible safety signal occurs subsequent to expansion of 2 dose cohorts to a maximum of 8 subjects each, then the study will be terminated. In addition, Dose Cohorts 2-9 may be expanded by up to 2 additional subjects each if eligible subjects are already in screening at the time 4 subjects have been entered into the dose cohort and there is no possible safety signal to warrant expansion of the dose cohort to a maximum of 8 subjects. Therefore, the maximum number of subjects allowed in the study is 53 (33 + 8 [4×2] + 12 [2×6]).

Dose levels for the multiple-dose cohorts (Dose Cohorts 6-8) have been be modified and is presented in Table 3.4.2-1 Doses for multiple IV dosing include one dose that provides incomplete inhibition of type I IFN gene signature, one dose that provides nearly complete inhibition of type I IFN gene signature, and one dose that is higher than the dose that provides nearly complete inhibition of type I IFN gene signature in the skin. The final doses selected were chosen from among those already tested in the single-dose cohorts (Dose Cohorts 1-4)..

3.4.3 Investigational Product Preparation

The dose of MEDI-546 for IV administration must be prepared by the investigational product manager using aseptic technique. Detailed instructions regarding MEDI-546 preparation can be found in the Investigational Product Manual that will be provided to the sites.

The volume of MEDI-546 for IV infusion is calculated on the basis of the subject's weight (to the nearest 0.1 kg) using the following formula:

Dose (mL) = [Subject weight (kg) × Dose (mg/kg)] ÷ Concentration (mg/mL)

Example: An 80.0 kg subject dosed at 1 mg/kg MEDI-546, using the 20 mg/mL formulation, will require 80.0 kg × 1 mg/kg ÷20 mg/mL = 4.0 mL for IV infusion.

The calculated dose of MEDI-546 should be rounded to the nearest 0.1 mL. Investigational product will be diluted in 0.9% normal saline after removing from the infusion bag containing 0.9% normal saline the volume equivalent to the dose of MEDI-546 and then adding to the bag the calculated dose of MEDI-546. Due to an approximately 10% overfill of normal saline, the final volume of the dilution will be greater than 100 mL. If the total volume of the study drug to be administered is greater than 75 mL, then a 250 mL bag of normal saline should be used (please see the investigational product manual for further instructions). The entire contents of the bag will be administered using an infusion pump over at least 60 minutes for IV doses ≤ 10 mg/kg or at least 120 minutes for IV doses of > 10 mg/kg. For doses > 10 mg/kg and for subjects weighing > 250 lbs. or 114 kg please call the medical monitor to discuss the infusion rate instructions.

3.4.4 Administration of Investigational Product

MEDI-546 should be dispensed by the pharmacist or qualified designee and administered as an IV infusion over at least 60 minutes for IV doses of ≤ 10 mg/kg or at least 120 minutes for IV doses of > 10 mg/kg. For doses > 10 mg/kg and for subjects weighing > 250 lbs. or 114 kg please call the medical monitor to discuss infusion rate instructions. MEDI-546 should be prepared in 0.9% normal saline. Due to approximately 10% bag overfill the final volume of the dilution will be greater than 100 mL or 250 mL. The entire contents of the bag should be administered.

Subjects should not be premedicated, since the primary objective of this study is to evaluate the safety and tolerability of the investigational product. However, if reactions to the IV

infusion occur during or after MEDI-546 administration, they should be treated appropriately and, for multiple-dosing cohorts, appropriate premedication should be considered for subsequent administrations.

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be monitored within 60 minutes before, about every 15 minutes during infusion, immediately after the end of the infusion, and about every 30 minutes after the end of the infusion for 2 hours or until stable, whichever is later. If an anaphylactoid-like infusion reaction or anaphylactic reaction occurs, vital signs will be taken more frequently, as warranted by the severity of the reaction. Blood pressure and heart rate also will be measured prior to discharge from the clinic on all days when study drug is administered.

Infusion reactions have been reported with the administration of intravenous gammaglobulin and nearly all approved monoclonal antibodies. For purposes of this protocol, infusion reactions are defined as anaphylactoid-like AEs related to the infusion of the investigational product itself that usually occur within the first 24 hours after infusion, especially within minutes to a few hours, and will be distinguished from true anaphylactic reactions by absence of measurable antibodies against the investigational product. Infusion reactions are characterized by a complex of signs and symptoms that include flu-like illness, fever, chills/rigors, nausea, urticaria, headache, bronchospasm, angioedema, hypotension, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. For purposes of this protocol, a classification of infusion reactions is given in Table 3.4.4-1, with suggested treatment options. Final treatment is at the discretion of the investigator and should reflect local standard of care.

Table 3.4.4-1 Classification and Suggested Treatments for Infusion Reactions

Severity of Symptoms	Treatment	Study Drug
Mild (Grade 1) Localized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 point change in systolic BP	• Stop study drug infusion immediately • Evaluate patient, including close monitoring of vital signs • At the discretion of the investigator, treat patient, for example with − Normal saline (~500-1000 mL/hour IV) − Diphenhydramine 50 mg IV − Acetaminophen 500-650 mg	• Option 1: Do not resume infusion; OR, at the discretion of the investigator, resume current infusion under observation and complete study drug infusion at no more than half the planned infusion rate • Option 2: Discontinue further administration of study drug ;OR, at the discretion of the investigator, continue study drug administration and consider slowing infusion rate and pretreating patient 1.5-0.5 hours prior to study drug administration, for example with − Diphenhydramine 50 mg IV − Acetaminophen 500-650 mg
Moderate (Grade 2) Above plus generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 point change in systolic BP	• Stop study drug infusion immediately • Evaluate patient, including close monitoring of vital signs • Treat patient, for example with − Normal saline (~500-1000 mL/hour IV) − Diphenhydramine 50 mg IV − Acetaminophen 500-650 mg	• Option 1: Do not resume infusion; OR, at the discretion of the investigator, resume current infusion under observation and complete study drug infusion at no more than half the planned infusion rate • Option 2: Discontinue further administration of study drug; OR, at the discretion of the investigator, continue study drug administration and consider slowing infusion rate and pretreating patient 1.5-0.5 hours prior to study drug administration, for example with − Diphenhydramine 50 mg IV − Acetaminophen 500-650 mg • If moderate event recurs in the same patient, discontinue further study drug administration

Table 3.4.4-1 Classification and Suggested Treatments for Infusion Reactions

Severity of Symptoms	Treatment	Study Drug
Severe (Grade 3) or Above plus fever with rigors, hypo- or hypertension with ≥ 40 point change in systolic BP, wheezing, angioedema, or stridor **Life threatening (Grade 4)** Defined as a reaction that is life threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion	• Stop study drug infusion immediately • Evaluate patient, including close monitoring of vital signs • Maintain airway, oxygen if available • Treat patient immediately, for example with − Normal saline (~500-1000 mL/hour IV) − Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local standard of care, example, epinephrine 1:1000, 0.5-1.0 mL administered SC for mild cases and IM for more severe cases − IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20-40 mg − Diphenhydramine 50 mg IV − Acetaminophen 500-650 mg • Call emergency medical transport for transport to hospital if − Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine − Grade 4 − At the discretion of the investigator	• Do not resume infusion • Discontinue further study drug administration

If an infusion reaction occurs during or after investigational product administration, the subject will remain at the study site for a minimum of 2 hours for observation after resolution of symptoms and undergo the following procedures unless transferred to an emergency or hospital facility is deemed warranted for a more severe reaction:

- Clinical evaluation, treatment, and stabilization of the subject according to standard medical practice, with suggested approaches outlined above;
- Close monitoring of vital signs, for example every 5 to 10 minutes for Grade 1 or Grade 2 infusion reactions and every 2 to 5 minutes for Grade 3 or Grade 4 infusion reactions until stable;
- Collect serum for assessment of safety biomarkers (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies) for Grade 1 or higher infusion reactions as soon as possible after the event, at 60 minutes after the event, and at discharge.

Because compatibility of MEDI-546 with IV medications and solutions other than 0.9% sodium chloride for injection, USP, is not known, the investigational product solution should not be infused through an IV line in which other solutions or medications are being administered.

MEDI-546 must be administered within 8 hours after preparation. If the dose is not administered within 8 hours, a new dose must be prepared using a new vial. If these conditions are not met, contact the sponsor for further instructions.

3.4.5 Concomitant Medications

Subjects may receive medications to treat scleroderma, other medical conditions, and AEs/SAEs throughout the trial, as deemed necessary by the investigator or the subject's physician, with the exception of medications at doses that meet exclusion criteria.

All concomitant medications given to the subject from signing of the informed consent through Study Day 84 (Dose Cohorts 1-5, and 9) or from signing of the informed consent through Study Day 105 (Dose Cohorts 6-8) will be recorded on the source document. The following medications are considered exclusionary, and the sponsor must be notified if a subject receives any of these during the study.

1) Investigational agents; or
2) Any live attenuated virus vaccine.

As possible, the dosages of concomitant antimalarials, mycophenolate, methotrexate, leflunomide, and azathioprine should remain constant from 28 days prior to Study Day 0 through Study Day 84 for subjects receiving single IV doses and through Study Day 105 for subjects receiving multiple IV doses. As possible, dosage of routine concomitant NSAIDs and oral corticosteroids should remain unchanged from 14 days prior to Study Day 0 through Study Day 84 for subjects receiving single IV doses and through Study Day 105 for subjects receiving multiple IV doses.

The sponsor must be notified if any subject receives prohibited concomitant medications.

3.5 Schedule of Subject Evaluations

All subjects who are assigned a SID and receive any investigational product will be followed according to the protocol regardless of the number of doses received, unless consent for follow-up is withdrawn. The investigator or designee must notify the sponsor or designee 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. Protocol deviations will be recorded on the source document with an explanation for the deviation. The investigator must comply with the applicable requirements related to the reporting of protocol deviations to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Subjects/legal representatives 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 or designee and made available to the sponsor or designee during monitoring visits.

A schedule of screening and on-study visit procedures for subjects receiving single IV doses of MEDI-546 (Dose Cohorts 1-5, and 9) is presented in Table 3.5-1; the schedule of screening and on-study procedures for subjects receiving multiple IV doses of MEDI-546 (Dose Cohorts 6-8) is presented in Table 3.5-2. The tables are followed by a detailed description of each visit.

Table 3.5-1 Schedule of Subject Evaluations for Subjects Receiving Single IV Doses of MEDI-546 (Dose Cohorts 1-5, and 9)

Evaluations	Study Day								
	Screening (-28 to -1)	**0**	**1**	**7**	**14**	**21**	**28**	**56**	**84/Discont[a]**
Written Informed Consent, and HIPAA (for US sites only)	X								
Verify Eligibility Criteria	X	X							
Medical History	X	X							
Physical Examination	X	X					X		X
ECG	X								X
Chest X-ray	X								
Pulmonary Function Tests	X						X	X	X
TB Skin Test	X								
Hepatitis A,B,C; HIV-1,-2	X								
Serum βHCG	X								
Urine βHCG		X							X
MEDI-546 ADMINISTRATION		**X**							
SAFETY ASSESSMENT									
Vital Signs	X	X	X	X	X	X	X	X	X
AE/SAE Assessment	X	X	X	X	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X	X
Serum Chemistry	X	X		X	X	X	X	X	X
Hematology	X	X		X	X	X	X	X	X
Urinalysis	X	X		X	X	X	X	X	X

Table 3.5-1 Schedule of Subject Evaluations for Subjects Receiving Single IV Doses of MEDI-546 (Dose Cohorts 1-5, and 9)

Evaluations	Study Day								
	Screening (-28 to -1)	**0**	**1**	**7**	**14**	**21**	**28**	**56**	**84/Discont[a]**
Viral Cultures		X					X	X	X
Safety Biomarkers		X							
DISEASE ACTIVITY AND PATIENT-REPORTED OUTCOMES									
HAQ-DI With Scleroderma NRS		X					X	X	X
Modified Rodnan Total Skin Score		X					X	X	X
European Disease Activity Index		X					X	X	X
ESR, CRP, Serum Complement C3 & C4		X					X	X	X
Autoantibody Levels		X					X	X	X
PK/IM/PD									
MEDI-546 Serum Concentration		X[b]	X	X	X	X	X	X	X
Anti-MEDI-546 Antibodies		X[c]					X	X	X
Whole Blood for Receptor Occupancy Analysis		X[b]	X	X	X	X	X	X	X
Whole Blood for Type I IFN-inducible Genes, Exploratory Analyses & Storage		X[c]	X	X	X		X	X	X
Skin Biopsy for Type I IFN-inducible Genes and Exploratory Studies		X[c]		X					

Table 3.5-1 Schedule of Subject Evaluations for Subjects Receiving Single IV Doses of MEDI-546 (Dose Cohorts 1-5, and 9)

Evaluations	Study Day								
	Screening (-28 to -1)	**0**	**1**	**7**	**14**	**21**	**28**	**56**	**84/Discont[a]**
CORRELATIVE STUDIES									
Serum for Exploratory Correlative Studies & Storage		X[c]	X	X	X		X	X	X
DNA Sample (optional)[C]		X							

[a] These evaluations will be performed in subjects who discontinue the study prematurely, unless the evaluation was performed within 2 weeks of the discontinuation visit, or in the case of repeat skin biopsy, if it was done at Study Day 7.

[b] Samples will be collected predose and 0.5 hours post end of infusion.

[C] Samples will be collected predose.

Table 3.5-2 Schedule of Subject Evaluations for Subjects Receiving Multiple IV Doses of MEDI-546 (Dose Cohorts 6-8)

	Study Day										
Evaluations	**Screening (-28 to -1)**	**0**	**1**	**7**	**14**	**21**	**22**	**28**	**56**	**84**	**105/Discont[a]**
Written Informed Consent and HIPAA (for US sites only)	X										
Verify Eligibility Criteria	X	X									
Medical History	X	X									
Physical Examination	X	X						X			X
ECG	X										X
Chest X-ray	X										
Pulmonary Function Tests	X							X	X	X	X
TB Skin Test	X										
Hepatitis A,B,C; HIV-1,-2	X										
Serum βHCG	X										
Urine βHCG		X		X	X	X					X
MEDI-546 ADMINISTRATION		**X**		**X**	**X**	**X**					
SAFETY ASSESSMENT											
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry	X	X		X	X	X		X	X	X	X
Hematology	X	X		X	X	X		X	X	X	X

Table 3.5-2 Schedule of Subject Evaluations for Subjects Receiving Multiple IV Doses of MEDI-546 (Dose Cohorts 6-8)

	Study Day										
Evaluations	**Screening (-28 to -1)**	**0**	**1**	**7**	**14**	**21**	**22**	**28**	**56**	**84**	**105/Discont[a]**
Urinalysis	X	X		X	X	X		X	X	X	X
Viral Cultures		X						X	X	X	X
Safety Biomarkers		X									
DISEASE ACTIVITY AND PATIENT-REPORTED OUTCOMES											
HAQ-DI with Scleroderma NRS		X						X	X	X	X
Modified Rodnan Total Skin Score		X						X	X	X	X
European Disease Activity Index		X						X	X	X	X
ESR, CRP, Serum Complement C3 & C4		X						X	X	X	X
Autoantibody Levels		X						X	X	X	X
PK/IM/PD											
MEDI-546 Serum Concentration		X[b]	X	X[c]	X[c]	X[b]	X	X	X	X	X
Anti-MEDI-546 Antibodies		X[c]						X	X	X	X
Whole Blood for Receptor Occupancy Analysis		X[b]	X	X[c]	X[c]	X[b]	X	X	X	X	X
Whole Blood for Type I IFN-inducible Genes, Exploratory Analyses & Storage		X[c]	X	X	X			X	X	X	X
Skin Biopsy for Type I IFN-inducible Genes and Exploratory Studies		X[c]						X			

Table 3.5-2 Schedule of Subject Evaluations for Subjects Receiving Multiple IV Doses of MEDI-546 (Dose Cohorts 6-8)

	Study Day										
Evaluations	**Screening (-28 to -1)**	**0**	**1**	**7**	**14**	**21**	**22**	**28**	**56**	**84**	**105/Discont[a]**
CORRELATIVE STUDIES											
Serum for Exploratory Correlative Studies & Storage		X[c]	X	X[c]	X[c]			X	X	X	X
DNA Sample (optional)[C]		X									

[a] These evaluations will be performed in subjects who discontinue the study prematurely, unless the evaluation was performed within 2 weeks of the discontinuation visit or, in the case of repeat skin biopsy, if it was done at Study Day 28.

[b] Samples will be collected predose and 0.5 hours post end of infusion.

[c] Samples will be collected predose.

Screening

Screening

Note: All screening laboratory assessments must be performed within 28 days before study entry (Study Day 0), unless otherwise specified. The screening evaluations may be carried out over more than one visit. Written informed consent and HIPAA (applies to covered entities in the US only) must be obtained prior to performing any study-related procedure, including screening evaluations. However, if evaluations that have been performed for other purposes prior to informed consent are otherwise suitable for use as screening evaluations, those studies need not be repeated if the subject/legal representative consents to allow use.

1) Written informed consent and HIPAA
2) Assign an SID
3) Verify eligibility criteria
4) Perform medical history
5) Perform physical examination
   Note: Items 4 and 5 above are designed to collect information on the subject once enrolled into the study and start the screening process. Any new physical exam finding, symptom, disease, or untoward medical event that begins after written informed consent has been obtained, but before receipt of investigational product, that is not related to a protocol requirement must be added to the baseline medical history or physical exam.
6) Perform ECG
7) Perform chest x-ray (anterior/posterior and lateral)
   Note: The chest x-ray may be substituted with documentation of a previous chest x-ray performed within the previous 6 months. A previous computerized tomography evaluation of the lungs may be substituted for the chest x-ray if performed within the last 6 months.
8) Perform pulmonary function tests
9) Perform TB skin test
10) Monitor for vital signs (includes temperature, blood pressure, pulse rate, respiratory rate)
11) Assess for SAEs and protocol-related AEs
12) Record concomitant medications
13) Collection of blood and urine
    - Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody, and HIV-1 and HIV-2 antibody
    - Serum β human chorionic gonadotropin (βHCG)

- Serum chemistry (includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, ALT, AST, bilirubin, alkaline phosphatase, and glucose [random])
- Hematology (includes CBC with differential and platelet count and hemoglobin)
- Urinalysis

Study Day 0

All Dose Cohorts

1) Verify eligibility criteria
2) Update screening history and physical examination (any new findings since screening)
3) Monitor vital signs
4) Assess for SAEs and protocol-related AEs
5) Update concomitant medications
6) Collection of blood, urine, and cultures (all prior to MEDI-546 administration and may be done up to 72 hours prior to dosing, except urine βHCG which must be on day of dosing)
   - Urine βHCG
   - Serum chemistry
   - Hematology
   - Urinalysis
   - Viral cultures
   - Safety biomarkers
   - Erythrocyte sedimentation rate (ESR), cross-reactive protein (CRP), serum complement C3, C4
   - Autoantibody levels (includes ANA, anti-topoisomerase I (anti-Scl70), and anti-centromere antibodies and potential assessment of anti-fibroblast and anti-endothelial cell antibodies)
   - MEDI-546 serum concentration
   - Receptor occupancy analysis
   - Type I IFN-inducible genes, exploratory analyses, and storage
   - Anti-MEDI-546 antibodies
   - Exploratory correlative studies and storage (serum)

- DNA sample (optional)

7) Assess health assessment questionnaire-disability index (HAQ-DI) with scleroderma numeric rating scales (may be done up to 72 hours prior to dosing and preferably prior to the mRTSS and the European disease activity index [DAI] and MEDI-546 administration)

8) Assess mRTSS (may be done up to 72 hours prior to dosing)

9) Assess European DAI (may be done up to 72 hours prior to dosing)

10) Skin biopsy for type I IFN-inducible genes and exploratory analyses (prior to MEDI-546 administration and may be done anytime between signing of the informed consent and Study Day 0)

11) Monitor vital signs within 60 minutes before administration of MEDI-546

12) **Administration of MEDI-546**

13) Monitor vital signs about every 15 minutes during infusion, immediately after the end of the infusion, and about every 30 minutes after the end of the infusion for 2 hours or until stable, whichever is later. Monitor blood pressure and heart rate prior to discharge from the study site.

14) Blood collection at 0.5 hours post end of infusion

- MEDI-546 serum concentration
- Receptor occupancy

15) Monitor for AEs and SAEs

Study Day 1

All Dose Cohorts

1) Monitor vital signs

2) Monitor for AEs and SAEs

3) Record concomitant medications

4) Collection of blood

- MEDI-546 serum concentration
- Receptor occupancy analysis
- Type I IFN-inducible genes, exploratory analyses, and storage
- Exploratory correlative studies and storage (serum)

Study Day 7 (± 1 day)

All Dose Cohorts

1) Monitor vital signs
2) Monitor AEs and SAEs
3) Record concomitant medications
4) Collection of blood and urine prior to MEDI-546 administration, if applicable
   - Serum chemistry
   - Hematology
   - Urinalysis
   - MEDI-546 serum concentration
   - Receptor occupancy analysis
   - Type I IFN-inducible genes, exploratory analyses, and storage
   - Exploratory correlative studies and storage (serum)

Dose Cohorts 1-5 and 9 only

5) Skin biopsy for type I IFN-inducible genes and exploratory studies

Dose Cohorts 6-8 only

6) Urine βHCG prior to MEDI-546 administration
7) Monitor vital signs within 60 minutes before administration of MEDI-546
8) **Administration of MEDI-546**
9) Monitor vital signs about every 15 minutes during infusion, immediately after the end of the infusion, and about every 30 minutes after the end of the infusion for 2 hours or until stable, whichever is later. Monitor blood pressure and heart rate prior to discharge from the study site.
10) Monitor for AEs and SAEs

Study Day 14 (± 2 days)

All Dose Cohorts

1) Monitor vital signs
2) Monitor for AEs and SAEs
3) Record concomitant medications
4) Collection of blood and urine prior to MEDI-546 administration, if applicable

- Serum chemistry
- Hematology
- Urinalysis
- MEDI-546 serum concentration
- Receptor occupancy analysis
- Type I IFN-inducible genes, exploratory analyses, and storage
- Exploratory correlative studies and storage (serum)

Dose Cohorts 6-8 only

5) Urine βHCG before MEDI-546 administration
6) Monitor vital signs within 60 minutes before administration of MEDI-546
7) **Administration of MEDI-546**
8) Monitor vital signs about every 15 minutes during infusion, immediately after the end of the infusion, and about every 30 minutes after the end of the infusion for 2 hours or until stable, whichever is later. Monitor blood pressure and heart rate prior to discharge from the study site.
9) Monitor for AEs and SAEs

Study Day 21 (± 2 days)

All Dose Cohorts

1) Monitor vital signs
2) Monitor for AEs and SAEs
3) Record concomitant medications
4) Collection of blood and urine prior to MEDI-546 administration, if applicable
   - Serum chemistry
   - Hematology
   - Urinalysis
   - MEDI-546 serum concentration
   - Receptor occupancy analysis

Dose Cohorts 6-8 only

5) Urine βHCG before MEDI-546 administration
6) Monitor vital signs within 60 minutes before administration of MEDI-546

7) **Administration of MEDI-546**

8) Monitor vital signs about every 15 minutes during infusion, immediately after the end of the infusion, and about every 30 minutes after the end of the infusion for 2 hours or until stable, whichever is later. Monitor blood pressure and heart rate prior to discharge from the study site.

9) Blood collection at 0.5 hour post end of infusion

- MEDI-546 serum concentration
- Receptor occupancy

10) Monitor for AEs and SAEs

Study Day 22 (± 2 days)

Dose Cohorts 6-8 only

1) Monitor vital signs
2) Monitor for AEs and SAEs
3) Record concomitant medications
4) Collection of blood
   - MEDI-546 serum concentration
   - Receptor occupancy analysis

Study Day 28 (± 2 days)

All Cohorts

1) Perform physical examination
2) Perform pulmonary function tests
3) Monitor vital signs
4) Monitor for AEs and SAEs
5) Record concomitant medications
6) Collection of blood, urine, and cultures
   - Serum chemistry
   - Hematology
   - Urinalysis
   - Viral cultures
   - ESR, CRP, serum complement C3, C4

- Autoantibody levels
- MEDI-546 serum concentration
- Receptor occupancy analysis
- Type I IFN-inducible genes, exploratory analyses, and storage
- Anti-MEDI-546 antibodies
- Exploratory correlative studies and storage (serum)

7) Assess HAQ-DI with scleroderma NRS (preferably performed prior to mRTSS and European DAI)
8) Assess mRTSS
9) Assess European DAI

Dose Cohorts 6-8 only

10) Skin biopsy for type I IFN-inducible genes and exploratory studies

Study Day 56 (± 4 days)

All Dose Cohorts

1) Perform pulmonary function tests
2) Monitor vital signs
3) Monitor for AEs and SAEs
4) Record concomitant medications
5) Collection of blood, urine, and cultures
   - Serum chemistry
   - Hematology
   - Urinalysis
   - Viral cultures
   - ESR, CRP, serum complement C3 & C4
   - Autoantibody levels
   - MEDI-546 serum concentration
   - Receptor occupancy analysis
   - Type I IFN-inducible genes, exploratory analyses, and storage
   - Anti-MEDI-546 antibodies
   - Exploratory correlative studies and storage (serum)

6) Assess HAQ-DI with scleroderma NRS (preferably performed prior to mRTSS and European DAI)
7) Assess mRTSS
8) Assess European DAI with Patient Reported Outcomes

Study Day 84 (± 7 days) or Study Discontinuation for Dose Cohorts 1-5 and 9

If a subject in Dose Cohorts 1-5 and 9 discontinues the study prematurely prior to Study Day 84, he or she should return to the study site and complete the following evaluations. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

All Dose Cohorts

1) Perform pulmonary function tests
2) Monitor vital signs
3) Monitor for AEs and SAEs
4) Record concomitant medications
5) Collection of blood urine, and cultures
   - Serum chemistry
   - Hematology
   - Urinalysis
   - Viral cultures
   - ESR, CRP, serum complement C3, C4
   - Autoantibody levels
   - MEDI-546 serum concentration
   - Receptor occupancy analysis
   - Type I IFN-inducible genes, exploratory analyses, and storage
   - Anti-MEDI-546 antibodies
   - Exploratory correlative studies and storage (serum)
6) Assess HAQ-DI with scleroderma NRS (preferably performed prior to mRTSS and European DAI)
7) Assess mRTSS
8) Assess European DAI

Dose Cohorts 1-5 and 9 only

9) Perform physical examination
10) Perform ECG
11) Urine βHCG

Study Day 105 (± 7 days) or Study Discontinuation for Dose Cohorts 6-8

If a subject in Dose Cohorts 6-8 discontinues the study prematurely prior to Study Day 105, he or she should return to the study site and complete the following evaluations. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

Dose Cohorts 6-8 only

1) Perform physical examination
2) Perform ECG
3) Perform pulmonary function tests
4) Monitor vital signs
5) Monitor AEs and SAEs
6) Record concomitant medications
7) Collection of blood, urine, and cultures
   - Urine βHCG
   - Serum chemistry
   - Hematology
   - Urinalysis
   - Viral cultures
   - ESR, CRP, total serum complement
   - Autoantibody levels
   - MEDI-546 serum concentration
   - Receptor occupancy analysis
   - Type I IFN-inducible genes, exploratory analyses, and storage
   - Anti-MEDI-546 antibodies
   - Exploratory correlative studies and storage (serum)

8) Assess HAQ-DI with scleroderma NRS (preferably performed prior to mRTSS and European DAI)

9) Assess mRTSS

10) Assess European DAI

Unscheduled Visit

Evaluations may be performed during unscheduled visits as deemed warranted by the investigator. Subjects who have anti-MEDI-546 antibodies present at the end of study may be contacted to return for further safety evaluations.

3.6 Subject Evaluation Methods

3.6.1 Medical History

A complete medical history by body system will be completed during screening. History of allergies and anaphylaxis, viral reactivation events, previous manifestations of scleroderma, and previous treatment of scleroderma with potentially disease-modifying therapy will be included. On Study Day 0, the medical history will be reviewed and any changes from screening will be documented.

3.6.2 Physical Examination

Physical examinations will be performed at intervals designated in Table 3.5-1 and Table 3.5-2 and will include the following assessments: head, eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal, musculoskeletal; neurological; dermatological; lymphatic; endocrine system; body weight; and body height (screening only).

Medically significant changes from the screening physical examination will be considered AEs or SAEs and recorded as such on the source document.

3.6.3 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be done at screening and at the end of study (Study Day 84 or 105) or at study discontinuation according to investigative site procedures. The principal investigator or qualified designee will review and indicate if the ECG is normal or abnormal. Any medically significant changes from the screening ECG will be recorded as an AE or SAE.

3.6.4 Chest X-ray

A chest X-ray (anterior/posterior and lateral) will be completed during the screening period. The chest x-ray may be substituted with documentation of a previous chest x-ray performed within the previous 6 months. A previous computerized tomography evaluation of the lungs may be substituted for the chest x-ray if performed within the last 6 months.

3.6.5 Pulmonary Function Tests

Pulmonary function tests will be performed at a qualified site according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller, 2005) on study days indicated in Table 3.5-1 and Table 3.5-2. Both the absolute measurement for FVC and DL_{CO} and the percentage of predicted normal values (Hankinson, 1999; Hankinson, 2003) will be recorded; the predicted value will be interpolated from an extension of the curve when the subject's values are out of range (eg, too tall or too short).

3.6.6 Tuberculosis Skin Test

A Purified Protein Derivative (PPD) test must be completed during screening, except subjects who report a previously positive reaction will not be tested. Subjects will have the skin of their forearm cleaned and 0.5 mL of 5 TU PPD will be injected intradermally using a tuberculin syringe and 27-gauge needle. PPD tests will be reviewed 48-72 hours after administration by a trained person. A positive result will be based on ≥ 10 mm of induration or the presence of blisters for subjects not on systemic immunosuppressive medication and ≥ 5 mm for subjects on systemic immunosuppressive medication as assessed by the investigator or designee. Subjects with a newly positive PPD skin test or history of latent TB without a history of appropriate treatment will be excluded from the study unless appropriate prophylaxis is provided.

3.6.7 Vital Signs

Vital signs, including temperature, blood pressure, pulse rate, and respiratory rate, will be recorded at every visit as described in Table 3.5-1 and Table 3.5-2. On days when MEDI-546 is administered, vital signs will be obtained within 60 minutes before MEDI-546 administration, about every 15 minutes during the infusion, immediately after the end of the infusion, and then about every 30 minutes for 2 hours after dosing or until stable, whichever is later. Blood pressure and pulse will be taken prior to discharge from the clinic on days when MEDI-546 is administered.

3.6.8 Concomitant Medications

All concomitant medications given to the subject from signing of the informed consent through Study Day 84 (Cohorts 1-5 and 9) or from signing of the informed consent through Study Day 105 (Cohorts 6-8) will be recorded on the source document. The medication, dose, unit, frequency, route, start date, stop date, and indication will be captured. If the subject is continuing on a medication at study termination, then the ongoing box shall be checked instead of a stop date.

3.6.9 Laboratory Evaluations

3.6.9.1 Routine Laboratory Tests

Routine laboratory tests during screening and during the study will be performed in a licensed central clinical laboratory. Medically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours). Routine laboratory assessments include the following:

1) Hematology includes CBC with differential and platelets and hemoglobin
2) Serum chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, ALT, AST, bilirubin, alkaline phosphatase, creatinine phosphokinase, and glucose (non-fasting)
3) Urinalysis to include dipstick tests

3.6.9.2 Pregnancy Tests

Urine pregnancy tests during the study will be performed in the clinic using a licensed test. The following tests will be used to monitor pregnancy in women of child-bearing potential:

1) Serum βHCG during screening only, for women of childbearing potential, unless surgically sterile or at least 2 years postmenopausal.
2) Urine pregnancy tests will be performed using a licensed test according to the study schedule for women of childbearing potential, unless surgically sterile or at least 2 years postmenopausal.

3.6.9.3 Other Laboratory Tests

Additional laboratory tests are listed below. A laboratory manual will be provided specifying procedures for collection, processing, storage, and shipping of samples.

1) Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody and HIV-1 and HIV-2 antibody (screening only)
2) ESR
3) CRP
4) Serum complement C3, C4
5) Autoantibody levels including ANA, anti-topoisomerase I (anti-Scl70), and anti-centromere antibodies and potential assessment of anti-fibroblast and anti-endothelial cell antibodies

3.6.10 Viral Cultures

Viral infections will be monitored through viral cultures as indicated in the study schedule. The investigator or qualified designee will collect oropharyngeal swabs for herpes simplex virus (HSV)-1 and HSV-2 testing. Vaginal swabs will be self collected for HSV-1, HSV-2, and human papilloma virus (HPV) testing. In addition, peripheral blood samples will be collected and tested for Epstein Barr virus (EBV) and CMV using polymerase chain reaction tests.

3.6.11 Safety Biomarkers

Serum will be collected for baseline assessment of safety biomarkers on Study Day 0 as described in Table 3.5-1 and Table 3.5-2. In addition, if a Grade 1 or higher infusion reaction occurs during or after investigational product administration, serum for assessment of safety biomarkers will be collected as soon as possible after the event, at 60 minutes after the event, and at discharge. Safety biomarkers include serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies.

3.6.12 Disease Activity and Patient Reported Outcomes

3.6.12.1 Health Assessment Questionnaire-Disability Index with Scleroderma Numeric Rating Scales

The Health Assessment Questionnaire-Disability Index (HAQ-DI) with scleroderma NRS (Appendix 2) asks subjects to assess over the past week with six numeric rating scales their difficulty in accomplishing activities of daily living and the impact of symptoms specific to scleroderma. The 20 items of the HAQ-DI assess 8 domains (dressing, arising, eating, hygiene, walking, reaching, grip, and errands and chores), and the use of aids/devices or

assistance from another person to complete these activities. The activities are rated from 0 (without any difficulty) to 3 (unable to do), where the highest score for each domain is the score for that domain. The final score is the mean of the 8 domains, where higher scores indicated greater activity limitations. The six NRS assess the subject's perception of interference with daily activities due to pain, Raynaud's phenomenon, digital ulcers, gastrointestinal symptoms, shortness of breath, and overall disease severity. Scores range from 0 to 100, where higher scores indicate higher pain or degree of limitation (Steen, 1997).

It is preferred that the HAQ-DI with scleroderma NRS assessment is performed prior to the mRTSS and the European DAI assessments.

3.6.12.2 Modified Rodnan Total Skin Score

The modified Rodnan total skin score (mRTSS) is a clinician-rated assessment of skin thickness at 17 body sites (fingers, hands, forearms, arms, face, chest, abdomen, thighs, legs, and feet). Scores range from 0-3 where 0 = normal skin, 1 = mild thickness, 2 = moderate thickness, and 3 = severe thickness. The final score is the sum of all 17 sites and ranges from 0 (no thickening in any area) to 51 (severe thickening in all 17 areas). As possible, the same investigator should conduct the mRTSS throughout the study.

3.6.12.3 European Disease Activity Index

The European DAI consists of 10 measures of disease activity (mRTSS, presence of scleroderma, change in skin, digital necrosis presence, change in vascular manifestations, presence of arthritis, carbon dioxide diffusing capacity, change in heart and lung, ESR, and serum complement). Three patient reported outcomes have been included as part of the European DAI to determine worsening as compared to the previous month (Appendix 4). The value for each item ranges from 0.5 to 2.0 and the final score is summed to 0 to 10, where higher scores indicate greater disease activity (Valentini, 2001; Valentini, 2003). As possible, the same investigator should conduct the European DAI throughout the study.

3.6.13 Immunogenicity Evaluation

Anti-MEDI-546 antibodies will be evaluated in serum on an ongoing, cumulative basis beginning after the first three dose cohorts have completed Study Day 28, then approximately every 2 months thereafter. A drug-tolerant assay will be used. The study schedules in Table 3.5-1 and Table 3.5-2 outline when these samples will be collected.

Instructions for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to the sites.

3.6.14 Pharmacokinetic and Pharmacodynamic Evaluations

The following PK and PD assessments will be made during the study:

- Serum will be collected at every study visit for the determination of MEDI-546 serum concentration. On Study Day 0 for both single- and multiple-dose administration and on Study Day 21 for multiple dose administration, PK sampling will occur pre-dose and at 0.5 hour post end of infusion. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to sites.
- Whole blood will be collected at visits specified in the study schedule (Table 3.5-1 and Table 3.5-2) to measure the level of receptor occupancy (flow cytometry measurement of the binding of labeled MEDI-546 in the presence of dosed levels of MEDI-546) and total IFNAR levels (using a separate anti-IFNAR1 antibody that binds to a distinct epitope from MEDI-546). On Study Day 0 for both single- and multiple-dose administration and on Study Day 21 for multiple dose administration, receptor occupancy sampling will occur pre-dose and at 0.5 hour post end of infusion. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to sites.
- Type I IFN-inducible genes also will be used to measure the PD of MEDI-546. Whole blood samples will be used to analyze the effects of MEDI-546 on levels of mRNA for type I IFN-inducible genes. This analysis is performed using Affymetrix whole genome expression array and taqMan-based assay on selected panel of genes. Whole blood will be collected at visits specified in the study schedule. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to sites.
- Skin biopsies will also be collected for type I IFN-inducible genes and exploratory studies. Baseline skin biopsy (one 6mm or two 3mm or two 4mm) should be obtained prior to MEDI-546 administration on Study Day 0 and can be obtained anytime between screening and MEDI-546 administration. Sites will be given specific instructions for sample collection, processing, storage, and shipment.

3.6.15 Correlative Studies

3.6.15.1 Serum for Exploratory Correlative Studies

Serum will be collected for exploratory correlative studies and storage at visits specified in Table 3.5-1 and Table 3.5-2. These studies may include autoantibody arrays and analyses of inflammatory proteins, such as cytokines and chemokines.

3.6.15.2 DNA Sample

To investigate characteristics associated with subjects' clinical response and safety such as genetic polymorphisms in type I IFN related genes, one blood sample (8.5 mL) will be collected on Study Day 0 and frozen at -80°C for DNA sample preparation. The sample will be frozen and stored until use in exploratory analyses. The specific tests include analyses for DNA single nucleotide polymorphisms (SNPs) and copy number variants (CNV) using the Affymetrix 6.0 SNP array to further evaluate both risk alelles and major DNA amplifications/deletions cis to specific genes involved inthe signaling pathway relevant to type 1 IFNs. Such variation will be evaluated for its role in association to patient response status and as a driver of gene expression patterns found to correlate with this status.

The collection of blood for DNA analysis is optional. The completion of a separate informed consent form (Informed Consent Form for Collection of Blood Samples for DNA Analysis) is requested but not required for participation in this study. Subjects who do not wish to have the DNA test done will still be eligible for the study. Subjects who elect to have the DNA test done may, at any time before the end of the study, request that the blood collected for DNA analysis be destroyed. Subjects who elect not to have the DNA test done will still be eligible for the study.

DNA specimens will be labeled with the study number and a unique sample accession number only. No subject information will be recorded on the samples at any time. Samples will be linked to a specific subject number via the sample requisition document. The sample requisition document includes the subject's SID number and the unique sample accession number. Documents linking the subject SID number to a specific individual will only be maintained by the investigational site. In the event that a subject requests to withdraw from participating in the MI-CP180 DNA sub-study, the investigator will notify MedImmune study personnel of the subject's wish not to participate in the DNA sub study and will also give MedImmune the sample accession number requesting this subject's DNA samples be

destroyed. The MedImmune Sample Management group at Mountain View, CA, USA will document destruction of the sample. All results of DNA testing are kept confidential.

Future Use of Specimens

In some cases MedImmune will keep leftover blood from this protocol for future unidentified research, providing the subject has consented for future use of their DNA sample. Upon closure of the MI-CP180 study all DNA samples without a consent for future use will be destroyed and documented by the MedImmune Sample Management group.

DNA samples that have an informed consent for future use on file are kept by the MedImmune Sample Management group in Mountain View, CA, USA. These DNA samples will initially retain the original accession number used in the MI-CP180 study. If a sample is requested for future use by a MedImmune researcher the sample is then given a new sample ID number prior to delivery of the sample to the MedImmune researcher. Once the new ID number is applied it will not be possible to link the sample to the original demographics. All DNA samples may be stored for up to 15 years and will be maintained at MedImmune (Mountain View, CA, USA) who will be responsible for destroying any blood samples that are left over after 15 years.

3.7 Completion of Study, Discontinuation of Study, and Loss to Follow-up

Subjects enrolled in Dose Cohorts 1-5 and 9 will be considered to have completed the study if they were followed through Study Day 84. Subjects enrolled in Dose Cohorts 6-8 will be considered to have completed the study if they were followed through Study Day 105. Multiple ascending dose cohorts (Cohorts 6, 7, 8) and single ascending dose cohorts (Cohort 9) will enroll simultaneously; End of Study is defined as the last subject last visit for either cohort 8 (Day 105/Discontinuation) or Cohort 9 (Day 85/Discontinuation) whichever comes later. If a subject discontinues prior to the end of study it should be specified on the source document when the subject discontinued and the reason for discontinuing the study early. If a subject discontinues his or her participation in the study prior to Study Day 84 for Dose Cohorts 1-5 and 9 and Study Day 105 for Dose Cohorts 6-8, the subject will return to the study site and complete the Study Discontinuation Visit evaluations. If a particular assessment has been performed within 2 weeks prior to the discontinuation visit, it need not be repeated. Repeat skin biopsies should be obtained if not already done.

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 84 (Dose Cohorts 1-5 and 9) or Study Day 105 (Dose Cohorts 6-8, . Investigators or qualified designees 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 ICH Guideline for Good Clinical Practice (CPMP/ICH/135/95), an adverse event (AE) is:

> Any untoward medical occurrence in a subject 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 dosage higher than that prescribed by a healthcare professional for clinical reasons, or a dosage 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 nonclinical reasons) of an investigational or marketed product;
- Adverse changes from baseline that are listed on the toxicity table in Attachment 1 for the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE V4.0); and
- An event related to a medical procedure or associated with the discontinuation of the previous use of an investigational or marketed product required by protocol (protocol-related AE).

4.1.2 Study Reporting Period for Adverse Events

The reporting period for AEs is the period immediately following the time the written informed consent is obtained through Day 84 (single-dose cohorts) or Day 105 (multiple-dose cohorts). Any AE that starts within the reporting period will be followed to resolution, even if the date extends beyond the reporting period, up to the end of the clinical study (Day 84, single-dose cohorts; Day 105, multiple-dose cohorts). New (nonserious) AEs that start after the reporting period will not be collected.

4.1.3 Recording of Adverse Events

All AEs will be recorded using the collection instrument provided. Adverse events will be reported using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies and whether the event meets criteria as a SAE and therefore requires immediate notification of the sponsor. See Section 4.2.1 for the definition of SAEs, and Section 4.3 and Section 4.4 for guidelines for assessment of severity and relationship, respectively. 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” it will be reported on the SAE REPORT FORM.

4.2 Serious Adverse Events

4.2.1 Definition of Serious Adverse Events

A SAE is any AE that:

- Results in death.
- Is immediately 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 inpatient 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 an 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.

  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 in offspring of the subject.

  A pregnancy should be reported to MedImmune Product Safety as an immediately reportable event (IRE. A pregnancy should be followed for outcome and the health status of the mother and the child. If the child is born with any congenital anomaly of birth defect, this should be reported to Product Safety as a SAE.

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

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

  A serious event related to a medical procedure required by protocol prior to dosing of the study medication should also be reported to Product Safety as an SAE (protocol-related SAE).

4.2.2 Study Reporting Period for Serious Adverse Events

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through the end of study (Study Day 84 for subjects receiving

single IV doses and Study Day 105 for subjects receiving multiple IV doses). After the initial SAE report the investigator is required to follow each subject proactively and provide further information on the subject's condition to MedImmune Product Safety.

All SAEs should be followed up to resolution by the investigator, even if this extends beyond the study reporting period. Resolution of an SAE 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 completion of the study, if an investigator or qualified designee becomes aware of an SAE that is suspected by the investigator or qualified designee to be related to investigational 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 investigational product, the investigator or qualified designee must enter the event information into the electronic data capture (EDC) system. As the investigator or qualified designee selects the appropriate serious criteria, an SAE notification will be automatically forwarded to the MedImmune Product Safety Department indicating that an SAE has occurred. The investigator or qualified designee will complete the SAE Report Form and fax the completed form to MedImmune Product Safety.

MedImmune contact information:

Product Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878
Fax: [redacted]

MedImmune, as sponsor of the study being conducted under an Investigational New Drug Application (IND), is responsible for reporting certain SAEs 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 SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators or designees submit additional information requested by MedImmune as soon as it becomes available.

Investigators should provide all available information at the time of form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune of an SAE. When additional information becomes available, submit a follow-up SAE report form with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Product Safety within 24 hours of learning of the new information.

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 SAEs to the IRB or IEC. The IRB or IEC must be informed in a timely manner by the principal investigator or a qualified designee of serious AEs 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 SAE REPORT FORM using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for severity, relationship to the investigational product, and possible etiologies. See Section 4.2.1 for the definition of SAEs, and Section 4.3 and Section 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 SAE REPORT FORM.

4.3 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by a health care professional who is qualified to review AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment and the severity categories of *Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5.* Severity of toxicity will be graded according to the NCI CTCAE V4.0, as described in detail in Attachment 1.

Grade refers to the severity of the AE. The NCI CTCAE V4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the general guideline:

Grade 1: Mild AE
Grade 2: Moderate AE
Grade 3: Severe AE
Grade 4: Life-threatening or disabling AE
Grade 5: Death related to AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.2.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

4.4 Assessment of Relationship

An AE is considered "product-related" for the purposes of regulatory reporting if the investigator, the medical monitor, or the product safety physician assesses the AE as possibly, probably, or definitely related to investigational product. 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 AE is treated as product-related for the purposes of reporting to regulatory authorities. An AE 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 AE is not product-related.

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. A number of factors should be considered in making this assessment including: 1) the temporal relationship of the event to the administration of investigational 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 AE to investigational product administration.

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

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

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

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

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

For AEs that occur prior to the administration of investigational product, an assessment of protocol relatedness must be made. Protocol-related AEs may occur as a result of procedures required during the screening process (eg, blood collection, washout of an existing medication) prior to the initial administration of investigational product. For AEs that occur before administration of investigational product, only those that are assessed by the investigator as protocol-related should be reported to the sponsor. The following guidelines should be used by investigators to assess the relationship of an AE to a protocol-required procedure:

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

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

4.5 Other Events Requiring Immediate Reporting

The following events must be reported ***within 24 hours*** by fax to MedImmune Product Safety using the fax notification form:

1) Any withdrawal of consent during the study
2) Pregnancy or intent to become pregnant*
3) All severe (Grade 3 or higher, according to the NCI CTCAE, V4.0) AEs that occur during or after administration of the investigational product through Study Day 84 (Dose Cohorts 1-5 and 9) or Study Day 105 (Dose Cohorts 6-8)
4) AEs that are considered to be allergic reactions related to investigational product
5) AEs that are considered (by the investigator) to be Grade 1 or higher infusion reactions related to the infusion of the investigational product itself. These usually occur within the first 24 hours after infusion and are characterized by a complex of symptoms that may include flu-like illness, fever, chills/rigors, nausea, urticaria, headache, bronchospasm, angioedema, hypotension, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock.
6) Symptoms suggestive of vasculitis
7) Any other event that, in the opinion of the investigator, contraindicates further dosing of the study subject
8) Any subject discontinuation from the study

* Subjects who become pregnant or intend to become pregnant during the study period must not receive additional doses of investigational product but will be followed for the duration of the study period and beyond as required to collect outcomes for the pregnancy including: pregnancy outcome and any spontaneous abortions, premature terminations, or stillbirths. The health status of the mother and child including date of delivery and the child's gender and weight should be reported to MedImmune Product Safety after delivery.

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 SAEs and timely review of other AEs reported during the study. The MedImmune Product Safety Specialist has responsibility for the day-to-day safety monitoring of the study, including the receipt, review, investigation, and follow-up of SAEs reported by the clinical study sites.

The SMC will independently review cumulative safety surveillance data, as well as the decisions of the medical monitor regarding dose escalation, on a regular basis throughout the study and make recommendations regarding further conduct of the study. The SMC will also review safety data at other time points in response to AEs felt to be medically significant by the medical monitor. The SMC is composed of at least 2 MedImmune physicians who are not directly involved in the day to day operations of the study, and at least 2 physicians who are not employees of MedImmune.

4.7 Interruption or Discontinuation of Study Dosing in Individual Subjects

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1) Withdrawal of consent
2) Pregnancy
3) Any life-threatening (Grade 4 according to the NCI CTCAE V4.0; Appendix 3) clinical event related to MEDI-546
4) Anaphylactic reaction (immediate life-threatening IgE-mediated allergic reaction with bronchoconstriction, angioedema, and/or hypotension) to MEDI-546
5) Disseminated herpes infection, herpes encephalitis, or ophthalmic herpes infection or serious active infection with CMV or EBV
6) Symptoms suggestive of vasculitis
7) Any event that, in the opinion of the investigator or medical monitor, contraindicates further dosing of an individual subject

Subjects who are permanently discontinued from MEDI-546 will be followed for the full study period (through Study Day 84 for subjects receiving single IV doses and Study Day 105 for subjects receiving multiple IV doses), including the collection of any protocol-specified blood or urine samples, unless consent is withdrawn.

4.8 Interruption or Discontinuation of Study Dosing and Entry

If any of the following occur, no further administration of investigational product will take place and no further subjects will be entered into the study:

1) Death of any subject in which the cause of death is assessed as related to MEDI-546
2) Any life-threatening clinical event related to MEDI-546
3) Anaphylactic reaction (immediate life-threatening IgE-mediated allergic reaction with bronchoconstriction, angioedema, and/or hypotension) to MEDI-546 in any subject
4) Disseminated herpes infection, herpes encephalitis, or ophthalmic herpes infection or serious active infection with CMV or EBV in any subject
5) The occurrence of a possible safety signal subsequent to expansion of 2 dose cohorts to a maximum of 8 subjects for safety information
6) Any event that, in the opinion of the medical monitor, contraindicates further dosing of study subjects

If one of the above-listed 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 dosing and study entry should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the SMC are required for resumption of the study in the event the study is interrupted because of one of the above-listed events.

4.9 Dose Escalation

Dose Cohort 1 (0.1 mg/kg MEDI-546 as a single IV dose to a single subject) will be started first. Decisions regarding dose escalation will be made by the medical monitor based on the review of all cumulative safety information from the stipulated number of subjects in the preceding lower dose cohort through Study Day 7 for single-dose cohorts (Dose Cohorts 1-5) or Study Day 28 for multiple-dose cohorts (Dose Cohorts 6 and 7) and all cumulative safety data available in all other cohorts.

If there is a possible safety signal from the analysis of safety information for a particular dose cohort (Dose Cohorts 2-9 only) that does not warrant discontinuation but does warrant further investigation prior to dose escalation, then the sponsor may add 4 subjects to the dose cohort for a maximum of 8 subjects in the dose cohort. A maximum of 2 dose cohorts may be expanded to a total of 8 subjects each. If a possible safety signal occurs subsequent to expansion of 2 dose cohorts to a maximum of 8 subjects each, then the study will be

terminated. The SMC, which includes physicians external to MedImmune, will independently review cumulative safety surveillance data and the medical monitor's decisions on dose escalation throughout the study and make recommendations regarding the study progression. The SMC can stop study entry and dosing as it deems necessary.

4.10 Monitoring of Dose Administration As with any foreign protein, infusion reactions and IgE-mediated allergic reactions to dose administration are possible. Therefore, appropriate drugs, such as epinephrine and diphenhydramine, and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat infusion reactions and allergic reactions such as anaphylaxis.

However, subjects should not be premedicated routinely, because the primary objective of this study is to evaluate the safety and tolerability of the investigational product. If infusion reactions or allergic reactions occur during or after investigational product administration, they should be treated appropriately. If a subject experiences an infusion reaction, premedication according to the physician's judgment should be considered prior to subsequent infusions.

5 Statistical Considerations

5.1 General Considerations

The analysis of study data is the responsibility of MedImmune or its designee. A comprehensive statistical analysis plan will be approved prior to the analysis of the study data.

All data will be provided in data listings sorted by dose cohort. Continuous variables will be summarized by descriptive statistics including N, mean, standard deviation, median, and range. Descriptive statistics for summarizing categorical variables include frequency and percentage. Missing data will be treated as missing and no data will be imputed.

5.2 Sample Size and Power Calculations

A minimum of 33 subjects are planned for this study, with dose cohorts of subjects receiving 6 single IV doses and 3 multiple IV doses of MEDI-546 as follows:

- Dose Cohort 1 (N=1): 0.1 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 2 (N=4): 0.3 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 3 (N=4): 1.0 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 4 (N=4): 3.0 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 5 (N=4): 10.0 mg/kg MEDI-546 as a single IV dose
- Dose Cohort 6 (N=4): 0.3 mg/kg MEDI-546 as a weekly IV dose × 4 doses
- Dose Cohort 7 (N=4): 1.0 mg/kg MEDI-546 as a weekly IV dose × 4 doses
- Dose Cohort 8 (N=4): 5.0 mg/kg MEDI-546 as a weekly IV dose × 4 doses
- Dose Cohort 9 (N=4): 20.0 mg/kg MEDI-546 as a single IV dose

If there is a possible safety signal from the analysis of safety information for a particular dose cohort (Dose Cohorts 2-9 only) that does not warrant discontinuation but does warrant further investigation (prior to dose escalation for Dose Cohorts 2-7), then the sponsor may add 4 subjects to the dose cohort for a maximum of 8 subjects in the dose cohort. A maximum of 2 dose cohorts may be expanded to a total of 8 subjects each. If a possible safety signal occurs subsequent to expansion of 2 dose cohorts to a maximum of 8 subjects each, then the study will be terminated. In addition, Dose Cohorts 2-9 may be expanded by up to 2 additional subjects each if eligible subjects are already in screening at the time 4 subjects have been entered into the dose cohort and there is no possible safety signal to warrant expansion of the dose cohort to a maximum of 8 subjects. Therefore, the maximum number of subjects allowed in the study is 53 (29 + 8 [4×2] + 12 [2×6]). No formal calculation was performed to determine sample size because safety is the primary outcome and this will be assessed with descriptive analyses.

Table 5.2-1 and Table 5.2-2 present the probability of observing at least one infrequently occurring event when assuming a range of potential observed event rates and exact binomial 95% confidence intervals to assess the precision of estimates of the event rate for each cohort (n=1 or n=4) and for some cohorts (n=8, 12, 16, 20, 24, 28, respectively) combined.

Table 5.2-1 Expected Number of Events and Probabilities of Observing at Least 1 or 2 Events Given the True Event Rates

N	True Event Rate (%)	Number of Events Expected	Probability of Observing at Least 1 Event (%)	Probability of Observing at Least 2 Events (%)
1	5.0	0	5.0	0.0
1	10.0	0	10.0	0.0
4	2.0	0	7.8	0.2
4	10.0	0	34.4	5.2
8	0.8	0	6.2	0.2
8	6.0	0	39.0	7.9
8	7.0	1	44.0	10.3
12	0.5	0	5.8	0.2
12	4.0	0	38.7	8.1
12	5.0	1	46.0	11.8
16	0.5	0	7.7	0.3
16	3.0	0	38.6	8.2
16	4.0	1	48.0	13.3
20	0.5	0	9.5	0.4
20	2.0	0	33.2	6.0
20	3.0	1	45.6	12.0
24	0.2	0	4.7	0.1
24	2.0	0	38.4	8.3
24	3.0	1	51.9	16.1
28	0.2	0	5.5	0.1
28	2.0	1	43.2	10.7

Table 5.2-2 Estimated Event Rates and 95% Exact Binomial Confidence Intervals Given the Number of Events Observed

N	Number of Events Observed	Estimated Event Rate (%)	95% Confidence Interval
1	0	0.0	(0.0%, 97.5%)
1	1	100.0	(2.5%, 100.0%)
4	1	25.0	(0.6%, 80.6%)
4	2	50.0	(6.8%, 93.2%)
8	1	12.5	(0.3%, 52.7%)
8	2	25.0	(3.2%, 65.1%)
12	1	8.3	(0.2%, 38.5%)
12	2	16.7	(2.1%, 48.4%)
16	1	6.3	(0.2%, 30.2%)
16	2	12.5	(1.6%, 38.3%)
20	1	5.0	(0.1%, 24.9%)
20	2	10.0	(1.2%, 31.7%)
24	1	4.2	(0.1%, 21.1%)
24	2	8.3	(1.0%, 27.0%)
28	1	3.6	(0.1%, 18.3%)
28	2	7.1	(0.9%, 23.5%)

5.3 Analysis Populations

All subjects who receive any investigational product will be included in all summaries. Missing data will be treated as missing. No data will be imputed.

5.4 Primary Endpoints

The safety and tolerability of MEDI-546 will be assessed primarily by summarizing treatment-emergent AEs and SAEs and by assessing changes in viral cultures, including oropharyngeal swabs for HSV-1 and HSV-2; vaginal swabs for HSV-1, HSV-2, and HPV; and peripheral blood test for EBV and CMV (using molecular assays). The occurrence of treatment-emergent AEs and SAEs will be summarized from the period immediately following the first administration of MEDI-546 through end of study (Study Day 84 for subjects receiving single IV doses and Study Day 105 for subjects receiving multiple IV doses). Treatment-emergent AEs and SAEs will be summarized by system organ class and

preferred terms, by severity, and by relationship to MEDI-546. Treatment-emergent AEs and SAEs will be summarized for each of the MEDI-546 dose cohorts, and for all MEDI-546 dose cohorts combined.

No formal statistical testing will be performed to compare treatment groups. Other variables used for the safety assessments include serum chemistry, CBC with differential and platelets, and urinalysis. These variables as well as their changes from baseline will be summarized descriptively.

5.5 Secondary Endpoints

The secondary endpoints of the study are to assess the PK, IM, and PD of single and multiple IV doses of MEDI-546 in adult subjects with scleroderma.

5.5.1 Pharmacokinetics

Serum MEDI-546 concentration data will be tabulated by dose cohort together with descriptive statistics. Individual and mean serum concentration-time profiles of MEDI-546 by dose cohort will be generated and included in the report. Noncompartmental PK data analysis will be performed using the software package WinNonlin®. For PK data analysis, time zero is defined as the end of infusion. The PK parameters to be obtained and reported include, but are not limited to:

- C_{max} - the maximum observed serum concentration of MEDI-546 following IV infusion
- T_{max} - the time of the observed C_{max}
- $AUC_{0-\infty}$ - the area under the serum concentration - time curve from time zero to infinity;
- AUC_{0-t} - the area under the serum concentration – time profile from time zero to the last measurable time point
- AUC_{0-7d} - the area under the serum concentration – time profile from time zero to 7 days post dose (for Dose Cohorts 6-8)
- t½ - the terminal elimination half-life;
- CL - systemic clearance;

Descriptive statistics of noncompartmental PK parameters by dose cohort will be provided in the report. If the data allow, compartmental modeling may be performed to further

characterize the PK and the PK-PD relationship of MEDI-546 in scleroderma subjects. However, due to the exploratory nature of the study, the actual modeling work may not be reported.

5.5.2 Immunogenicity

The presence of anti-MEDI-546 antibodies in serum will be assessed. Immunogenicity test results will be available for safety review at approximately 2-month intervals, with assays to be run after the first three cohorts have completed Study Day 28 and about every 2 months thereafter. Immunogenicity results will be analyzed by summarizing the number and percentage of scleroderma subjects who develop detectable anti-MEDI-546 antibodies by treatment and dose cohort.

5.5.3 Pharmacodynamics

The level of receptor occupancy will be determined by flow cytometry as a measure of the binding of labeled MEDI-546 in the presence of dosed levels of MEDI-546. Total type I IFNAR levels will be assessed using a separate anti-IFNAR1 antibody that binds to a distinct epitope from MEDI-546.

The level of expression of type I IFN-inducible genes will be determined in whole blood and skin mRNA, using Affymetrix technology. Results will be listed by dose group with mean and individual results at different time points. Changes from baseline will be described and PD assessed. Relationships between receptor occupancy and inhibition of type I IFN gene signature will be explored.

5.6 Exploratory Endpoints

5.6.1 Effect of MEDI-546 on Disease Activity and Patient-reported Outcomes

Measures of disease activity will include pulmonary function tests (FVC and DL_{CO} as absolute value and percent predicted), mRTSS, and the European DAI. Patient-reported outcomes will include the HAQ-DI with scleroderma NRS scores (Steen, 1997; Appendix 2), and DAI with a numeric rating scale to assess changes in skin, changes in vascular manifestations, and changes in heart/lung. The mRTSS, European DAI, and the HAQ-DI with scleroderma NRS will be computed. These measures of disease activity, as well as their

respective changes from baseline, will be summarized descriptively at each visit by dose cohort and all cohorts combined.

5.6.2 Effect of MEDI-546 on Gene and/or Protein Expression

The effect of MEDI-546 on the expression of other genes and/or proteins in whole blood, serum, skin and on immunohistopathology of the skin will be assessed using descriptive statistics. These will include expression of collagen I and III genes and proteins in skin and the N-terminal propeptide of procollagens I and III in serum.

5.6.3 Relationship of Type I IFN-related DNA Polymorphisms and Safety

Polymorphisms in type I IFN-related genes associated with safety signals to MEDI-546 may be assessed using descriptive statistics.

5.7 Interim Analyses

The following interim analyses may be conducted:

- Type I IFN gene expression will be assessed cumulatively in blood and skin after each Dose Cohort reaches Study Day 28.
- After all subjects in Dose Cohort 4 complete Study Day 14, an interim analysis of cumulative data on PK and type I IFN gene signatures may was completed to determine whether dose adjustments need to be made in the multiple dose cohorts (Dose Cohorts 6-8). Target doses for multiple IV dosing are to include one dose that provides incomplete inhibition of type I IFN gene signature defined as ≥ 70% inhibition in < 3 patients per cohort, one dose that provides nearly complete inhibition of type I IFN gene signature defined as ≥ 70% inhibition in at least 3 subjects per cohort, and one dose that is approximately ½ log higher than the dose that provides nearly complete inhibition of type I IFN gene signature in the skin.

6 Data Collection and Monitoring

The study will be monitored by MedImmune or its designee on a regular basis throughout the study period. During monitoring visits, the investigator or designee will provide direct access to all source documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, informed consent forms, treatment notes, laboratory reports, pharmacy records, radiographs, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB/IEC review, or regulatory inspection.

Data recorded on source documents will be transcribed onto a validated data collection instrument (a paper case report form or electronic data screen) provided by MedImmune or designee. The investigator must ensure the accuracy and completeness of the data reported, and its consistency with the source documentation.

Data will be collected on all subjects who provide written informed consent. For subjects who fail the screening process, the following data will be collected:

1) Subject demographics
2) The reason the subject was not entered (ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn)

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 monitored/audited for the purposes of the study.

Study documents (including subject records, copies of collected data, study notebook, and pharmacy records) must be kept secured in accordance with MedImmune policies and applicable regulatory requirements for a period of 2 years following marketing of MEDI-546 or for 2 years after sites 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, the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and Investigational New Drug Application (21 CFR 312).

The protocol will be reviewed and approved by the IRB or IEC of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to the sponsor and to the IRB/IEC, and the investigator or designee 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/legal representative that participation is voluntary and that they can withdraw/can withdraw the subject at any time. Written informed consent will be obtained from each subject/legal representative prior to the screening procedures required for entry into the study. A copy of the signed consent form will be given to every subject/legal representative 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 SID will be stored separately in another locked file cabinet. Study records may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject/legal representative, except as necessary for monitoring by regulatory authorities or the sponsor of the clinical study. 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 or Independent Ethics Committee

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

Any documents that the IRB/IEC may need to fulfill its responsibilities, such as protocol amendments, and information concerning subject recruitment, payment or compensation procedures, or information from the sponsor will be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol, the informed consent form, and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product 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 form 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.

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 informed consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Subjects or their legal representatives must be informed that the study involves research. They 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 of the subject, if the subject should become pregnant) that are currently unforeseeable.

They must also be informed of the study procedures to be followed and alternative treatment available to them. Subjects or their legal representatives 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 subjects or their legal representatives must be informed that participation is voluntary and that they are free to withdraw or withdraw their child 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 subject records must be defined, and subjects or their legal representatives must be informed that applicable data protection legislation will be complied with. They 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 study 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/legal representative. 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 subject, 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 the sponsor will be returned to the sponsor upon study completion. The investigator will notify the IRB/IEC when the study has been completed.

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 the sponsor. All changes to the protocol must be submitted to the applicable regulatory agencies and IRBs/IECs, and must be approved by the IRB/IEC prior to their implementation. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

The original protocol ([redacted]) was amended to Protocol Amendment 1 on [redacted]. The major changes include updating the adverse event reporting period; increasing the investigational product infusion time from 30 minutes to 60 minutes; revising exclusion criteria #18 to exclude subjects with prior malignancy despite apparent curative treatment; deleting the Type 1 IFN-inducible genes sample from the screening visit; revising the European DAI; clarifying the biopsy sample amount to 6 mm or two 3 mm or 4 mm. Changes to the protocol are described in Appendix 5 and are incorporated in the body of Protocol Amendment 1. No subjects were entered into the study under the original protocol.

Protocol Amendment 1 [redacted]) was amended to Protocol Amendment 2 on ([redacted]). The major changes include identifying a new medical monitor ([redacted]); revising exclusion criteria # 22 to allow subjects with documented myositis to enroll into the study in spite of elevated AST/ALT results; changing the timing of the interim analysis was from Cohort 3 to Cohort 4 to increase the number of subjects included in the analysis; adding CPK and changing hemolytic complement to serum complement; updating Section 3.6.15.2, DNA Sample, to more clearly describe DNA sample acquisition and processes and added language describing future use of specimens handling; updating Health Assessment Questionnaire-Disability Index with Scleroderma Numeric Rating Scale final question and correcting the number of boxes on the visual analogue scale; and updating

European Disease Activity Index to the US version (commas replaced with decimals). Changes to the protocol are described in Appendix 5 and are incorporated in the body of Protocol Amendment 2. Six subjects have entered into the study under Protocol Amendment 1 to date.

Protocol Amendment 2 ([redacted]) was amended to Protocol Amendment 3 on [redacted]. The major changes include summarizing histopathology findings from a 9-month non-human primate (cynomolgus monkey) chronic toxicology study of MEDI-546, adding exclusion criterion #25 to exclude subjects with a history of vasculitis, reporting symptoms suggestive of vasculitis as an immediately reportable event and discontinuing subjects who develop vasculitis from further dosing.

Protocol Amendment 3 [redacted]) was amended to Protocol Amendment 4 on [redacted]. The major changes to the protocol include adding one single ascending dose (SAD) cohort (cohort 9, 20 mg/kg). Dose Cohort 9 (N=4) has been added to evaluate safety and tolerability at higher doses and to enable greater flexibility in dosing regimens during later phases of clinical development. Following the [redacted] interim analysis of PK and Type 1 IFN gene signature, dosing in the multiple ascending dose (MAD) cohorts (cohorts 6 - 8) was changed to 0.1, 0.3, 5.0 mg/kg respectively from the original dosing estimates of 0.1, 0.3, 3.0 mg/kg. This change will allows testing of a higher dose and greater flexibility in dosing regimens during later phases of clinical development . The top line interim analysis results have been outlined in Section 1.4. For decisions regarding dose escalation the medical monitor will assess cumulative safety information for the MAD cohorts (cohorts 6-8) at Day 28 (changed from Day 14) to insure dose escalation decisions are based on subjects receiving the complete dosing schedule (x 4 doses over 3 weeks). Intravenous infusion time has been increased from 60 minutes to 120 minutes for doses > 10mg/kg to guard against potential infusion reactions at higher doses. The medical monitor has been changed from [redacted] to [redacted].

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Appendix 1 1980 Criteria for the Classification of Systemic Sclerosis

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum. 1980; 23:581-90

Glossary of clinical terms used in description or classification of systemic sclerosis

1) Typical sclerodermatous skin changes: tightness, thickening, and non-pitting induration, excluding the localized forms of scleroderma (morphea or linear scleroderma)
   a) Sclerodactyly: above-indicated changes limited to (fingers and toes)
   b) Proximal scleroderma: above-indicated changes proximal to the metacarpophalangeal or metatarsophalangeal joints, affecting other parts of the extremities, face, neck, or trunk (thorax or abdomen); usually bilateral, symmetrical and almost always including sclerodactyly
2) Other skin manifestations attributable to systemic sclerosis or comparison disorders
   a) Digital pitting scars or loss of substance from the finger pad: depressed areas at tips of digits or loss of digital pad tissue as a result of digital ischemia rather than trauma or exogenous causes
   b) Bilateral finger or hand edema: firm but pitting edema, especially involving fingers (includes puffy sausage-like swelling of fingers) or the dorsal aspect of the hands
   c) Abnormal skin pigmentation: hyperpigmentation often containing areas of punctate or patchy hypopigmentation or depigmentation ("pepper and salt")
   d) Raynaud's phenomenon: at least two-phase color change in fingers and often toes consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion, as determined by patient's history or physician's observation
3) Visceral manifestations
   a) Bibasilar pulmonary fibrosis: bilateral reticular pattern of linear or lineonodular densities which are most pronounced in basilar portions of the lungs on standard chest roentgenogram; may assume appearance of diffuse mottling or "honeycomb lung," and should not be attributable to primary lung disease
   b) Lower (distal) esophageal dysphagia: substernal discomfort on swallowing or sensation of food holdup in the retrosternal location
   c) Lower (distal) esophageal dysmotility: hypoperistalsis or aperistalsis, as demonstrated by either cine esophagram or fluoroscopy or by manometric study, often accompanied by evidence of decrease in lower esophageal sphincter tone with reflux of gastric contents into the esophagus

d) Colonic sacculations: wide-mouthed diverticula of colon located along the antimesenteric border; found on barium enema examination; these sacculations may also occur in ileum and jejunum

* The text explains the derivation of this "combination" variable which was not on the SCCS form.

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Appendix 2 Health Assessment Questionnaire-Disability Index with Scleroderma Numeric Rating Scales

SCLERODERMA HEALTH ASSESSMENT QUESTIONNAIRE

In this section we are interested in learning how your illness affects your ability to function in daily life.

Please check the response that best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty	**With SOME difficulty**	**With MUCH difficulty**	**UNABLE to do**
	(0)	**(1)**	**(2)**	**(3)**
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
-Shampoo your hair?	_____	_____	_____	_____
ARISING				
Are you able to:				
-Stand up from a straight chair?	_____	_____	_____	_____
-Get in and out of bed?	_____	_____	_____	_____
EATING				
Are you able to:				
-Cut your meat?	_____	_____	_____	_____
-Lift a full cup or glass to your mouth?	_____	_____	_____	_____
-Open a new milk carton?	_____	_____	_____	_____
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	_____	_____	_____	_____
-Climb up five stairs?	_____	_____	_____	_____

Please check any AIDS or DEVICES that you usually use for any of these activities:

_____ Cane

_____ Devices for dressing (button hook, zipper pull, long-handled shoe horn, etc.)

_____ Walker

_____ Crutches

_____ Wheelchair

_____ Built up or special utensils

_____ Special or built-up chair

_____ Other (specify:_____)

Please check any categories for which you usually need ASSISTANCE FROM ANOTHER PERSON:

_____ Dressing and grooming

_____ Arising

_____ Eating

_____ Walking

Please check the one response that best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty	**With SOME difficulty**	**With MUCH difficulty**	**UNABLE to do**
	(0)	**(1)**	**(2)**	**(3)**
HYGIENE				
Are you able to:				
-Wash and dry your body?	_____	_____	_____	_____
-Take a tub bath?	_____	_____	_____	_____
-Get on and off the toilet?	_____	_____	_____	_____
REACH				
Are you able to:				
-Reach and get down a 5 pound object (such as a bag of sugar) from just over your head?	_____	_____	_____	_____
-Bend down and pick up clothing off the floor?	_____	_____	_____	_____
GRIP				
Are you able to:				
-Open car doors?	_____	_____	_____	_____
-Open jars that have been previously opened?	_____	_____	_____	_____
-Turn faucets on and off?	_____	_____	_____	_____
ACTIVITIES				
Are you able to:				
-Run errands and shop?	_____	_____	_____	_____
-Get in and out of a car?	_____	_____	_____	_____
-Do chores such as vacuuming or yard work?	_____	_____	_____	_____

Please check any **AIDS or DEVICES** that you usually use for any of these activities:

_____ Raised Toilet Seats _____ Bathtub Bar _____ Bathtub Seat

_____ Long-Handled Appliances for Reach _____ Jar Opener (for jars previously opened)

_____ Long-Handled Appliances in Bathroom _____ Other (Specify: _____ _____)

Please check any categories for which you usually need **HELP FROM ANOTHER PERSON:**

_____ Hygiene _____ Gripping and Opening Things

_____ Reach _____ Errands and Chores

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness **IN THE PAST WEEK?**

PLACE AN X IN THE BOX THAT BEST DESCRIBES THE SEVERITY OF THE PAIN.

0		100
NO PAIN	☐ ☐	**VERY SEVERE PAIN**

IN THE PAST WEEK, how much have your intestinal problems interfered with your daily activities?

PLACE AN X IN THE BOX THAT BEST DESCRIBES THE LIMITATION OF ACTIVITY.

0		100
INTESTINAL PROBLEMS DO NOT LIMIT ACTIVITIES	☐ ☐	**VERY SEVERE LIMITATION**

IN THE PAST WEEK, how much have your breathing problems interfered with your daily activities?

PLACE AN X IN THE BOX THAT BEST DESCRIBES THE LIMITATION OF ACTIVITY.

0		100
BREATHING PROBLEMS DO NOT LIMIT ACTIVITIES	☐ ☐	**VERY SEVERE LIMITATION**

IN THE PAST WEEK, how much has Raynaud's interfered with your daily activities?

PLACE AN X IN THE BOX THAT BEST DESCRIBES THE LIMITATION OF ACTIVITY.

0		100
RAYNAUD'S DOES NOT LIMIT ACTIVITIES	☐ ☐	**VERY SEVERE LIMITATION**

IN THE PAST WEEK, how much have your finger ulcers interfered with your daily activities?

PLACE AN X IN THE BOX THAT BEST DESCRIBES THE LIMITATION OF ACTIVITY.

	0	100	
FINGER ULCERS DO NOT LIMIT	☐ ☐		**VERY SEVERE LIMITATION**

IN THE PAST WEEK, how much have your overall disease (scleroderma) problems interfered with your activities?

PLACE AN X IN THE BOX THAT BEST DESCRIBES THE LIMITATION OF ACTIVITY.

	0	100	
DOES NOT LIMIT ACTIVITIES	☐ ☐		**VERY SEVERE LIMITATION**

Appendix 3 National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

https://cabig.nci.nih.gov/News_Folder/CTCAE_v4.0/

Appendix 4 European Scleroderma Study Group Activity Index

Criteria	Score
mRTSS > 14	**1**
Scleredema	**0.5**
Δ-Skin*	**2**
Digital necrosis	**0.5**
Δ-Vascular*	**0.5**
Arthritis	**0.5**
↓DLCO	**0.5**
Δ-Heart/Lung*	**2**
ESR > 30	**1.5**
Hypocomplementaemia	**1**
Total maximum disease activity index	**10**
The disease is considered to be active if the index results ≥ 3	

European Scleroderma Study Group activity index (continued)

* Any worsening in the relevant organ/system as evaluated by the patient with respect to the previous month; mRss= modified Rodnan skin score[8]; Scleredema: increase in soft tissue mass (particularly at fingers); Digital necrosis: active digital ulcers ranging from small infarcts of the digital tips to the digital gangrene; Arthritis: Symmetric swelling and tenderness of peripheral joints; ↓DLCO: DLCO less than 80% the predicted value as evaluated by single breath method[9] ; ESR: Westergreen method ; Hypocomplementaemia: low C3 or low C4 by whatever method.

For Subject Completion ONLY
Confidential
MEDI-546 CP180

Subject Initials __ __ __ **SID __ __ __ __ __ __ __**

Visit __ __ __ **Date: __ __ / __ __ __ /__ __**

We are interested in learning if the following symptoms have changed in the past month. Please place an X in the box that best describes your symptoms.

1) In the past month, how have your skin symptoms been such as skin itchiness or skin thickening?

0 **100**
None ☐ **Maximum Symptoms**

2) In the past month, how have your Raynaud or ulcers been?

0 **100**
None ☐ **Maximum Symptoms**

3) In the past month, how have your heart and lung symptoms been, such as coughing, chest pain or rapid or irregular heart beat?

0 **100**
None ☐ **Maximum Symptoms**

Appendix 5 Summary of Amendments to the Original Protocol

Protocol Amendment 1, [redacted]

All text revisions for this amendment are incorporated in the body of Protocol Amendments 1. Major changes to the protocol are described below.

1) Study Abstract: Updated for consistency with changes made to the body of the protocol.
2) Section 2.4 (Overview, Study Design): Number of study sites increased to 10 to 15 to increase enrollment into the study.
3) Sections 2.4 (Overview, Study Design), 3.4.2 (Treatment Regimens), 3.4.3 (Investigational Product Preparation), and 3.4.4 (Administration of Investigational Product): Investigational product infusion time increased from 30 to 60 minutes to decrease subject risk for potential infusion reactions.
4) Section 3.1.2 (Exclusion Criteria): Exclusion criterion #18 revised to decrease potential risk to subjects who have a history of malignancies.
5) Section 3.4.1 (Investigational Product Supplies and Accountability) and Section 3.4.3 (Investigational Product Preparation): The term Clinical Trial Material (CTM) Manual was changed to Investigational Product Manual, and CTM Manager was changed to investigational product manager.
6) Section 3.5 (Schedule of Subject Evaluations [Table 3.5-1 and 3.5-2] and Screening): Collection of sample for Whole Blood Type 1 IFN-inducible Genes and Exploratory Analysis & Storage at screening was deleted.
7) Section 3.5 (Schedule of Subject Evaluations, Table 3.5-1 and 3.5-2): Footnote added to clarify that samples for anti-MEDI-546 antibodies, whole blood for Type I IFN-inducible genes, skin biopsy for Type I IFN-inducible genes, serum for exploratory correlative studies, and optional DNA sample will be collected predose.
8) Section 3.6.9.1 (Routine Laboratory Tests): Glucose testing changed from “random” to “non-fasting.”
9) Section 3.6.12.2 (Modified Rodnan Total Skin Score): Text added that same investigator should conduct the mRTSS throughout the study to increase evaluation consistency.
10) Section 3.6.12.3 (European Disease Activity Index): The European DAI was revised to add 3 questions to assess changes in skin, changes in vascular manifestations, and changes in heart/lung to determine worsening as compared to the previous month. Text added that same investigator should conduct the European DAI throughout the study to increase evaluation consistency.

11) Section 3.16.14 (Pharmacokinetic and Pharmacodynamic Evaluations): Size of skin biopsies (one 6 mm, or two 3 mm, or 4 mm) was added.

12) Section 3.6.15.2 (DNA Sample): Text changed for DNA specimen collection to remove subject identifiers from the blood sample.

13) Section 4.1.2 (Study Reporting Period for Adverse Events): Reporting period for adverse events revised to include period immediately following the time the written informed consent is obtained.

14) Section 4.3 (Assessment of Severity), Section 4.5 (Other Events Requiring Immediate Reporting), Section 4.7 (Interruption or Discontinuation of Study Dosing in Individual Subjects) and Appendix 3: The NCI CTCAE was changed from version 3 to version 4.0.

15) Section 5.6.1 (Effect of MEDI-546 on Disease Activity and Patient-reported Outcomes): European Disease Activity Index (DAI) added to patient-reported outcomes assessments.

16) Section 5.7 (Interim Analyses): The definitions of incomplete and nearly complete inhibition of Type 1 IFN gene signature in the skin were updated. Incomplete inhibition is now defined as ≥ 70% inhibition in < 3 patients per cohort, one dose that provides nearly complete inhibition of type I IFN gene signature, defined as ≥ 70% inhibition in at least 3 subjects per cohort, and one dose that is approximately ½ log than the does that provides nearly complete inhibition of type 1 IFN gene signature in the skin.

17) Appendix 5 (Summary of Amendments to the Protocol): Appendix 5 was added to describe changes from the original protocol.

Protocol Amendment 2, [redacted]

Text revisions for this amendment are incorporated into the body of Protocol Amendment 2. Major changes to the protocol are described below.

1. Section 3.1.2 (Exclusion Criteria): Exclusion criteria #22 was clarified to exclude subjects with AST/ALT if results were > 2.5 ULN unless due to documented myositis to recruit the appropriate subject population.
2. The medical monitor has been changed from [redacted] to [redacted] effective as of December 1, 2009.
3. Sections Study Abstract, 3.4.2 (Treatment Regimens), 5.7 (Interim Analysis): The interim analysis will be conducted after all subjects in Cohort 4 complete study Day 14 to increase the interim analysis sample size. The interim analysis originally included all subjects up to cohort 3.
4. Section 3.5 (Schedule of Subject Evaluations), Table 3.5-1 & 3.5-2, Section 3.6.9.3 (Other Laboratory Evaluations): Clarified that C3 & C4 are to be analyzed to assess for hypocomplimentia. Total Hemolytic Complement was changed to serum complement.
5. Section 3.6.9.1 (Laboratory Evaluations): CPK was added to the serum chemistry panel to more clearly assess clinical response. Additionally, CPK was added to the list of abbreviations.

6. Section 3.6.15.2 (DNA Sample): The section was enhanced to more clearly describe the DNA sampling processes. Additionally, a paragraph was added clarifying the process for future use of specimens for unidentified research.
7. Appendix 3: (Health Assessment Questionnaire-Disability Index with Scleroderma Numberic Rating Scale): Final question revised to read, "In the past week, how much have your overall disease (scleroderma) problems interfered with your activities?"
8. Appendix 3: (Health Assessment Questionnaire-Disability Index with Scleroderma Numberic Rating Scale): The number of boxes on the visual analogue scale was increased by 1 for all questions to allow for a count of 5/box starting at 0 and equaling 100.
9. Appendix 4: (European Disease Activity Index [EDAI] : European format was updated to US version (commas replaced with decimals in numbering).

Protocol Amendment 3, [redacted]

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 3. Major changes to the protocol are described below.

1. Section 1.3 (Nonclinical Experience with MEDI-546): Added the results from the most recent histopathology findings from a 9-month non-human primate (cynomolgus monkey) chronic toxicology study of MEDI-546 where in a total of 5 male animals (5/24, 21%) and 0 female animals (0/24, 0%) exposed to MEDI-546, there were histopathology signs of focal arteritis in small and medium sized arteries.

2. Section 1.4 (Clinical Experience): Text updated to indicate the phase 1 study (CP 180) has been initiated and is presently active. Ten subjects have been enrolled and dosed through Cohort 4 (3.0mg/kg) where 1 subject has been dosed. To date, the safety profile is acceptable to continue future clinical testing.

3. Section 3.1.2 (Exclusion Criteria): Exclusion criteria #25 was added to exclude subjects

4. with a history of vasculitis. This exclusion was added due to findings from a 9-month

5. non-human primate (cynomolgus monkey) were histopathology signs of focal arteritis in

6. small and medium sized arteries were found.

7. Section 4.5 (Other Events Requiring Immediate Reporting): Text added instructing the investigator to report symptoms suggestive of vasculitis as an immediately reportable event.

8. Section 4.8 (Interruption or Discontinuation of Study Dosing and Entry): Text added instructing the investigator to discontinue further dosing of any subject who develops symptoms suggestive of vasculitis.

Protocol Amendment 4, [redacted]

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 4. Major changes to the protocol are described below.

Global Changes: Text was updated throughout the body of the protocol for the following changes:

I. A single ascending dose cohort was added (cohort 9, 20 mg/kg) to test a higher dose of MEDI-546 for safety and tolerability and to enable greater flexibility in dosing regimens during later phases of clinical development.

II. The dosing for Cohort 6-8 reflect the interim analysis results completed on 14Jul2010. Top line results of the interim analysis are described in sections 1.4. Text was deleted describing Cohort 4 interim analysis guidelines as this analysis has been completed.

III. Text was updated throughout the body of the protocol regarding the minimum sample size of 33 (increased from 29) due to the addition of cohort 9 (N=4). Text was also updated for the maximum number of subjects calculations; the maximum number of subjects allowed in the study is 53 (addition of N=4 (cohort 9), plus the addition of 2 subjects if a subject is in screening at the time 4 subjects have been entered into the dose cohort 53 (33+8 [4x2] + 12 [2x6]).

1. Study Abstract: Updated for consistency with changes made to the body of the protocol.
2. Section 1.2 (Description of MEDI-546), Section 1.3 (Nonclinical Experience with MEDI-546): Section 1.2, detailed manufacturing language has been deleted as this information is included in the Investigator Brochure. Section 1.3 was updated to describe binding characteristics of MEDI-546.
3. Sections 1.4 (Clinical Experience with Medi-546): Text updated to indicate a total of 17 subjects have been enrolled and dosed through cohort 5 (10.0 mg/kg). Text has also been added indicating an interim analysis of cumulative data on PK and type I IFN gene signatures was performed on all subjects treated through the completion of Study Day 14 of Cohort 4 to determine whether dose adjustments needed to be made in the multiple dose cohorts (Dose Cohorts 6-8). The PK and PD data from the single dose cohorts was modeled to predict PK profiles and PD response with various doses given weekly x 4 as described in the protocol. The results indicate that doses of 0.3, 1.0 and 5.0 mg/kg respectively, best target the pre-specified criteria as defined in the protocol of one dose that provides incomplete inhibition of type I IFN gene signature defined as ≥ 70% inhibition in < 3 patients per cohort, one dose that provides nearly complete inhibition of type I IFN gene signature defined as ≥ 70% inhibition in at least 3 subjects per cohort, and one dose that is approximately ½ log higher than the dose that provides nearly complete inhibition of type I IFN gene signature.

4. Section 1.5 (Rationale for Study): Text was added to indicate a single IV dose cohort of 20.0 mg/kg (cohort 9). Dosing for the multiple ascending dose cohorts (cohorts 6, 7, and 8) has changed from the original protocol as confirmed by the 14July2010 interim analysis to allow 5 mg/kg dosing in Cohort 8. This was changed from 3 mg/kg. The 5 mg/kg dose will enable greater flexibility in dosing regimens during later phases of clinical development. Dosing for cohorts 7 and 8 has not changed from the original protocol.
5. Section 2.4 (Overview, Study Design): The number of study sites was increased from approximately 15 to 20 to enhance enrollment into the study. Text was added to indicate that Cohort 9 (20 mg/kg) may be dosed simultaneously to the MAD Cohorts 6, 7, or 8. Simultaneous dosing may occur as cumulative safety data of the lower single ascending dose cohorts (Cohorts 1-5) were evaluated for safety and progression to higher doses approved; the multiple ascending dose cohort 6, 7 and 8 (0.3, 1.0, 5.0 mg/kg) are lower doses than Cohort 9. Text was updated to increase the IV infusion time from 60 minutes to 120 minutes for doses > 10mg/kg to guard against potential infusion reactions at higher doses.
6. Sections 2.4 (Overview, Study Design), 3.4.2 (Treatment Regimens), 3.4.3 (Investigational Product preparation) and 3.4.4 (Administration of Investigational Product): Text was added that for doses > 10 mg/kg and for subjects weighing > 250 lbs. or 114 kg the medical monitor should be called to discuss infusion rate instructions. The highest dose tested to date is 10 mg/kg for a subject weighing 250 lbs/114 kg; in order guard against infusion reactions at higher protein doses the sponsor would like to calculate the infusion rate (for Cohort 9, 20 mg/kg) with the site to insure the rate of protein infusion is adequate.
7. Figure 2.4-1, Section 3.4.2, Table 3.4.2-1, Table 3.5-1, (Schedule of Subject Evaluations for SAD) Section 4.9 (Dose Escalation): Figure 2.4-1 and Table 3.4.2-1 were updated to reflect the addition of cohort 9, (20 mg/kg) and the change in dose for Cohort 8 from 3 mg/kg to 5 mg/kg. Text in the footnote of figure 2.4-1 and in Section 4.9 (Dose Escalation) were updated to indicate that dose escalation for the MAD cohorts will occur at Day 28 to more accurately assess safety in these cohorts. Table 3.5-1 was updated to include Cohort 9.
8. Section 3.4.2 (Treatment Regimen): Test describing the interim analysis was deleted as the interim analysis is now complete. Text was updated indicating Cohort 9 may enroll simultaneous to the multiple ascending dose cohorts 6, 7 and 8 and that IV infusion time will be increased from 60 minutes to 120 minutes for doses > 10mg/kg to guard against potential infusion reactions at higher doses. Text was also deleted indicating that the final doses chosen for the multiple ascending dose cohorts "will not exceed 3.0 mg/kg". The original protocol assumptions did not include that subjects from Cohort 5 (10 mg/kg) would be included in the interim analysis. However because recruitment in Cohort 5 proceeded quickly, 3 subjects from Cohort 5 were included in the interim analysis for safety. Cohort 5 has also completed enrollment (N=4); safety has been reviewed by the medical monitor and approval to proceed to the next highest dosing cohort was granted. Therefore since safety has been confirmed through Cohort 5 (10 mg/kg), the doses chosen for the multiple ascending

dose cohorts will exceed 3 mg/kg. The highest dose in the multiple ascending dose cohorts will be 5 mg/kg.

9. Section 3.2 (Enrollment and Study Entry), Section 3.4.1 Investigational Product Supplies and Accountability: [redacted] n section 3.4.1, text was deleted referencing where MEDI-546 is manufactured as this information is covered in the Investigational Brochure and is redundant.

10. Section 3.4.3 (Investigational Product Preparation), Section 3.4.4 (Administration of Investigational Product): Section 3.4.3, text was added to clarify that if the total volume of the study drug to be administered is greater than 75 mL, then a 250 mL bag of normal saline should be used. Section 3.4.4, Text was updated to increase the IV infusion time from 60 minutes to 120 minutes for doses > 10mg/kg to guard against potential infusion reactions at higher doses.

11. Section 3.7 (Completion of Study, Discontinuation of Study, and Lost to Follow-up): Text was updated to define End of Study given Cohorts 6, 7, 8 and 9 will enroll simultaneously, "Cohorts 6, 7, 8 and 9 will enroll simultaneously; End of Study is defined as the last subject last visit for either cohort 8 (Day 105/Discontinuation) or Cohort 9 (Day 85/Discontinuation) whichever comes later".

12. Section 5.6.3 (Relationship to Type 1 IFN-related DNA Polymorphisms and Safety): Text was updated to indicate that Polymorphisms in type 1 IFN-related genes associated with safety signals to MEDI-546 may (was will) be assessed using descriptive statistics. This has been changed to allow greater flexibility in the analysis.

13. Section 5.7 (Interim Analyses), Study Abstract (Treatment, Interim Analysis): References to the interim analysis design have been deleted in the Study Abstract as this design is summarized in Section 5.7. Text was deleted indicating an interim analysis of IM, PK, and PD data may be performed when all subjects in Dose Cohort 8 complete Study Day 56. This interim analysis is planned to occur only 1.6 months prior to the end of the study and is now considered unnecessary.

14. Section 10 (Changes in The Protocol): The major changes to Protocol Amendment 4 have been summarized as above.

15. Administrative changes: Study personnel have been updated, the List of Abbreviations was updated; other editorial changes have been made.