A Phase 2, Open-label Extension Study to Evaluate Long-term Safety of MEDI-546 in Adults with Systemic Lupus Erythematosus

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Abbreviation or Specialized Term	Definition
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
ANA	antinuclear antibody
AST	aspartate transaminase
AUC	area under the concentration-time curve
β-HCG	beta-human chorionic gonadotropin
BCG	Bacillus of Calmette and Guerin
BP	blood pressure
C1q	multivalent for attachment to the complement fixation sites of immunoglobulin
C_{max}	Maximum observed serum concentration
CML	chronic myelogenous leukemia
CRF	case report form
CRO	contract research organization
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ds	double-stranded
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECL	electrochemiluminescent
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ePPND	enhanced pre-and post-natal development
EU	European Union
Fc	fragment, crystallizable
FcγRIA/IIA/IIIB/III	Fc gamma receptor I/IIA/IIB/IIIA
FcRn	Fc gamma neonatal receptor
GCP	Good Clinical Practice
GD20	Gestation Day 20
GMP	Good Manufacturing Practice
HbA1c	glycosylated hemoglobin
HBc	hepatitis B core (antibody)
HBV	hepatitis B virus
HBV DNA	hepatitis B virus deoxyribonucleic acid
HDL	high-density lipoprotein

Abbreviation or Specialized Term	Definition
HED	human equivalence dose
HIPAA	Health Insurance Portability and Accountability Act
HRQL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IFN-α/β	interferon-alpha/beta
IFNAR1	subunit 1 of the type I interferon receptor
Ig	Immunoglobulin
IgG1κ	immunoglobulin G1 kappa
IM	Immunogenicity
IRB	Institutional Review Board
IV	Intravenous
IVRS/IWRS	interactive voice/web response system
LD28	Lactation Day 28
LDL	low-density lipoprotein
MAb	Monoclonal antibody
MCS	Mental Component Summary
mDC	myeloid dendritic cell
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NOAEL	no-observable-adverse-effect-level
NSAID	non-steroidal anti-inflammatory drug
NZB/W	New Zealand black/white
OCS	oral corticosteroids
OLE	open-label extension
PAD	pharmacologically active dose
Pap	Papanicolaou smear
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PCS	Physical Component Summary
PD	pharmacodynamics
pDC	Plasmacytoid dendritic cell
PK	pharmacokinetics
PP	per protocol
Q4W	every 4 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks

Abbreviation or Specialized Term	Definition
Q48W	every 48 weeks
QFT-GIT	QuantiFERON-TB Gold In-tube
RBC	red blood cell
RNA	ribonucleic acid
RNP	ribonucleoprotein
SAE	serious adverse event
SC	subcutaneous
SF-36v2	Short Form-36 Version 2
SID	subject identification
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index - 2000
SLICC/ACR	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
Sm	Smith
SOC	standard of care
SSc	systemic sclerosis
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
TB	Tuberculosis
TBD	to be determined
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TLR	Toll-like receptor
ULN	upper limit of normal
USA	United States of America
USP	United States Pharmacopeia
WBC	white blood cell
w/v	weight/volume

STUDY ABSTRACT

TITLE

A Phase 2, Open-label Extension Study to Evaluate Long-term Safety of MEDI-546 in Adults with Systemic Lupus Erythematosus

OBJECTIVES

Primary Objective: To evaluate the long-term safety and tolerability of intravenous (IV) MEDI-546 in adult subjects with chronic, moderately-to-severely active systemic lupus erythematosus (SLE).

Secondary Objective: To evaluate the immunogenicity (IM) of MEDI-546.

Exploratory Objectives: [redacted]

STUDY DESIGN

This is an open-label, multinational, multicenter study to evaluate the long-term safety and tolerability of MEDI-546 in adult subjects with chronic, moderately-to-severely active SLE who were previously treated with investigational product (MEDI-546 or placebo) and completed Study CD-IA-MEDI-546-1013 through treatment and follow-up. The study will be conducted in approximately 240 subjects at approximately up to 100 study sites.

Once subjects have completed treatment and follow-up in Study CD-IA-MEDI-546-1013 (through Day 422), signed the informed consent form (ICF), and met all study eligibility criteria, they may be enrolled in this open-label extension (OLE) study. The start of this OLE study (defined as the day [Day 1] the subject receives their first dose of open-label MEDI-546) should occur within 28 days of the Day 422 visit of Study CD-IA-MEDI-546-1013 (with the exception of those subjects in the regions of Donetsk and Lugansk in the Ukraine, where the political situation necessitated a suspension of study activities) or at the discretion of the medical monitor if the start of this OLE study occurs outside the 28-day window. All subjects will receive IV MEDI-546 as a 300 mg fixed dose administered as an IV infusion over at least 30 minutes every 4 weeks (Q4W) starting at Day 1 (Week 0) for up to 3 years or until the sponsor discontinues development of MEDI-546 for SLE, whichever comes first. All subjects will be followed for 85 days after receiving their last dose of MEDI-546.

At every visit, the investigator will evaluate the subject's clinical status and perform a risk/benefit analysis based on clinical judgment to determine if the subject should continue to receive MEDI-546 in the study.

SUBJECT POPULATION

The subjects in this study will be adult male or female subjects with chronic, moderately-to-severely active SLE who were previously treated with investigational product (MEDI-546 or placebo) and completed Study CD-IA-MEDI-546-1013 through treatment and follow-up.

TREATMENT REGIMEN

Subjects will receive MEDI-546 300 mg administered as an IV infusion Q4W starting at Day 1 (Week 0) for up to 3 years or until the sponsor discontinues development of MEDI-546 for SLE, whichever comes first.

ASSESSMENT OF ENDPOINTS

Primary endpoint: The safety and tolerability of MEDI-546 will be assessed primarily by summarizing treatment-emergent adverse events and treatment-emergent serious adverse events. Other variables used for the safety assessments will include serum chemistry, hematology, urinalysis, vital signs, physical examination, electrocardiogram, and concomitant medications.

Secondary endpoint: Immunogenicity results will be analyzed by summarizing the number and percentage of subjects who develop detectable anti-drug antibodies (ADA). The titer of ADAs will also be summarized. The association of ADA titers with adverse events, PK, Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K), and PD markers will also be evaluated.

Exploratory endpoints [redacted]

[redacted]

INTERIM ANALYSIS

Although no formal interim analyses of the extension period data are planned, analyses of the accumulating data during the extension period may be performed to assess the ongoing safety and risk/benefit of the study treatment and to assist with Phase 3 planning. The final analysis of extension period data will take place after the last on-study subject completes the extension period follow-up visit or discontinues from the study.

SAMPLE SIZE AND POWER CALCULATIONS

[redacted]

1 INTRODUCTION

1.1 Disease Background

Systemic Lupus Erythematosus

The disease pathogenesis of systemic lupus erythematosus (SLE) includes activation of innate immunity, with increased production of type I interferons (IFNs), including interferon-alpha (IFN-α), and increased numbers of plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDCs) in involved tissue (Bengtsson et al, 2000; Baechler et al, 2003; Crow and Wohlgemuth, 2003; Ronnblom and Alm, 2003; Baechler et al, 2004; Banchereau et al, 2004; Dall'era et al, 2005; Crow, 2010). Specific parts of the humoral and cellular immune systems are activated. Autoantibodies are present universally and may precede development of clinically apparent disease (Arbuckle et al, 2003). Systemic lupus erythematosus-associated autoantibodies include anti-double-stranded (ds) deoxyribonucleic acid (DNA), anti-nucleosomes, anti-ribonucleoprotein (RNP) complex, and anti-Smith (Sm) antibodies (Rahman and Isenberg, 2008). Immune complexes containing anti-dsDNA or anti-RNP antibodies can activate type I IFN production (Bengtsson et al, 2000; Ronnblom and Alm, 2003).

Multiple lines of evidence indicate a role of type I IFNs in the pathogenesis of SLE:

- Genetic polymorphisms associated with type I IFNs are associated with susceptibility to SLE (Criswell, 2008; Sigurdsson et al, March 2008; Sigurdsson et al, September 2008).
- High IFN-α levels and type I IFN activity have been reported in SLE (Bengtsson et al, 2000; Dall'era et al, 2005).
- Increased levels of messenger ribonucleic acid (mRNAs) whose transcriptions are induced by type I IFNs (type I IFN signature) are prominent in peripheral blood mononuclear cells (PBMCs) and whole blood in approximately 60% of SLE patients and are associated with greater disease activity (Baechler et al, 2003; Bennet et al, 2003; Crow and Wohlgemuth, 2003; Kirou et al, 2004; Kirou et al, 2005; Feng et al, 2006). Transcripts induced by type I IFN are the most overexpressed transcripts in SLE (Yao et al, 2010).
- Proteins induced by IFN are increased in SLE patients (Hylton et al, 1986; Okamoto et al, 2004; Huang et al, 2008).
- Overexpression of type I IFN, type I IFN signature, and proteins induced by type I IFNs have been associated with greater disease activity and organ system involvement in SLE. High IFN-α levels, type I IFN activity, and increased type I IFN signature have been associated with greater disease activity (Bengtsson et al, 2000; Dall'era et al, 2005). Patients with high anti-dsDNA antibody titers, lupus nephritis, and progressive skin

rashes have high serum levels of type I IFN (Bengtsson et al, 2000). In addition, patients with acute skin involvement tend to have elevated IFN in blood and skin (Dall'era et al, 2005). Skin biopsies from patients with SLE also show increased type I IFN signature (Blomberg et al, 2001; Farkas et al, 2001; Yao et al, 2009). Proteins induced by IFN are increased in patients with active central nervous system symptoms (Okamoto et al, 2004).

- Immune complexes containing SLE autoantibodies, such as anti-dsDNA or anti-RNP antibodies, can activate type I IFN production (Bengtsson et al, 2000; Ronnblom and Alm, 2003). After internalization through Fc receptors, autoantibody-containing immune complexes bind endosomal Toll-like receptor 7 (TLR7) and TLR9, stimulating production of type I IFN. Type I IFN stimulates mDC maturation, which promotes loss of tolerance and generation of autoreactive T and B cells, autoantibody production, immune complex formation, and further production of type I IFN, creating a self-perpetuating cycle of autoimmunity (Banchereau et al, 2004; Ronnblom and Pascual, 2008; Pascual et al, 2006).
- Treatment with IFN-α has been associated with the development of SLE autoantibodies and clinical features of the disease (Ioannou and Isenberg, 2000; Niewold and Swedler, 2005).

These clinical observations in humans are supported by data that show a key role for type I IFN in animal models of SLE. Interferon-alpha can induce glomerulonephritis in normal mice and accelerate the onset of the spontaneous autoimmune disease of New Zealand black/white (NZB/W) mice (Mathian et al, 2005). Autoimmune-predisposed mice deficient in the interferon-alpha/beta (IFN-α/β) receptor exhibit significantly reduced anti-erythrocyte autoantibodies, hemolytic anemia, anti-DNA autoantibodies, kidney disease, and mortality (Santiago-Raber et al, 2003). Together, these human and animal data support the hypothesis that inhibiting type I IFN may reduce disease activity in patients with SLE.

1.2 MEDI-546 Background

MEDI-546 is briefly described below. Refer to the current Investigator's Brochure (IB) for details.

1.2.1 Product Derivation

[redacted]

[redacted]

[redacted]

1.2.2 Summary of Nonclinical Experience

[redacted]

[redacted]

[redacted]

[redacted]

1.2.3 Summary of Clinical Experience

MEDI-546 has been or is being investigated in 4 MedImmune/AstraZeneca-sponsored clinical studies in adult subjects with systemic sclerosis (SSc) or SLE. One study in SSc is complete (Study MI-CP180) and 3 studies in SLE, including the current study, are ongoing (Studies CD-IA-MEDI-546-1013, CD-IA-MEDI-546-1145, and D3461C00002).

[redacted]

Study CD-IA-MEDI-546-1013, a Phase 2b, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of MEDI-546 in adult subjects with chronic, moderately-to-severely active SLE with an inadequate response to standard of care treatment for SLE, is currently ongoing and remains blinded. Enrollment in this study is complete. An interim analysis was conducted after the 210th randomized subject completed the Day 169 visit or discontinued from study treatment early. A total of 307 subjects have been randomized in a 1:1:1 ratio to receive a fixed IV dose of MEDI-546 (300 or 1000 mg) or placebo every 4 weeks (Q4W) for 48 weeks on Days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309 and 337 for a total of 13 doses. There is an 85-day follow-up period in Study CD-IA-MEDI-546-1013, which the subjects must complete to be considered for enrollment into Study CD-IA-MEDI-546-1145.

Study D3461C00002, a Phase 2, multicenter, open-label, dose-escalation study to evaluate the safety and tolerability of MEDI-546 in adult Japanese subjects with active SLE, is

currently ongoing. Enrollment in this study is complete. A total of 17 subjects are receiving a fixed IV dose of MEDI-546 (100, 300, or 1000 mg) Q4W for 48 weeks for a total of 13 doses followed by a fixed IV dose of MEDI-546 (300 or 1000 mg) Q4W for 104 weeks for a total of 27 doses.

1.3 Research Hypothesis

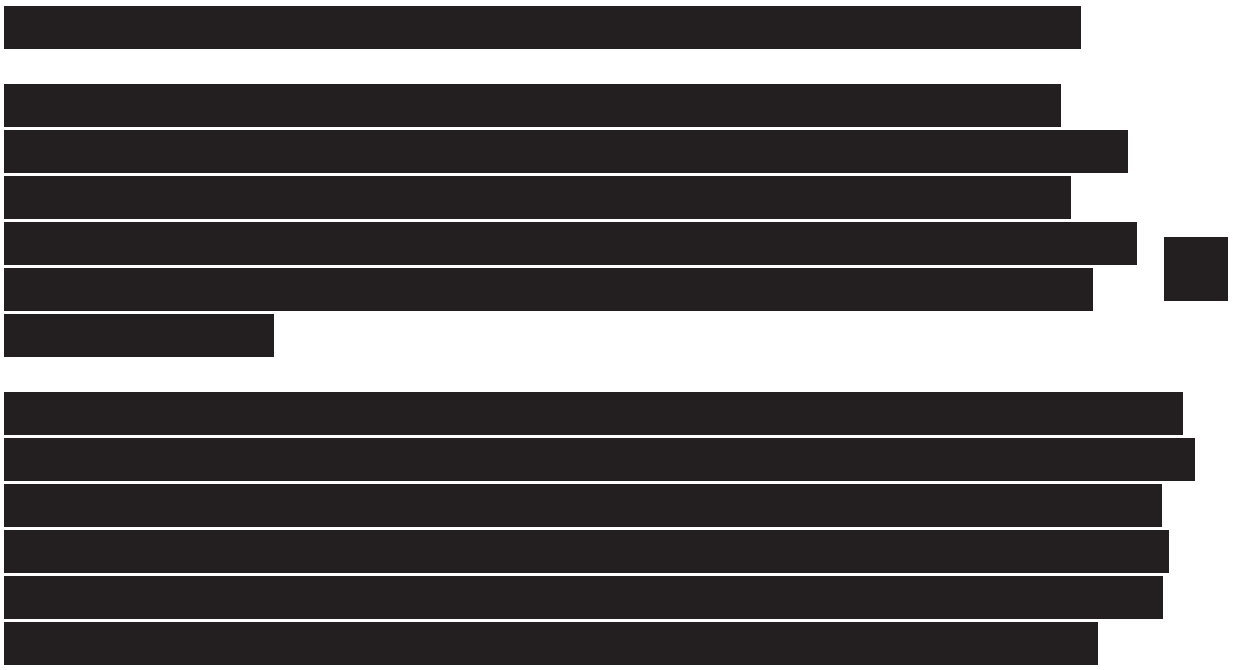
The research hypothesis is that neutralization of IFN signaling through the human type I IFN receptor with MEDI-546 in subjects with chronic, moderately-to-severely active SLE is safe and well tolerated when administered at a fixed dose of 300 mg Q4W.

1.4 Rationale for Study Conduct

Systemic lupus erythematosus is a serious and potentially life-threatening condition with significant unmet medical need. There is an increasing body of data from multiple investigators indicating a pivotal role for type I IFN in the genesis and maintenance of active SLE (Baechler et al, 2003; Baechler et al, 2004; Crow and Wohlgemuth, 2003; Dall'era et al, 2005; Kirou et al, 2005).

The purpose of this open-label extension (OLE) study is to evaluate the long-term safety and tolerability of MEDI-546 when administered IV to adult subjects with chronic, moderately-to-severely active SLE.

1.5 Benefit-risk and Ethical Assessment



[redacted]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of IV MEDI-546 in adult subjects with moderately-to-severely active SLE.

2.2 Secondary Objective

The secondary objective of this study is to evaluate the IM of MEDI-546.

2.3 Exploratory Objectives

[redacted]

3 STUDY DESIGN

3.1 Overview of Study Design

This is an open-label, multinational, multicenter study to evaluate the long-term safety and tolerability of MEDI-546 in adult subjects with chronic, moderately-to-severely active SLE who were previously treated with investigational product (MEDI-546 or placebo) and completed Study CD-IA-MEDI-546-1013 through treatment and follow-up. The study will be conducted in approximately 240 subjects at up to 100 study sites.

Once subjects have completed treatment and follow-up in Study CD-IA-MEDI-546-1013 (through Day 422), signed the informed consent form (ICF), and met all study eligibility criteria, they may be enrolled in this OLE study. The start of this OLE study (defined as the day [Day 1] the subject receives their first dose of open-label MEDI-546) should occur within 28 days of the Day 422 visit of Study CD-IA-MEDI-546-1013 (with the exception of those subjects in the regions of Donetsk and Lugansk in the Ukraine, where the political situation necessitated a suspension of study activities) or at the discretion of the medical monitor if the start of this OLE study occurs outside the 28-day window. All subjects will receive IV MEDI-546 as a 300 mg fixed dose administered as an IV infusion over at least 30 minutes Q4W starting at Day 1 (Week 0) for up to 3 years or until the sponsor discontinues development of MEDI-546 for SLE, whichever comes first. All subjects will be followed for 85 days after receiving their last dose of MEDI-546.

At every visit, the investigator will evaluate the subject's clinical status and perform a risk/benefit analysis based on clinical judgment to determine if the subject should continue to receive MEDI-546 in the study.

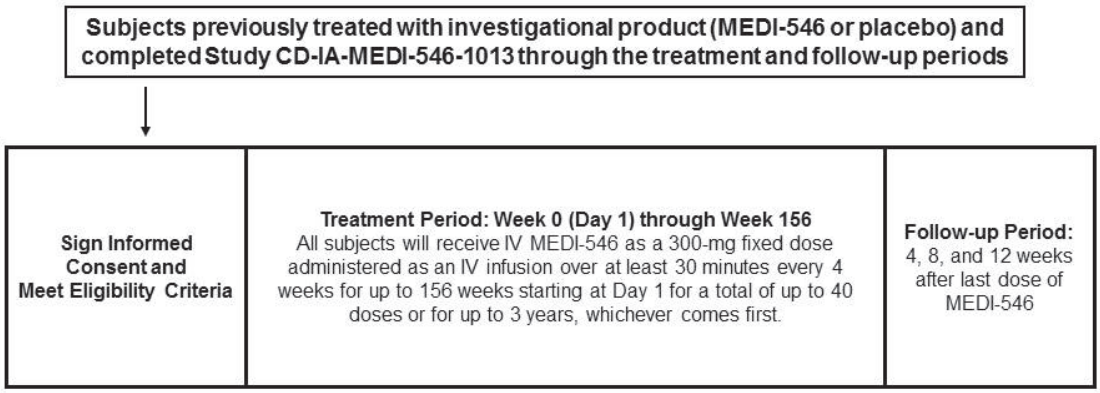


Figure 3.1-1 Study Flow Diagram

IV = intravenous

The endpoints to be measured in this study are described in Section 7.3.

3.2 Estimated Duration of Subject Participation

Subjects will be in this study for approximately 168 weeks (156 weeks for treatment and 12 weeks for follow-up).

3.3 Study-stopping Criteria

If any event(s) occur that, in the opinion of the DSMB or sponsor, contraindicates further dosing of additional subjects, the sponsor will conduct a prompt cumulative review of safety data and the circumstances of the event in question will be conducted to determine whether dosing and study enrollment should be stopped, whether the protocol will be modified, or whether the study will be discontinued permanently. Review by the DSMB and sponsor decision to resume (with or without modifications) is required for resumption of the study in the event the study is interrupted. Where applicable, the regulatory authorities and Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) will be notified of any actions taken with the study.

Any subjects who have already received investigational product and are currently in the study at the time study-stopping criteria are met will continue to be followed by the investigator for safety. In the unanticipated event that dosing is suspended, until a decision is reached by the sponsor, subjects will continue with regularly scheduled visits.

Withdrawal criteria for individual subjects are provided in Section 4.2.3.

3.4 Rationale for Study Design, Doses, and Control Groups

3.4.1 Rationale for Study Design

This is an open-label, long-term safety and tolerability study of MEDI-546. The subjects in this study will be male or female with moderately-to-severely active SLE despite standard of care (SOC) who have been previously treated with investigational product (MEDI-546 or placebo) and completed Study CD-IA-MEDI-546-1013 through the treatment and follow-up periods. All subjects in this OLE study will receive a fixed IV dose of 300 mg MEDI-546.

3.4.2 Rationale for MEDI-546 Dose

[redacted]

4 SUBJECT SELECTION, TREATMENT, AND WITHDRAWAL

4.1 Subject Participation and Identification

Study participation begins once written informed consent is obtained (see Section 10.3 for details) for this OLE study. Once informed consent is obtained, a subject identification (SID) number will be assigned to each subject by a central system interactive voice/web response system (IVRS/IWRS). The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all pretreatment period failures (ie, subjects who are consented but do not meet study eligibility criteria), including the reason(s) for pretreatment period failure (see Section 9.1 for details).

4.2 Subject Selection and Withdrawal

The subjects in this study will be adult male or female subjects with chronic, moderately-to-severely active SLE who were previously treated with investigational product (MEDI-546 or placebo) and completed Study CD-IA-MEDI-546-1013 through treatment and follow-up.

The investigator (physician) or qualified designee will discuss the study with a subject who is considered a potential candidate for the study and provide the subject with the study-specific ICFs approved by the IRB/IEC. The investigator or designee will address any questions and/or concerns that the subject may have and, if there is continued interest, will secure written informed consent for participation in the study. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] authorization in the United States of America [USA], European Union [EU] Data Privacy Directive authorization in the EU) will be obtained prior to conducting any protocol-specific procedures, including Day 1 evaluations or medication washouts. See Section 10.3 for additional details concerning informed consent.

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1. Written informed consent and any locally required authorization (eg, HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including Day 1 evaluations.
2. Must have qualified for and received investigational product (MEDI-546 or placebo) and completed the treatment period plus the follow-up period (through Day 422) in Study CD-IA-MEDI-546-1013. Subjects who discontinued from Study CD-IA-MEDI-546-1013 are not eligible for this study, with the exception of those subjects in the regions of Donetsk and Lugansk in the Ukraine, where the political situation necessitated a suspension of study activities, and all other inclusion and exclusion criteria were met.
3. Females of childbearing potential who are sexually active with a nonsterilized male partner must use 2 methods of effective contraception for 28 days prior to Day 1, and must agree to continue using such precautions for 85 days after the final dose of investigational product; cessation of contraception after this point should be discussed with a responsible physician. Subjects must continue the use of their effective contraception as used in Study CD-IA-MEDI-546-1013. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.
    - Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy).
    - Postmenopausal is defined as 12 months with no menses without an alternative medical cause.

- Subjects must use 2 acceptable methods of effective contraception as described in Table 4.2.1-1.

4. Nonsterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 4.2.1-1) from Day 1 for 85 days after receipt of the final dose of investigational product.

Table 4.2.1-1 Effective Methods of Contraception (Two Methods Must be Used)

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
• Male condom plus spermicide • Cap plus spermicide • Diaphragm plus spermicide	• Copper T • Progesterone T [a] • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[a] This is also considered a hormonal method.

5. Willing to forgo other forms of experimental treatment during the study.
6. Has adequate peripheral venous access.
7. Able to complete the study period.
8. Has adequate reading and writing abilities (in their native language), in the opinion of the investigator, such that the subject can comprehend and complete the informed consent, and all protocol-related subject assessments.

4.2.2 Exclusion Criteria

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

General Exclusion Criteria

1. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results.
2. Major surgery within 8 weeks before signing the ICF or elective major surgery planned during the study period (see Appendix 2 for guidance on major surgery).

Exclusion Criteria Related to Concomitant Medications:

3. Receipt of any of the following within the last 12 weeks:
   - Azathioprine > 200 mg/day.
   - Mycophenolate mofetil/mycophenolic acid > 2.0 g/day.
   - Oral, SC, or intramuscular methotrexate > 25 mg/week.

4. Receipt of any of the following:
    - Any live or attenuated vaccine within 4 weeks prior to signing the ICF (administration of killed vaccines is acceptable, the sponsor recommends investigators ensure all subjects are up to date on required vaccinations prior to study entry).
    - Bacillus of Calmette and Guerin (BCG) vaccine within 1 year of signing the ICF.

4.2.3 Withdrawal Criteria

Permanent discontinuation of investigational product: 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 or lost to follow-up.
2. Adverse event (AE) that, in the opinion of the investigator or the sponsor, contraindicates further dosing with investigational product.
3. The investigator or the MedImmune medical monitor determines that withdrawal is in the subject's best interest.
4. Pregnancy, positive pregnancy test, or subject expresses an interest in becoming pregnant at any time from Day 1 through the active treatment period of the study (see Section 6.4.3.3).
5. Malignancy, except squamous or basal cell carcinoma of the skin with documented success of curative therapy.
6. An opportunistic or systemic fungal infection or any infection (viral, bacterial) of a serious nature (ie, requiring hospitalization or treatment with IV anti-infectives), that in the opinion of the investigator or medical monitor, contraindicates further dosing of investigational product after resolution.
7. Isolated hepatitis B core (HBc) positivity with hepatitis B virus (HBV) DNA detected by the central laboratory.
8. Receipt of any of the following medications (other than MEDI-546 administered as per protocol) any time from the last MEDI-546 dose in Study CD-IA-MEDI-546-1013 to 85 days post last MEDI-546 dose in Study CD-IA-MEDI-546-1145:
    - Cyclophosphamide
    - IV corticosteroids > 1g Solu-Medrol or equivalent
    - IFN therapy (alpha 2a & 2b, beta 1a & 1b, and pegylated IFNs alpha 2a & 2b)
    - Investigational agents
    - Biologics (including belimumab)
    - Plasmapheresis
    - Any immunoglobulin (Ig) therapy
    - BCG vaccine

9. A diagnosis of active tuberculosis (TB), premature discontinuation of treatment for latent TB, or noncompliance with TB therapy

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study (see Section 4.7).

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 6.4, including the collection of any protocol-specified blood or urine specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. Twenty-eight days (± 7 days) after the last dose of investigational product, subjects will begin the follow-up period by completing the Visit 41/Early Discontinuation Visit assessments. Two subsequent follow-up visits will also be completed 59 and 85 days (± 7 days) after the last dose of investigational product as per the schedule of study procedures. A subject who receives any SLE medication or SLE treatment listed in Appendix 3 (other than those prohibited medications or treatments listed above) may be allowed to continue receiving investigational product only if permission from the sponsor is obtained.

Concomitant medications that require the sponsor to be notified immediately and the medical monitor to be consulted to determine if a subject may continue to receive investigational product include, but are not limited to:

- Corticosteroids with a long biologic half-life (eg, dexamethasone, betamethasone)
- Increase in oral corticosteroids (OCS) treatment above a total dose > 40 mg/day for a dosing period > 14 days, dosing with MEDI-546 may be continued, unless there is a safety concern. However, it should be noted that frequent steroid use above Study CD-IA-MEDI-546-1013 baseline for SLE disease control (> 2 times every 6 months, higher doses [> 40 mg/day], and/or longer duration than permitted by the protocol) after 12 months of open-label MEDI-546 should result in discontinuation of MEDI-546 administration for failure to achieve a favorable benefit:risk profile.

Withdrawal of consent: If consent is withdrawn, the subject will not receive any further investigational product or further study observation. Note that the subject may need to undergo additional tests or tapering of treatment to withdraw safely.

Lost to follow-up: Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed (as defined in Section 4.9) such that there is insufficient information to determine the subjects' status as of their last visit.

- Note: Subjects refusing to return to the site or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to the protocol.

4.2.4 Replacement of Subjects

Subjects in this OLE study will not be replaced.

4.3 Treatment Assignment

Each subject who meets the eligibility criteria will be assigned open-label investigational product using an IVRS/IWRS. A subject is considered enrolled into the study when the investigator or delegated site personnel notifies the IVRS/IWRS that the subject meets the eligibility criteria and the IVRS/IWRS provides the assignment of the investigational product kit numbers to the subject. Confirmation of this information is sent to the investigator/designee who dispenses the investigational product to the subject per the communication and records the appropriate information in the subject's medical records and investigational product accountability log.

Investigational product (MEDI-546) must be administered on the same day that the visit is logged into the IVRS/IWRS. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified *immediately*.

4.4 Blinding

This study is not blinded.

4.5 Study Medications

4.5.1 [redacted]

[redacted]

[redacted]

4.5.1.1 Investigational Product Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

4.5.1.2 Reporting Product Complaints

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

Product defects may be related to component, product, or packaging and labeling issues. The list below includes, but is not limited to, descriptions of product complaints that should be reported.

- **Component Issue:** Defect in container or dosing mechanism of the investigational product. The component defect may be damaged, missing, or broken. Component examples include vials, stoppers, caps, spray barrels, spray nozzles, or plungers.
- **Product Issue:** Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description.
- **Packaging/Labeling Issue:** Defect in the packaging or labeling of the product. The packaging or labeling defects may be damaged or unreadable, or the label may be missing.

When reporting a product complaint, site staff must be prepared to provide the following information:

1. Customer information: reporter name, address, contact number, and date of complaint
2. Product information: product name, packaging kit number or lot number, expiry date, and clinical protocol number
3. Complaint information: complaint issue category and description

MedImmune contact information for reporting product complaints:

4.5.2 Other Study Medications

Permitted SOC SLE medications include OCS (up to 40 mg/day of prednisone or equivalent), intramuscular corticosteroids, intra-articular/tendon sheath/bursa corticosteroid injections, antimalarials, slow-acting immunosuppressants (methotrexate, mycophenolate mofetil/mycophenolic acid, and azathioprine), prescription NSAIDs, analgesics/nonprescription NSAIDs, and topical therapy. However, when OCS medications are > 40 mg/day of prednisone (or equivalent) for greater than 14 days, dosing with MEDI-546 may be continued, unless there is a safety concern.

However, it should be noted that frequent steroid use above Study CD-IA-MEDI-546-1013 baseline for SLE disease control (> 2 times every 6 months, higher doses [> 40 mg/day], and/or longer duration than permitted by the protocol) after 12 months of open-label MEDI-546 should result in discontinuation of MEDI-546 administration for failure to achieve a favorable benefit:risk profile.

All permitted SOC SLE medications received from initiation from Day 1 through the end of the study will be recorded on the source document and include the specific indication for use (eg, general SLE activity, skin involvement, nephritis, pleurisy) as well as the dose, start and stop dates, frequency, and route of administration. In addition, any change in permitted SOC SLE medications and reason for change must be documented. All OCS's taken during the study for a burst or a taper must be identified if the OCS is being taken for an SLE condition or a non-SLE condition.

4.5.2.1 Corticosteroids

When OCS treatment is above a total dose > 40 mg/day for a dosing period > 14 days, dosing with MEDI546 may be continued, unless there is a safety concern.

However, it should be noted that frequent steroid use above Study CD-IA-MEDI-546-1013 baseline for SLE disease control (> 2 times every 6 months, higher doses [> 40 mg/day], and/or longer duration than permitted by the protocol) after 12 months of open-label MEDI-546 should result in discontinuation of MEDI-546 administration for failure to achieve a favorable benefit:risk profile.

4.5.2.2 Slow-acting Immunosuppressants

If subjects are on slow-acting immunosuppressants, dosing must not exceed the following:

- Azathioprine > 200 mg/day
- Mycophenolate mofetil/mycophenolic acid > 2.0 g/day
- Oral, SC, or intramuscular methotrexate > 25 mg/week

4.5.2.3 Background SOC SLE Medications (OCS, Antimalarials, and Immunosuppressants)

Subjects may undergo changes in their background SOC SLE medication (OCS, antimalarials or immunosuppressants) doses, based on the opinion of the investigator. On treatment days, changes in doses will commence after all assessments have been completed and investigational product has been administered.

Investigators should change background SOC SLE medications based on disease activity in all subjects throughout the study. There is no minimum dose requirement for background SOC SLE medications, and subjects are encouraged to taper off as permitted by disease activity. Due to variability in subject responses to background SOC SLE medications and tolerability of taper, investigators are asked to use their clinical judgment with respect to the taper schedule. An example of a tapering schedule is provided in Appendix 6 as guidance. If the subject experiences an increase in SLE disease activity secondary to background SOC SLE medications, the dose may be adjusted according to the investigator's clinical judgment but may not exceed maximally permitted doses as defined by exclusionary criteria.

4.5.2.4 Use of Other Medications for Increased Disease Activity

If during the course of the study permitted SOC SLE medications are not adequate for the treatment of increased SLE disease activity, a subject may receive other medications as deemed necessary by the investigator or the subject's treating physician after notifying the medical monitor. However, if the subject receives (or is intended to receive) any medications/treatments listed in Appendix 3, the sponsor must be notified immediately and procedures outlined in Section 4.2.3 must be followed. The subject may only continue to receive investigational product with sponsor approval.

4.5.3 Treatment Regimen

Subjects will receive MEDI-546 300 mg administered as an IV infusion Q4W starting at Day 1 (Week 0) or the visit following approval of this amendment (for those subjects who

have already been dosed in this study) for up to 3 years or until the sponsor discontinues development of MEDI-546 for SLE, whichever comes first.

4.5.4 Investigational Product Dose Preparation

No incompatibilities between MEDI-546 and 100 mL 0.9% w/v saline polyolefin bags have been observed. Additional studies also demonstrated that MEDI-546 is compatible with IV bags and ancillaries comprised of materials including: polyolefin, glass, polyethylene, polyvinylchloride, polypropylene, polybutadiene, and ethylene polyvinyl acetate. Because compatibility of MEDI-546 with IV medications and solutions other than normal saline (0.9% sodium chloride for injection), is not known, the investigational product solution should not be infused through an IV line in which other solutions or medications are being administered.

Additional studies demonstrate that MEDI-546 is compatible with IV bags and ancillaries comprised of materials are presented in Table 4.5.4-1 and Table 4.5.4-2.

Table 4.5.4-1 Compatible Materials of Construction for IV Bags

IV Bag Diluent	Materials of Construction
0.9% saline	Glass
0.9% saline	Polyolefin copolymer, ethylene and propylene
0.9% saline	PVC and DEHP
0.9% saline	Polyethylene
0.9% saline	Ethylene polyvinyl acetate
0.9% saline	Polypropylene

DEHP = diocytl-phthalate; IV = intravenous; PVC = polyvinylchloride

Table 4.5.4-2 Compatible Materials of Construction for Ancillaries

Materials of Construction
Polyethylene
PVC with DEHP
PVC with 2-ethylhexyltrimellitate
Polybutadiene

DEHP = diocytl-phthalate; PVC = polyvinylchloride

4.5.4.1 Dose Calculation

All subjects will receive MEDI-546 300 mg administered as an IV infusion. Dose calculations for MEDI-546 Drug Product using the 100 and 150 mg/mL formulations are presented in Table 4.5.4.1-1.

[redacted]

4.5.4.2 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. MEDI-546 is supplied in cartons of either 10 vials (100 mg/mL formulation) or 3 vials (150 mg/mL formulation) per kit. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton). Each vial contains either 1.0 mL (100 mg/mL formulation) or 2.3 mL (150 mg/mL formulation) of a clear, colorless to slightly yellow liquid that is free from visible particles. Ensure that all vials within a kit are of the same dosage strength. The 100 and 150 mg/mL formulations may not be mixed to prepare a dose.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section for further instructions.

4.5.4.3 Dose Preparation Steps

[redacted]

[redacted] [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
					[redacted]	[redacted]

[redacted]
[redacted]

[redacted].

4.5.5 Treatment Administration

The first day of dosing is considered Day 1.

Every dose of investigational product should be administered using the following guidelines:

- Females of childbearing potential must have a negative urine pregnancy test prior to receiving investigational product.
- MEDI-546 must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product.
- MEDI-546 does not contain preservatives and any unused portion must be discarded. The dose of MEDI-546 must be prepared using aseptic technique. Total in-use storage time from needle puncture of the first vial of MEDI-546 for investigational product preparation to start of administration should not exceed 4 hours at room temperature or

24 hours at 2°C-8°C (36°F to 46°F). If storage time exceeds these limits, a new dose must be prepared from new vials.

- Administration should be performed using an extension line with a low protein-binding 0.2-µm in-line filter. The entire contents of the IV bag should be administered using an infusion pump over at least 30 minutes.
- MEDI-546 should be administered over at least 30 minutes. If a subject has a history of infusion reactions, MEDI-546 administration may be lengthened per the investigator's discretion. The subject's vital signs (temperature, blood pressure [BP], pulse rate, and respiratory rate) should be taken after the first 15 (± 5) minutes of infusion of investigational product into the subject and the subject should be assessed for signs of an infusion reaction.
- Immediately following the initial dosing, up to an additional 25 mL of saline will be given via infusion pump at the same pump speed utilized at the completion of the initial dosing.
- The duration of the MEDI-546 infusion and duration of MEDI-546 administration will be calculated as follows:
    - **Duration of Infusion:** The amount of time elapsed from the infusion start time to the infusion stop time. Infusion start time is defined as the time point where MEDI-546 is first infused into the subject. Infusion stop time is defined as the time point where the infusion pump completes infusion of MEDI-546, not including the saline flush.
        - For example: An infusion with a start time of 12:00 PM would have a duration of infusion recorded as at least 30 minutes (a time of at least 12:30 PM).
    - **Duration of Administration:** The amount of time elapsed from the infusion pump start time to the infusion pump stop time PLUS the time required to complete the additional flush of saline. The duration of administration will always be greater than the duration of infusion and will always include the additional flush of saline.
- Both the duration of the investigational product infusion and the duration of investigational product administration will be recorded.
- Subjects should not be premedicated unless they have had a prior infusion reaction to MEDI-546. However, if a prior infusion reaction has been documented, the investigator may elect to administer an antihistamine or acetaminophen/paracetamol prophylactically for the comfort and safety of the subject prior to subsequent infusions. Prophylactic use of glucocorticosteroids prior to subsequent infusions is not permitted.
- Because compatibility of MEDI-546 with IV medications and solutions other than 0.9% sodium chloride for injection, United States Pharmacopeia (USP), is not known, MEDI-546 solution should not be infused through an IV line in which other solutions or medications are being administered.

4.5.6 Monitoring of Dose Administration

Vital signs (temperature, BP, pulse rate, and respiratory rate) will be obtained with the subject in a sitting position and monitored at the following times:

- Shortly before the IV infusion (within 15 minutes of the beginning of the investigational product infusion)
- Every 15 [± 5] minutes during infusion
- Immediately after completion of administration of investigational product, including postdose saline flush (within 15 [± 5] minutes after completion of investigational product administration)
- At 30 [± 5] and 60 [± 5] minutes after completion of investigational product administration, and every 30 [± 5] minutes thereafter or until stable and ready for discharge (as judged by the investigator).

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.

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

4.5.6.1 Anaphylaxis, Hypersensitivity, and Infusion Reactions

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, such as investigational product.

For the purposes of this study, MedImmune is providing the following definition as a simple and rapid means to make the diagnosis of anaphylaxis during infusion with investigational product. This definition was a product of a symposium convened by the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network (Sampson et al, 2006).

In adults, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips, tongue and/or uvula) AND AT LEAST ONE OF THE FOLLOWING:
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
   - Reduced BP (see #3 below for definition) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):
   - Involvement of the skin-mucosal tissue (eg, generalized hives, itch, flush, swollen lips, tongue and/or uvula).
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
   - Reduced BP (see #3 below for definition) or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
   - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
3. Reduced BP after exposure to known allergen for that subject (minutes to several hours); for adults a systolic BP of less than 90 mm Hg or greater than 30% decrease from that subject's baseline BP (taken at or immediately prior to start of the infusion), whichever BP is lower.

For the purposes of this study, a hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both during infusion of investigational product (but does not meet the definition of anaphylaxis described above).

For the purposes of this study, an infusion reaction is defined as any other reaction occurring during infusion of investigational product or felt to be temporally related to the infusion within 24 hours of investigational product administration.

Subjects should not be premedicated unless they have had a prior infusion reaction to MEDI-546. However, if a prior infusion reaction has been documented, the investigator may elect to administer prophylactically an antihistamine and/or acetaminophen/paracetamol for the comfort and safety of the subject prior to subsequent infusions. Prophylactic use of glucocorticosteroids prior to subsequent infusions is not permitted.

An approach to these reactions based on severity of symptoms is given in Table 4.5.6.1-1, with suggested treatment options. Final treatment is at the discretion of the investigator and should reflect local standard of care.

Table 4.5.6.1-1 An Approach to Management of Anaphylactic, Hypersensitivity, and Infusion Reactions

Severity of Symptoms	Treatment	MEDI-546
Mild reactions (infusion and hypersensitivity) Mild infusion reactions such as headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mmHg change in systolic BP from pre-infusion measurement	• Evaluate subject, including close monitoring of vital signs • At the discretion of the investigator, treat subject, (for example) with: • Normal saline (~500-1000 mL/hour IV) and/or • Diphenhydramine 50 mg IV or equivalent and/or • Acetaminophen 500-650 mg or equivalent dose of paracetamol and/or • Topical antihistamines and/or low-potency topical corticosteroid preparations and/or • Anti-nausea medication, as needed	• Stop MEDI-546 infusion immediately • Option 1: Do not resume MEDI-546 infusion; OR at the discretion of the investigator, resume current MEDI-546 infusion under observation and complete infusion at no more than half the planned infusion rate • Option 2: Discontinue any further administration of MEDI-546; OR at the discretion of the investigator, continue future administrations and consider slowing infusion rate and pretreating subject 0.5-1.5 hours prior to MEDI-546 administration (for example) with: • Diphenhydramine 50 mg IV or equivalent • Acetaminophen 500-650 mg or equivalent dose of paracetamol

Table 4.5.6.1-1 An Approach to Management of Anaphylactic, Hypersensitivity, and Infusion Reactions

Severity of Symptoms	Treatment	MEDI-546
Moderate reactions (infusion) Infusion reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below)	• Evaluate subject, including close monitoring of vital signs • Treat subject (for example) with: • Normal saline (~500-1000 mL/hour IV) and/or • Diphenhydramine 50 mg IV or equivalent and/or • Acetaminophen 500-650 mg or equivalent dose of paracetamol and/or • Anti-nausea and/or antiemetic intramuscular, as needed	• Stop MEDI-546 infusion immediately • Option 1: Do not resume MEDI-546 infusion; OR based on risk/benefit evaluation, at the discretion of the investigator, resume current infusion under observation and at no more than half the planned infusion rate after treatment of current signs and symptoms as suggested (eg, normal saline and/or acetaminophen and/or topical antihistamines) **Additional options for future administration of MEDI-546** • Discontinue any further administrations of MEDI-546; OR • Further MEDI-546 infusions, at the discretion of the investigator, continue administration and consider slowing infusion rate and pretreating subject 0.5-1.5 hours prior to MEDI-546 administration (for example) with: • Diphenhydramine 50 mg IV or equivalent • Acetaminophen 500-650 mg or equivalent dose of paracetamol • Anti-nausea and/or antiemetic PO • Prior to next administration of MEDI-546, consider initiating at a slower infusion rate and pretreating subject 0.5-1.5 hours prior to next administration of MEDI-546 (for example) with: • Diphenhydramine 50 mg IV or equivalent • Acetaminophen 500-650 mg or equivalent dose of paracetamol • If moderate event recurs in the same subject, discontinue further MEDI-546 administration

Table 4.5.6.1-1 An Approach to Management of Anaphylactic, Hypersensitivity, and Infusion Reactions

Severity of Symptoms	Treatment	MEDI-546
Moderate hypersensitivity reactions Infusion reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mmHg change in systolic BP from pre-infusion measurement	• Evaluate subject, including close monitoring of vital signs • Treat subject (for example) with: • Normal saline (~500-1000 mL/hour IV) and/or • Diphenhydramine 50 mg IV or equivalent and/or • Acetaminophen 500-650 mg or equivalent dose of paracetamol and/or • IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20-40 mg	• Stop MEDI-546 infusion immediately • DO NOT resume current infusion • Discontinue any further administrations of MEDI-546 • Consider need for additional oral antihistamine administration or OCS administration to prevent reoccurrence of symptoms over subsequent 2-3 days

Table 4.5.6.1-1 An Approach to Management of Anaphylactic, Hypersensitivity, and Infusion Reactions

Severity of Symptoms	Treatment	MEDI-546
Severe Above plus fever with rigors, hypo- or hypertension with ≥ 40 mmHg change in systolic BP, signs of end organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope, incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor OR Life threatening 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	• Evaluate subject, including close monitoring of vital signs • Maintain airway, oxygen if available • Treat subject 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 intramuscular for more severe cases • IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20-40 mg • Diphenhydramine 50 mg IV or equivalent • Acetaminophen 500-650 mg or equivalent dose of paracetamol • Call emergency medical transport for transport to emergency hospital based on judgment of the investigator • Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine • Grade 4 event At the discretion of the investigator	• Stop MEDI-546 infusion immediately • Do not resume current infusion • Permanently discontinue MEDI-546 administration • Consider need for additional oral antihistamine administration or OCS administration to prevent reoccurrence of symptoms over subsequent 2-3 days

BP = blood pressure; IV = intravenous; OCS = oral corticosteroid; PO = orally; SC = subcutaneous

4.5.7 Treatment Compliance

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

4.6 Concomitant Medications

4.6.1 Permitted Non-SLE Concomitant Medications

Investigators may prescribe non-SLE concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 4.6.2.

The following concomitant medications are permitted from Day 1 through the end of the study for the treatment of AEs or for supportive care (eg, menstrual discomfort):

1. Prescription and over-the-counter medications (including analgesics and NSAIDs, etc.)
2. Herbal supplements/teas and vitamins
3. Increase in OCS treatment above a total dose > 40 mg/day for a dosing period > 14 days. Dosing with MEDI-546 may be continued, unless there is a safety concern. However, it should be noted that frequent steroid use above Study CD-IA-MEDI-546-1013 baseline for SLE disease control (> 2 times every 6 months, higher doses [> 40 mg/day], and/or longer duration than permitted by the protocol) after 12 months of open-label MEDI-546 should result in permanent discontinuation of MEDI-546 for failure to achieve a favorable benefit:risk profile.

All concomitant medications (SLE and non-SLE) taken during the study period should be recorded. All OCS's taken during the study for a burst or a taper must be identified if the OCS is being taken for an SLE condition or a non-SLE condition.

4.6.2 Excluded Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary if given from Day 1 to the end of the study.

1. Etanercept
2. Adalimumab, infliximab, or golimumab
3. Rituximab or certolizumab pegol
4. Azathioprine > 200 mg/day
5. Mycophenolate mofetil/mycophenolic acid > 2.0 g/day

6. Oral, SC, or intramuscular methotrexate > 25 mg/week
7. Any change in route of administration of oral, SC, or intramuscular methotrexate
8. Cyclophosphamide and leflunomide
9. IV corticosteroids
10. IFN therapy (alpha 2a & 2b, beta 1a & 1b, and pegylated IFNs alpha 2a & 2b)
11. Live or attenuated vaccines (the sponsor recommends that investigators ensure all subjects are up to date with required vaccinations prior to entry into the study)
12. Investigational agents
13. Biologics (including belimumab)
14. Plasmapheresis
15. Any Ig therapy
16. BCG vaccine

4.7 Subject Completion

An individual subject will be considered to have completed the study if the subject was followed up through 85 days post the subject's last dose (Section 4.9).

Subjects will be considered to have not completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.2.3).

4.8 Site Completion

Site completion is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study at the given site. All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon site completion of the study, as directed by the site monitor. The investigator will notify the IRB/IEC when the study has been completed at his/her site.

4.9 End of the Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

5 STUDY PROCEDURES

5.1 Schedule of Study Procedures

All subjects will be assigned a SID number and receive 300 mg MEDI-546 unless consent is withdrawn. The investigator must notify the sponsor or designee of 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 and any study-specific case report forms (CRFs) or logs designated for capturing protocol deviations, if applicable for the study. The investigator must comply with the applicable requirements related to the reporting of protocol deviations to the IRB/IEC.

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

A Schedule of Study Procedures is presented in Table 5.1-1 for the treatment period and in Table 5.1-2 for the 85-day follow-up period, followed by a description of each visit. A description of the study procedures is included in Section 5.2.

If Day 1 of this study occurs on the same day as Day 422 (+ 28 days) of Study CD-IA-MEDI-546-1013, then many of the procedures and samples only need to be collected one time and will be utilized for both studies (see Table 5.1-1 for more detailed information). However, the informed consent for this study must be signed prior to using any of the Study CD-IA-MEDI-546-1013 data.

If Day 1 of this study occurs 28 days after Day 422 of Study CD-IA-MEDI-546-1013, then Day 1 procedures and samples of this study will need to be collected (see Table 5.1-1 for more detailed information).

Table 5.1-1 Schedule of Study Procedures for the Treatment Period

Interval	Treatment Period					
	Day 1	Q4W	Q12W	Q24W	Q48W	LTV
Week	**0**	**4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152**	**12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144**	**24, 48, 72, 96, 120, 144**	**48, 96, 144**	**156**
Procedure / Visit Number	**V1**	**V2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39**	**V4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37**	**V7, 13, 19, 25, 31, 37**	**V13, 25, 37**	**V40**
Written informed consent/HIPAA information/ assignment of SID number	X [a]					
Verify eligibility criteria	X [b]					
SF-36v2 (should be completed prior to any clinical assessments)	X [b]			X		X
Concomitant medications	X [b]	X	X	X	X	X
Review medical history and add any AEs/SAEs/AESIs from Study CD-IA-MEDI-546-1013 (if appropriate)	X [b]					
Physical examination (For Day 1 assessment only: if Day 422 [+ 28 days] of Study CD-IA-MEDI-546-1013 occurs on the same day as Day 1 of this study, then the data only need to be collected one time and will be used for both studies)	X					X
Weight (For Day 1 assessment only: if Day 422 [+ 28 days] of Study CD-IA-MEDI-546-1013 occurs on the same day as Day 1 of this study, then the data only need to be collected one time and will be used for both studies)	X				X	
Vital signs	X [b]	X	X	X	X	X

Table 5.1-1 Schedule of Study Procedures for the Treatment Period

Interval	Treatment Period					
	Day 1	Q4W	Q12W	Q24W	Q48W	LTV
Week	**0**	**4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152**	**12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144**	**24, 48, 72, 96, 120, 144**	**48, 96, 144**	**156**
Procedure / Visit Number	**V1**	**V2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39**	**V4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37**	**V7, 13, 19, 25, 31, 37**	**V13, 25, 37**	**V40**
ECG (from Day 396 of Study CD-IA-MEDI-546-1013; required at Day 1 if not done at Day 396 of Study CD-IA-MEDI-546-1013)	X				X	X
Assessment of Cushingoid features (For Day 1 assessment only: if assessment of Cushingoid features was performed on Day 365 of Study CD-IA-MEDI-546-1013, then the data can also be used for Day 1 of this study)	X				X	
Blood sample collection for: (For the Day 1 samples only [excluding lipid profile]: if Day 422 [+ 28 days] of Study CD-IA-MEDI-546-1013 occurs on the same day as Day 1 of this study, then the samples only need to be collected one time and will be used for both studies.)						
Serum chemistry	X [b]	X (Weeks 4 and 8 only)	X			X
Hematology	X [b]	X (Weeks 4 and 8 only)	X			X
Lipid profile (Subjects will be required to fast for at least 8 hours prior to this assessment. If a subject has not fasted, the assessment should be performed under fasted conditions at the next visit.)		X (Week 4 only)			X	

Table 5.1-1 Schedule of Study Procedures for the Treatment Period

Interval	Treatment Period					
	Day 1	Q4W	Q12W	Q24W	Q48W	LTV
Week	**0**	**4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152**	**12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144**	**24, 48, 72, 96, 120, 144**	**48, 96, 144**	**156**
Procedure / Visit Number	**V1**	**V2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39**	**V4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37**	**V7, 13, 19, 25, 31, 37**	**V13, 25, 37**	**V40**
HBV DNA PCR TaqMan (Subjects with isolated hepatitis B core antibody positivity during Study CD-IA-MEDI-546-1013 or at any time during this study will be tested monthly for HBV DNA. To remain eligible for this study, the subject's HBV DNA levels must remain undetectable as per the central lab [ie, < 29 IU/mL HBV DNA detected]).	X [b]	X (if appropriate)				X
QFT-GIT test (TB testing, only if negative or if indeterminate at any visit during Study CD-IA-MEDI-546-1013)	X [b]		X [c]		X	X
SLEDAI-2K-associated lab tests (C3, C4, CH50, anti-dsDNA)	X [b]		X			X
Immunology profile (ANA, extractable nuclear antigens [RNP, Sm, SSA, SSB], quantitative immunoglobulins)	X [b]			X	X	X
Pap smear in females only					X [d]	
Predose sample Q12W-First Year: (For the Day 1 samples only: if Day 422 [+ 28 days] of Study CD-IA-MEDI-546-1013 occurs on the same day as Day 1 of this study, then the samples only need to be collected one time and will be used for both studies.)						
PK (MEDI-546 serum concentration)	X [b]		X (Weeks 12, 24, 36, 48 only)			

Table 5.1-1 Schedule of Study Procedures for the Treatment Period

Interval	Treatment Period					
	Day 1	Q4W	Q12W	Q24W	Q48W	LTV
Week	**0**	**4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152**	**12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144**	**24, 48, 72, 96, 120, 144**	**48, 96, 144**	**156**
Procedure / Visit Number	**V1**	**V2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39**	**V4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37**	**V7, 13, 19, 25, 31, 37**	**V13, 25, 37**	**V40**
PD (type I IFN signature 21-gene assay)	X [b]		X (Weeks 12, 24, 36, 48 only)			
IM (ADA to MEDI-546)	X [b]		X (Weeks 12, 24, 36, 48 only)			
Predose type I IFN signature 4-gene assay (diagnostic test)	X [b]					
Predose sample Q24W (starting at Week 72) After First Year:						
PK MEDI-546 serum concentration				X		X
PD (type I IFN signature 21-gene assay)				X		X
IM (ADA to MEDI-546)				X		X
Proteomics/biomarkers, 1st year Q12W (optional)	X		X (Weeks 12, 24 and 48 only)			
Proteomics/biomarkers, after 1st year Q24W (optional)				X		X
Urine sample collection: (For the Day 1 samples only: if Day 422 [+ 28 days] of Study CD-IA-MEDI-546-1013 occurs on the same day as Day 1 of this study, then the samples only need to be collected one time and will be used for both studies.)						
Urinalysis	X [b]		X			X

Table 5.1-1 Schedule of Study Procedures for the Treatment Period

Interval	Treatment Period					
	Day 1	Q4W	Q12W	Q24W	Q48W	LTV
Week	**0**	**4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152**	**12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144**	**24, 48, 72, 96, 120, 144**	**48, 96, 144**	**156**
Procedure / Visit Number	**V1**	**V2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39**	**V4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37**	**V7, 13, 19, 25, 31, 37**	**V13, 25, 37**	**V40**
Urine β-HCG (dipstick)	X [b]	X	X	X	X	X
SLEDAI-2K-associated tests: urine protein/ creatinine ratio	X [b]		X			X
Urine biomarker (optional)	X [b]		X			
Disease Evaluations						
SLEDAI-2K (For Day 1 SLEDAI-2K only: if Day 422 [+ 28 days] of Study CD-IA-MEDI-546-1013 occurs on the same day as Day 1 of this study, then the data only need to be collected one time and will be used for both studies.)	X [b]		X			X
SLICC/ACR Damage Index	X [b]			X		
Assess worsening and/or flare of SLE disease activity	X [b]	X				X
Assessment of AEs/SAEs/AESIs (nonserious AEs will only be captured during the first year of the subject's participation in the study; however, nonserious AEs that result in interruption of investigational product and/or discontinuation from the study will be captured at any time during the subject's participation in the study)	X [b]	X	X	X	X	X
Evaluate subject for signs and symptoms of TB using a TB surveillance form	X	X	X	X	X	X

Table 5.1-1 Schedule of Study Procedures for the Treatment Period

Interval	Treatment Period					
	Day 1	Q4W	Q12W	Q24W	Q48W	LTV
Week	**0**	**4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152**	**12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144**	**24, 48, 72, 96, 120, 144**	**48, 96, 144**	**156**
Procedure / Visit Number	**V1**	**V2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39**	**V4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37**	**V7, 13, 19, 25, 31, 37**	**V13, 25, 37**	**V40**
Investigational product administration (Q4W)	**X**	**X**	**X**	**X**	**X**	**X**

AE = adverse event; AESI = adverse event of special interest; ADA = anti-drug antibodies; ANA = antinuclear antibody; β-HCG = beta human chorionic gonadotropin; CH50 = 50% hemolytic complement; DNA = deoxyribonucleic acid; ds = double-stranded; ECG = electrocardiogram; HBV = hepatitis B virus; HIPAA = Health Insurance Portability and Accountability Act; IFN = interferon; IM = immunogenicity; LTV = Last Treatment Visit; Pap = Papanicolaou; PCR = polymerase chain reaction; PD = pharmacodynamic; PK = pharmacokinetic; Q4W = every 4 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; Q48W = every 48 weeks; QFT-GIT = QuantiFERON-TB Gold In-tube; RNP = ribonucleoprotein; SAE = serious adverse event; SF-36v2 = Short Form-36 Version 2; SID = subject identification; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; Sm = Smith; SSA = ; SSB = ; TB = tuberculosis; TBD = to be determined; V = visit.

[a] Informed consent needs to be signed prior to using any of the Study CD-IA-MEDI-546-1013 data for this study.

[b] These procedures need to be performed on the same day as investigational product administration on Day 1 or unless otherwise noted.

[c] Subjects whose QFT-GIT test result is indeterminate at Day 1 or at any time during this study must be retested Q12W for the duration of the trial; subjects whose test result is negative at Day 1 are to be tested annually.

[d] Only at Visit 37, Week 144.

Table 5.1-2 Schedule of Study Procedures for the 85-day Follow-up Period

Days After Last Dose	28 Days (± 7 Days)	59 Days (± 7 Days)	85 Days (± 7 Days)
Procedure / Visit Number	**V41/EDV (Safety Follow-up V1)**	**V42 (Safety Follow-up V2)**	**V43 (Safety Follow-up V3)**
SF-36v2			X
Concomitant medications	X	X	X
Vital signs	X	X	X
ECG			X
Evaluate subject for signs and symptoms of TB using a TB surveillance form	X	X	X
Blood sample collection for:			
Serum chemistry	X		X
Hematology	X		X
Lipid profile (Subjects will be required to fast for at least 8 hours prior to this assessment.)			X
SLEDAI-2K-associated lab tests (C3, C4, CH50, anti-dsDNA)	X		X
Immunology profile (ANA, extractable nuclear antigens [RNP, Sm, SSA, SSB], quantitative immunoglobulins)	X		X
PK MEDI-546 serum concentration	X		X
PD (type I IFN signature 21-gene assay)	X		X
IM (ADA to MEDI-546)	X		X
Proteomics/biomarkers, after 1st year Q24W (optional)	X		X
Urine sample collection			
Urinalysis	X		X
Urine β-HCG (dipstick)	X	X	X
SLEDAI-2K-associated tests: urine protein/creatinine ratio	X		X
Urine biomarker (optional)	X		X
Disease Evaluations			
SLEDAI-2K	X		X
SLICC/ACR Damage Index			X

Table 5.1-2 Schedule of Study Procedures for the 85-day Follow-up Period

Days After Last Dose	28 Days (± 7 Days)	59 Days (± 7 Days)	85 Days (± 7 Days)
Procedure / Visit Number	**V41/EDV (Safety Follow-up V1)**	**V42 (Safety Follow-up V2)**	**V43 (Safety Follow-up V3)**
Assess worsening and/or flare of SLE disease activity	X	X	X
Assessment of AEs/SAEs/AESIs (nonserious AEs will only be captured during the first year of the subject's participation in the study; however, nonserious AEs that result in interruption of investigational product and/or discontinuation from the study will be captured at any time during the subject's participation in the study)	X	X	X

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; ANA = antinuclear antibody; β-HCG = beta human chorionic gonadotropin; CH50 = 50% hemolytic complement; DNA = deoxyribonucleic acid; ds = double-stranded; ECG = electrocardiogram; EDV = Early Discontinuation Visit; IFN = interferon; IM = immunogenicity; PD = pharmacodynamic; PK = pharmacokinetic; Q24W = every 24 weeks; RNP = ribonuclear protein; SAE = serious adverse event; SF-36v2 = Short Form-36 Version 2; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; Sm = Smith; TB = tuberculosis; V = visit.

5.1.1 Pretreatment Period

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including Day 1 eligibility criteria. In this OLE study, the written informed consent will explain that certain specified clinical data results collected in Study CD-IA-MEDI-546-1013 may be used for pretreatment period purposes and to determine eligibility for Study CD-IA-MEDI-546-1145.

5.1.2 Treatment Period

The visit windows during the treatment period are ± 7 days; however, in this long-term study, this may not always be possible; therefore, the IVRS/IWRS will be programmed to ensure that consecutive doses are administered more than 14 days apart, which will not be considered a protocol deviation.

5.1.2.1 Week 0; Day 1: First Infusion (Visit 1)

These procedures should be performed before using any of the Study CD-IA-MEDI-546-1013 data for this study:

1. Obtain written informed consent and appropriate privacy act document authorization (eg, HIPAA)
2. Assign an SID number

These procedures should be performed on the same day as investigational product administration on Day 1:

3. Verify eligibility criteria
4. Administer Short Form-36 Version 2 (SF-36v2; should be completed prior to any clinical assessments)
5. Review medical history and add any AEs/serious adverse events (SAEs)/AESIs (if appropriate)
6. Record concomitant medications (if appropriate)
7. Electrocardiogram (ECG; data to be used from Day 396 of Study CD-IA-MEDI-546-1013; required at Day 1 if not done at Day 396 of Study CD-IA-MEDI-546-1013)
8. Assess for Cushingoid features (if this assessment was performed on Day 365 of Study CD-IA-MEDI-546-1013, then data can also be used for Day 1 of this study)

If Day 1 of this study occurs on the same day as Day 422 (+ 28 days) of Study CD-IA-MEDI-546-1013, then the following procedures and samples can be collected one time and can be utilized for both studies; if Day 1 of this study does not occur on the

same day as Day 422 (+ 28 days) of Study CD-IA-MEDI-546-1013, then the following procedures and samples should be collected at Day 1:

9. Perform physical examination (if applicable, record new findings as AEs or SAEs)
10. Measure weight
11. Collect **predose** blood samples
    - Serum chemistry
    - Hematology
    - Hepatitis B virus DNA polymerase chain reaction (PCR) TaqMan (subjects with isolated hepatitis B core antibody positivity during Study CD-IA-MEDI-546-1013 or at any time for the duration of this study will be tested monthly for HBV DNA. To remain eligible for this study, the subject's HBV DNA levels must remain undetectable as per the central lab [ie, < 29 IU/mL HBV DNA detected])
    - QuantiFERON-TB Gold (QFT-GIT; TB testing, only if negative or if indeterminate at any visit during Study CD-IA-MEDI-546-1013)
    - Immunology profile (antinuclear antibodies [ANA], extractable nuclear antigens [RNP, Sm, SSA, SSB], quantitative immunoglobulins)
    - Proteomics/biomarkers (optional)
    - Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K)-associated lab tests (C3, C4, 50% hemolytic complement [CH50], anti-dsDNA)
    - Pharmacokinetics (MEDI-546 serum concentration)
    - Type I IFN signature with 4-gene assay (one-time collection only)
    - Pharmacodynamics (type I IFN signature with 21-gene assay)
    - Immunogenicity (ADA to MEDI-546)
12. Collect urine samples:
    - Urinalysis
    - Urine beta-human chorionic gonadotropin (β-HCG); dipstick (females of childbearing potential only, ensure result is negative)
    - SLEDAI-2K-associated lab tests: urine protein/creatinine ratio
    - Urine biomarker (optional)
13. Perform SLEDAI-2K
14. Perform Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR)
15. Assess worsening and/or flare of SLE disease activity using SLE Increase in Disease Activity CRF and complete for SLE related AEs that are not serious, if applicable
16. Evaluate subject for signs and symptoms of TB using a TB surveillance form

17. Take vital signs before administration of investigational product (within 15 minutes of the beginning of the investigational product infusion)
18. Administer investigational product
    - Take vital signs (BP, pulse, respiration, and temperature) approximately every 15 (± 5) minutes during the infusion, immediately after completion of the infusion, approximately 30 (± 5) and 60 (± 5) minutes after completion of administration of investigational product, and every 30 (± 5) minutes thereafter or until stable and ready for discharge (as judged by the investigator)
19. Assess for AEs/SAEs/AESIs

5.1.2.2 Every 4 Weeks; Weeks 4 to 152: Second through Thirty-ninth Infusion (Visits 2 to 39)

The following procedures and assessments are to be performed **Q4W starting at Week 4 through Week 152**:

1. Record concomitant medications
2. Collect **predose** blood samples for:
    - Serum chemistry (Weeks 4 and 8 only)
    - Hematology (Weeks 4 and 8 only)
    - Lipid profile (Week 4 only; subjects will be required to fast for at least 8 hours prior to this assessment. If a subject has not fasted, the assessment should be performed under fasted conditions at the next visit)
    - Hepatitis B virus DNA PCR TaqMan (if appropriate; Subjects with isolated hepatitis B core antibody positivity during Study CD-IA-MEDI-546-1013 or at any time for the duration of this study will be tested monthly for HBV DNA. To remain eligible for this study, the subject's HBV DNA levels must remain undetectable as per the central lab [ie, < 29 IU/mL HBV DNA detected])
3. Collect **predose** urine sample for:
    - Urine β-HCG (dipstick; females of childbearing potential only, ensure result is negative)
4. Assess worsening and/or flare of SLE disease activity using SLE Increase in Disease Activity CRF and complete for SLE related AEs that are not serious, if applicable
5. Evaluate subject for signs and symptoms of TB using a TB surveillance form
6. Take vital signs before administration of investigational product (within 15 minutes of the beginning of the investigational product infusion)
7. Administer investigational product
    - Take vital signs (BP, pulse, respiration, and temperature) approximately every 15 (± 5) minutes during the infusion, immediately after completion of the infusion, approximately 30 (± 5) and 60 (± 5) minutes after completion of administration of

investigational product, and every 30 (± 5) minutes thereafter or until stable and ready for discharge (as judged by the investigator)

8. Assess for AEs/SAEs/AESIs (nonserious AEs will only be captured during the first year of the subject's participation in the study; however, nonserious AEs that result in interruption of investigational product and/or discontinuation from the study will be captured at any time during the subject's participation in the study)

5.1.2.3 Every 12 Weeks; Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144 (Visits 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, and 37)

In addition to procedures and assessments performed Q4W, the following are to be performed **every 12 weeks (Q12W)**:

1. Collect **predose** blood samples for:
   - Serum chemistry
   - Hematology
   - QuantiFERON-TB Gold (QFT-GIT; TB testing, only if indeterminate at any visit during Study CD-IA-MEDI-546-1013)
   - SLEDAI-2K-associated lab tests (C3, C4, CH50, anti-dsDNA)
   - Pharmacokinetics (MEDI-546 serum concentration; Weeks 12, 24, 36 and 48 only)
   - Pharmacodynamics (type I IFN signature with 21-gene assay; Weeks 12, 24, 36 and 48 only)
   - Immunogenicity (ADA to MEDI-546; Weeks 12, 24, 36 and 48 only)
   - Proteomics/biomarkers (Weeks 12, 24 and 48 only; optional)
2. Collect urine sample for:
   - Urinalysis
   - SLEDAI-2K-associated lab tests: urine protein/creatinine ratio
   - Urine biomarker (optional)
3. Perform SLEDAI-2K

5.1.2.4 Every 24 Weeks; Weeks 24, 48, 72, 96, 120 and 144 (Visits 7, 13, 19, 25, 31, and 37)

1. Administer SF-36v2 (should be completed prior to any clinical assessments)
2. Immunology profile (ANA, extractable nuclear antigens [RNP, Sm, SSA, SSB], quantitative immunoglobulins)
3. Perform SLICC/ACR Damage Index

In addition to procedures and assessments performed Q4W, the following are to be performed **every 24 Weeks (Q24W)** starting at Week 72:

4. Collect **predose** blood samples for:
   - Pharmacokinetics (MEDI-546 serum concentration)
   - Pharmacodynamics (type I IFN signature with 21-gene assay)
   - Immunogenicity (ADA to MEDI-546)
   - Proteomics/biomarkers (optional)

5.1.2.5 Every 48 Weeks; Weeks 48, 96, and 144 (Visits 13, 25, and 37)

In addition to procedures and assessments performed Q4W, the following are to be performed every 48 weeks (Q48W) starting at Week 48:

1. Record weight
2. Assess for Cushingoid features
3. Perform Papanicolaou (Pap) smear examination in females only (only at Visit 37, Week 144)
4. Perform ECG
5. Collect blood samples for:
   - Lipid profile (Subjects will be required to fast for at least 8 hours prior to this assessment. If a subject has not fasted, the assessment should be performed under fasted conditions at the next visit)
   - Immunology profile (ANA, extractable nuclear antigens [RNP, Sm, SSA, SSB], quantitative immunoglobulins)

5.1.2.6 Week 156; Last Treatment Visit (Visit 40)

1. Administer SF-36v2 (should be completed prior to any clinical assessments)
2. Perform physical examination
3. Perform ECG
4. Take vital signs (within 15 minutes of the beginning of the investigational product infusion)
5. Record concomitant medications
6. Collect **predose** blood samples for:
   - Serum chemistry
   - Hematology
   - Hepatitis B virus DNA PCR TaqMan (Subjects with isolated hepatitis B core antibody positivity during Study CD-IA-MEDI-546-1013 or at any time for the

duration of this study will be tested monthly for HBV DNA. To remain eligible for this study, the subject's HBV DNA levels must remain undetectable as per the central lab [ie < 29 IU/mL HBV DNA detected])

- QFT-GIT test (only if negative or if indeterminate at any visit during Study CD-IA-MEDI-546-1013)
- SLEDAI-2K-associated lab tests (C3, C4, CH50, anti-dsDNA)
- Immunology profile (ANA, extractable nuclear antigens [RNP, Sm, SSA, SSB], quantitative immunoglobulins)
- Pharmacokinetics (MEDI-546 serum concentration)
- Pharmacodynamics (type I IFN signature with 21-gene assay)
- Immunogenicity (ADA to MEDI-546)
- Proteomics/biomarkers (optional)

7. Collect urine sample for:
   - Urinalysis
   - Urine β-HCG; dipstick (females of childbearing potential only, ensure result is negative)
   - SLEDAI-2K-associated lab tests: urine protein/creatinine ratio
8. Assess worsening and/or flare of SLE disease activity using SLE Increase in Disease Activity CRF and complete for SLE related AEs that are not serious, if applicable
9. Perform SLEDAI-2K
10. Evaluate subject for signs and symptoms of TB using a TB surveillance form
11. Administer investigational product
    - Take vital signs (BP, pulse, respiration, and temperature) approximately every 15 (± 5) minutes during the infusion, immediately after completion of the infusion, approximately 30 (± 5) and 60 (± 5) minutes after completion of administration of investigational product, and every 30 (± 5) minutes thereafter or until stable and ready for discharge (as judged by the investigator).
12. Assess for AEs/SAEs/AESIs (nonserious AEs will only be captured during the first year of the subject's participation in the study; however, nonserious AEs that result in interruption of investigational product and/or discontinuation from the study will be captured at any time during the subject's participation in the study)

5.1.3 Follow-up Period

5.1.3.1 28 Days after the Last Dose (+/- 7 Days): First Safety Follow-up Visit or Early Discontinuation Visit (Visit 41)

1. Record concomitant medications
2. Take vital signs
3. Collect blood samples for:

- Serum chemistry
- Hematology
- SLEDAI-2K-associated lab tests (C3, C4, CH50 complement, anti-dsDNA)
- Immunology profile (ANA, extractable nuclear antigens [RNP, Sm, SSA, SSB], quantitative immunoglobulins)
- Pharmacokinetics (MEDI-546 serum concentration)
- Pharmacodynamics (type I IFN signature with 21-gene assay)
- Immunogenicity (ADA to MEDI-546)
- Proteomics/biomarkers (optional)

4. Collect urine sample for:
    - Urinalysis
    - Urine β-HCG (dipstick; females of childbearing potential only, ensure result is negative)
    - SLEDAI-2K-associated lab tests: urine protein/creatinine ratio
    - Urine biomarker (optional)
5. Perform SLEDAI-2K
6. Assess worsening and/or flare of SLE disease activity using SLE Increase in Disease Activity CRF and complete for SLE related AEs that are not serious, if applicable.
7. Evaluate subject for signs and symptoms of TB using a TB surveillance form
8. Assess for AEs/SAEs/AESIs (nonserious AEs will only be captured during the first year of subject's participation in the study; however, nonserious AEs that result in interruption of investigational product and/or discontinuation from the study will be captured at any time during the subject's participation in the study)

5.1.3.2 59 Days after the Last Dose (+/- 7 Days): Second Safety Follow-up Visit (Visit 42)

1. Record concomitant medications
2. Take vital signs
3. Collect urine sample for:
    - Urine β-HCG (dipstick, females of childbearing potential only, ensure result is negative)
4. Assess worsening and/or flare of SLE disease activity using SLE Increase in Disease Activity CRF and complete for SLE related AEs that are not serious, if applicable
5. Evaluate subject for signs and symptoms of TB using a TB surveillance form
6. Assess for AEs/SAEs/AESIs (nonserious AEs will only be captured during the first year of subject's participation in the study; however, nonserious AEs that result in interruption

of investigational product and/or discontinuation from the study will be captured at any time during the subject's participation in the study)

5.1.3.3 85 Days after the Last Dose (+/- 7 Days): Third Safety Follow-up Visit (Visit 43)

1. Administer SF-36v2 (should be completed prior to any clinical assessments)
2. Record concomitant medications
3. Take vital signs
4. Perform ECG
5. Collect blood samples for:
   - Serum chemistry
   - Hematology
   - Lipid profile
   - SLEDAI-2K-associated lab tests (C3, C4, CH50, anti-dsDNA)
   - Immunology profile (ANA, extractable nuclear antigens [RNP, Sm, SSA, SSB], quantitative immunoglobulins)
   - Pharmacokinetics (MEDI-546 serum concentration)
   - Pharmacodynamics (type I IFN signature with 21-gene assay)
   - Immunogenicity (ADA to MEDI-546)
   - Proteomics/biomarkers (optional)
6. Collect urine sample for:
   - Urinalysis
   - Urine β-HCG (dipstick; females of childbearing potential only, ensure result is negative)
   - SLEDAI-2K-associated lab tests: urine protein/creatinine ratio
   - Urine biomarker (optional)
7. Perform SLEDAI-2K
8. Perform SLICC/ACR Damage Index
9. Assess worsening and/or flare of SLE disease activity using SLE Increase in Disease Activity CRF and complete for SLE related AEs that are not serious, if applicable
10. Evaluate subject for signs and symptoms of TB using a TB surveillance form
11. Assess for AEs/SAEs/AESIs (nonserious AEs will only be captured during the first year of the subject's participation in the study; however, nonserious AEs that result in interruption of investigational product and/or discontinuation from the study will be captured at any time during the subject's participation in the study)

5.1.4 Unscheduled Visit

1. Perform physical examination (if applicable, record new findings as AEs or SAEs)
2. Record concomitant medications
3. Take vital signs
4. Collect blood samples for:
    - Serum chemistry
    - Hematology
    - Lipid profile (Subjects will be required to fast for at least 8 hours prior to this assessment. If a subject has not fasted, the assessment should be performed under fasted conditions at the next visit)
    - SLEDAI-2K-associated lab tests (C3, C4, CH50, anti-dsDNA)
    - Pharmacokinetics (MEDI-546 serum concentration)
    - Immunogenicity (ADA to MEDI-546)
5. Collect urine sample for:
    - Urinalysis
    - Urine β-HCG (if appropriate; dipstick; females of childbearing potential only, ensure result is negative)
    - SLEDAI-2K-associated lab tests: urine protein/creatinine ratio
    - Urine biomarker (optional)
6. Perform SLEDAI-2K
7. Perform SLICC/ACR Damage Index
8. Assess worsening and/or flare of SLE disease activity using SLE Increase in Disease Activity CRF and complete for SLE related AEs that are not serious, if applicable
9. Evaluate subject for signs and symptoms of TB using a TB surveillance form
10. Assess for AEs/SAEs/AESIs (nonserious AEs will only be captured during the first year of the subject's participation in the study; however, nonserious AEs that result in interruption of investigational product and/or discontinuation from the study will be captured at any time during the subject's participation in the study)

5.2 Description of Study Procedures

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

5.2.1 Medical History

A complete medical history by body system will be documented for each subject and will include any viral reactivation events as well as the subject's full SLE and non-SLE history. The SLE history includes all previous manifestations of SLE including SLE medication history. Only new events or worsening of previous events that occur between Day 422 of Study CD-IA-MEDI-546-1013 and prior to signing of informed consent of Study CD-IA-MEDI-546-1145 should be recorded in the Medical History CRF. On Day 1, the medical history will be reviewed and any changes will be documented, if applicable.

5.2.2 Physical Examination, ECG, Weight, Cushingoid Features, and Pap Smear

A complete physical examination will be performed at intervals designated in the schedule of study procedures and include the following examinations: head, eyes, ears, nose and throat, lungs, heart, abdomen, joints, muscles and soft tissues, neurologic system, skin, and lymph nodes; body weight will be captured according to the Schedule of Study Procedures (Table 5.1-1). Medically significant changes from Day 1 physical examination will be recorded as AEs.

A computerized 12-lead ECG will be performed according to the Schedule of Study Procedures (Table 5.1-1 and Table 5.1-2). The investigator or qualified designee will review and indicate if the ECG is normal or abnormal. Any medically significant changes from the Study CD-IA-MEDI-546-1013 Day 396 ECG will be recorded as an AE.

Subjects will be assessed for Cushingoid features at Day 1 (if appropriate) and at Q48W. Features, such as moon face, buffalo hump, purple or violaceous striae, central obesity, hirsutism, acne, easy bruising, and fragile skin, will be captured separately to evaluate whether resolution of same can occur over time with OCS reduction.

A Pap smear will be performed in females only at Week 144 (Visit 37). Subjects with an abnormal Pap smear result of high-grade squamous intraepithelial lesion (CIN-3/CIN III carcinoma in situ) or endocervical adenocarcinoma in situ will discontinue investigational product. In the event a female subject discontinues prematurely, a repeat Pap smear must be performed as part of the Early Discontinuation Visit.

5.2.3 Vital Signs

Vital signs (temperature, BP, pulse rate, and respiratory rate) will be obtained at each study visit. On infusion days, subjects will be monitored for vital signs taken in a sitting position at the following times:

- Shortly before the IV infusion (within 15 minutes of the beginning of the infusion)
- Every 15 (± 5) minutes during the infusion
- Immediately after completion of MEDI-546 infusion, including post-dose saline flush (within 15 minutes [± 5] after completion of MEDI-546 infusion)
- At 30 (± 5) and 60 (± 5) minutes after completion of MEDI-546 infusion, and every 30 (± 5) minutes thereafter or until stable and ready for discharge (as judged by the investigator).

If anaphylaxis, a hypersensitivity reaction, or an infusion-related reaction occurs during the IV infusion, vital signs will be taken more frequently, based on investigator judgment and as warranted by the severity of the reaction (see Section 4.5.6.1).

5.2.4 Tuberculosis Testing

A QFT-GIT will be performed at Day 1 for all subjects who tested negative or indeterminate at Day 337 in Study CD-IA-MEDI-546-1013. If a subject missed being tested at Day 1, a QFT-GIT should be performed at the next scheduled visit and then per protocol. An annual TB screen is not required for subjects who have tested positive and have been treated for latent TB in Study CD-IA-MEDI-546-1013.

Upon approval of Study CD-IA-MEDI-546-1145 Protocol Amendment 4, any subject whose last QFT-GIT result was negative or indeterminate (whether in this study or in Study CD-IA-MEDI-546-1013) and has not had a QFT-GIT performed in the previous year (from local approval date) should have it performed at the next scheduled visit and then per protocol.

All subjects must be evaluated by the physician for clinical signs/symptoms of active TB prior to each scheduled infusion visit using a TB surveillance form. If the evaluation raises suspicion that a subject may have a new or reactivated TB, an immediate and thorough investigation should be undertaken, including where possible, consultation with experts specializing in TB. Please note that TB in immunocompromised subjects may present as disseminated disease or with extrapulmonary features and should be referred for appropriate treatment.

5.2.4.1 Indeterminate Results

A newly indeterminate QFT-GIT test at Day 1 for subjects who had a negative result in Study CD-IA-MEDI-546-1013 must be repeated as soon as possible at least one time by the central laboratory. If the result remains indeterminate, a chest radiograph shows no evidence of active TB, there are no signs or symptoms of active TB, no recent contact with anyone

with active TB, and there is no history of latent (unless diagnosed with documentation of completion of appropriate treatment) or active TB, the subject may be enrolled in Study CD-IA-MEDI-546-1145. The subject will have additional QFT-GIT testing performed Q12W if the result remains indeterminate. If the subject has been in contact with anyone with active TB, or if the subject shows signs or symptoms of active TB, the subject should be referred to a physician specializing in TB to undergo additional evaluation prior to randomization and, if warranted, receive appropriate treatment for latent TB at or before the first administration of investigational product.

A QFT-GIT test will be performed at Day 1 for subjects whose results in Study CD-IA-MEDI-546-1013 were indeterminate and remain indeterminate in this study. If the result remains indeterminate, the chest radiograph from Study CD-IA-MEDI-546-1013 shows no evidence of active TB, there are no signs or symptoms of active TB, there has been no recent contact with anyone with active TB, and there is no history of latent (unless diagnosed with documentation of completion of appropriate treatment) or active TB, the subject may be enrolled in Study CD-IA-MEDI-546-1145. The subject will have additional QFT-GIT testing performed Q12W if the result remains indeterminate. If the subject has been in contact with anyone with active TB, or if the subject shows signs or symptoms of active TB, the subject should be referred to a physician specializing in TB to undergo additional evaluation prior to randomization and, if warranted, receive appropriate treatment for latent TB at or before the first administration of investigational product.

5.2.4.2 Positive Results

If, during the study, a subject is determined to have a positive QFT-GIT test result, the local country guidelines should be consulted for acceptable anti-TB treatment regimens. If no local guidelines exist for immunocompromised individuals, then USA guidelines must be followed:

To aid in the early detection of new or reactivated TB, subjects will be evaluated for signs and symptoms of TB at every visit (prior to drug infusion) using a TB surveillance form. If the evaluation raises suspicion that a subject may have a new or reactivated TB infection, an immediate and thorough investigation should be undertaken, including where possible, consultation with experts specializing in TB. Please note that TB in immunocompromised subjects may present as disseminated disease or with extrapulmonary features and should be referred for appropriate treatment.

A subject must be withdrawn from study treatment if they are diagnosed with active TB, if they prematurely discontinue treatment for latent TB, or if they are noncompliant with latent TB treatment.

5.2.5 Clinical Laboratory Tests

Clinical laboratory safety tests will be performed in a central clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Subjects will be required to fast for at least 8 hours prior to the assessment of lipid profile (high-density lipoprotein [HDL], low-density lipoprotein [LDL], cholesterol, and triglycerides) according to the Schedule of Study Procedures (Table 5.1-1 and Table 5.1-2).

The following clinical laboratory tests will be performed (see Table 5.1-1 and Table 5.1-2 for the schedule of tests):

Serum Chemistry

- Calcium
- Chloride
- Potassium
- Sodium
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Alkaline phosphatase (ALP)
- Gamma glutamyl transferase (GGT)
- Blood urea nitrogen (BUN)
- Creatinine
- Total bilirubin (reflexively fractionated if elevated)
- Glucose
- Albumin
- Creatine kinase (CK)

Note for serum chemistries: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Bilirubin
- Microscopy including WBC/high power field (HPF), RBC/HPF

Pregnancy Test (females of childbearing potential only)

- Urine human chorionic gonadotropin (HCG)

Note: Any female subject who is postmenopausal based on documented results from the serum follicle-stimulating hormone test will not require urine HCG tests in this study. Any female subject who feels that they have had a change in status to postmenopausal at any point during this study can request a serum follicle-stimulating hormone test. If the results show that the subject is postmenopausal, then the subject will not require any further urine HCG tests.

Additional Tests

- Lipid profile (HDL, LDL, cholesterol, triglycerides, direct LDL when triglycerides are > 400 mg/dL) requiring a fasting blood sample of at least 8 hours
- Immunology profile: ANA, extractable nuclear antigen (RNP, Sm, SSA, SSB), quantitative immunoglobulins
- Isolated HBc with HBV DNA detected by reflex testing at any time during Study CD-IA-MEDI-546-1013 or at any time for the duration of this study. To remain eligible for this study, the subject's HBV DNA levels should remain undetectable as per the central lab (ie, < 29 IU/mL HBV DNA detected).

SLEDAI-2K-related Laboratory Tests

- C3
- C4
- CH50 complement
- Anti-dsDNA
- Urine protein/creatinine ratio

5.2.6 Optional Urine Biomarker Testing

Urine will be collected for exploratory studies during visits specified in the Schedule of Study Procedures (see Table 5.1-1 and Table 5.1-2). These studies will include but are not limited to SLE biomarker testing and may serve as an ideal source for biomarkers of renal diseases. Urine for exploratory studies will only be collected from subjects who provide written consent for this procedure. A subject may withdraw their consent to have their urine samples used for exploratory studies at any time. Urine for exploratory studies will be analyzed at a central laboratory using established methods.

5.2.7 Pharmacokinetic Evaluation and Methods

Details for collection, aliquoting, storage, and shipment of serum samples for PK evaluations are presented in a separate Laboratory Manual. All PK laboratory evaluations will be performed by MedImmune or a contract laboratory. MEDI-546 serum concentrations will be measured by electrochemiluminescent (ECL) immunoassay at multiple time points as indicated in the Schedule of Study Procedures (Table 5.1-1 and Table 5.1-2). Sera that are collected may be used for additional PK analyses.

A subject should not have predose PK samples redrawn after administration of MEDI-546.

5.2.8 Immunogenicity Evaluation and Methods

Details for collection, aliquoting, storage, and shipment of serum samples for IM evaluations are presented in a separate Laboratory Manual. All IM laboratory evaluations will be performed by MedImmune or a contract laboratory. MEDI-546 antibody detection will be measured using an ECL bridging immunoassay at multiple time points as indicated in the Schedule of Study Procedures (Table 5.1-1 and Table 5.1-2). Sera that are collected may be used for additional MEDI-546 antibody assays.

5.2.9 Optional Proteomics/Biomarkers

Serum will be collected for exploratory correlative studies during visits specified in the Schedule of Study Procedures (see Table 5.1-1 and Table 5.1-2). These studies will include the analyses of protein analytes associated with inflammatory pathways and SLE. Serum for proteomics/biomarkers will only be collected from subjects who provide written consent for this procedure. A subject may withdraw their consent to have their serum samples used for exploratory correlative studies at any time.

[redacted]

[redacted]

5.2.11 Pharmacodynamic Assay using 21-gene Assay

[redacted]

5.2.12 Disease Evaluation and Methods

5.2.12.1 Systemic Lupus Erythematosus Disease Activity Index-2000

The SLEDAI-2K index consists of a list of organ manifestations, each with a definition. A certified investigator or designated physician will complete the SLEDAI-2K assessment and decide whether each manifestation is "present" or "absent" in the last 4 weeks. The assessment also includes the collection of whole blood for analysis of CH50, C3, C4, and anti-dsDNA.

The SLEDAI-2K assessment consists of 24 SLE-related items. It is a weighted instrument, in which descriptors are multiplied by a particular organ's "weight." For example, renal descriptors are multiplied by 4 and central nervous descriptors by 8 and these weighted organ manifestations are totaled into the final score. The SLEDAI-2K score range is 0-105 points with 0 indicating inactive disease. The SLEDAI-2K scores are valid, reliable, and sensitive clinical assessments of SLE disease activity. The SLEDAI-2K calculated using a timeframe of 30 days prior to a visit for clinical and laboratory values has been shown to be similar to the SLEDAI-2K with a 10-day window (Touma et al, 2010). A timeframe of 28 days will be used in this study.

The "Clinical" SLEDAI-2K score is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic measures. Its use may permit earlier clinical decisions to be made without waiting for immunologic measures (including anti-dsDNA and C3, C4 and CH50 complement levels). However, in any circumstance where the "Clinical" SLEDAI-2K score is used, sites must subsequently

update the SLEDAI-2K assessment when laboratory data become available so that the full SLEDAI-2K score is made available to the sponsor.

Anyone assessing the SLEDAI-2K at the sites must have had appropriate training prior to conducting the SLEDAI-2K.

5.2.12.2 Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index was developed to assess irreversible damage in SLE patients independently of its cause (ie, SLE activity, therapy, comorbidities), but occurring after disease onset. Damage (ie, irreversible impairment since onset of SLE) is usually defined as a clinical feature that must be continuously present for at least 6 months to score. In addition, some irreversible events such as myocardial infarction or a cerebrovascular accident score as damage on their occurrence. Damage is defined for 12 organ systems: peripheral vascular (0-5); ocular (0-2); neuropsychiatric (0-6); renal (0-3); pulmonary (0-5); cardiovascular (0-6); gastrointestinal (0-6); musculoskeletal (0-7); skin (0-3); endocrine (diabetes; 0-1); gonadal (0-1); and malignancies (0-2). Damage over time can be stable or increase, theoretically to a maximum of 47 points (Stoll et al, 2004).

5.2.13 Adverse Events of Special Interest

The investigator is required to assess for AESIs. The investigator should use medical or scientific judgment in deciding whether the identified AESI is serious or nonserious. An AESI that meets one of the seriousness outcomes listed in Section 6.1.2 will be treated as an SAE for the purposes of follow-up responsibility and safety reporting. A nonserious AESI will be treated as an AE.

5.2.14 SLE Flares and Increase in SLE Disease Activity

The worsening and/or flare of SLE disease activity will be captured in the disease activity assessments or other study-specific CRFs (ie, SLE Increase in Disease Activity CRF), and not recorded as an AE, unless it meets the definition for an SAE or AESI. The SLE Increase in Disease Activity CRF does not need to be completed for SAEs of SLE Increase in Disease Activity.

5.2.15 Patient-reported Outcomes

5.2.15.1 Short Form-36 Version 2

The SF-36v2 is a general HRQL instrument that consists of 36 items (see Appendix 7). These 36 items yield 8 domains of functional health and well-being. These domains include Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health. The 8 domains can further be combined to provide 2 summary measures: 1) Physical Component Summary (PCS); and 2) Mental Component Summary (MCS). It is a validated instrument for measuring a person's general health status over the past 4 weeks (Ware et al, 2008). The range of SF-36v2 score and scales is 0-100, with a higher score indicating better HRQL. Scale scores and the 2 summary measures are standardized to have a mean score of 50 and a standard deviation of 10. The SF-36v2 should be completed prior to any clinical assessments.

5.2.16 Estimate of Volume of Blood to Be Collected

An estimate of blood volumes for each visit during the study is provided in Table 5.2.16-1.

Table 5.2.16-1 Estimated Volume of Blood to be Collected per Visit

Visit/Week	Estimated Blood Volume (mL)
Visit 1/Week 0	72.5 mL
Visit 2/Week 4	4.5 mL
Visit 3/Week 8	4.5 mL
Visit 4/Week 12	28.5 mL
Visit 7/Week 24	29.5 mL
Visit 10/Week 36	22 mL
Visit 13/Week 48	32.5 mL
Visit 16/Week 60	7 mL
Visit 19/Week 72	32 mL
Visit 22/Week 84	9.5 mL
Visit 25/Week 96	32.5 mL
Visit 28/Week 108	7 mL
Visit 31/Week 120	32 mL
Visit 34/Week 132	9.5 mL
Visit 37/Week 144	29.5 mL
Visit 40/LTV Week 156	40 mL
Visit 41/EDV (Safety Follow-up Visit 1)	29.5 mL
Visit 43 (Safety Follow-up Visit 3)	29.5 mL
Unscheduled/Optional Visit	44.5 mL

Table 5.2.16-1 Estimated Volume of Blood to be Collected per Visit

Visit/Week	Estimated Blood Volume (mL)
Total Volume	496.5 mL

EDV = Early Discontinuation Visit; LTV = Last Treatment Visit.

6 ASSESSMENT OF SAFETY

6.1 Safety Parameters

6.1.1 Adverse Events

The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

- Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE. The worsening and/or flare of SLE disease activity will be captured in the disease activity assessments or other study-specific CRFs (ie, SLE Increase in Disease Activity CRF), and not recorded as an AE, unless it meets the definition for an SAE or AESI. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine RBC increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

Nonserious AEs will only be captured during the first year of subject's participation in the study; however, nonserious AEs that result in interruption of investigational product and/or discontinuation from the study will be captured at any time during the subject's participation in the study. Serious adverse events and AESIs will be captured throughout the entire study participation.

6.1.2 Serious Adverse Events

An 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 may have led to death.

- 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.

- Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive

treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

6.1.3 Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the investigational product and requires close monitoring. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

Both serious and nonserious AESIs will be captured at any time during the subject's participation in the study.

6.1.3.1 Hepatic Function Abnormality

Adverse events of hepatic function abnormality of special interest to the sponsor are defined as any increase in ALT or AST to greater than 3 × upper limit of normal (ULN) **and concurrent** increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

If ALT or AST is greater than 3 × ULN, please refer to Guidance for Abnormal Liver Function Tests Management in Appendix 8.

6.1.3.2 New or Reactivated and Latent TB Infection

For the purposes of this study, new or reactivated TB infection is defined as any new or reactivated clinical pulmonary or extra-pulmonary infection with the *Mycobacterium tuberculosis* bacterium, with associated clinical signs/symptoms and/or other evidence (radiologic, clinical laboratory, microbiologic) of active infection. Latent TB infection in this study is defined as a new positive and confirmed QFT-GIT test result with no evidence of active TB.

6.1.3.3 Herpes Zoster Infection

For the purposes of this study, herpes zoster infection is defined as an infection caused by reactivation of the varicella zoster virus from a previous chickenpox infection, with typical manifestations of painful herpetiform vesicles on an erythematous base. The manifestations

are usually preceded by radicular pain and confined to cutaneous surfaces innervated by one sensory nerve, but sometimes involve multiple dermatomes, or can be generalized and/or can involve non-cutaneous organs.

6.1.3.4 Malignancy

For the purposes of this study, malignancy is defined as a malignant neoplasm of any type, including solid tumors and hematologic malignancies, typically characterized by cells with abnormal features, uncontrolled rapid growth with invasive and/or metastatic tendencies and diagnosed based on standard pathologic and clinical assessments. The nature, extent, and type (subtype) of tumor should be characterized, as clinically appropriate, for evaluation and treatment. This does not include benign neoplasms.

6.1.3.5 Infusion, Hypersensitivity, and Anaphylactic Reactions

Infusion Reactions

For the purposes of this study, an infusion reaction is defined as any other reaction occurring during infusion of investigational product or felt to be temporally related to the infusion within 24 hours of investigational product administration (see Section 4.5.6.1).

Hypersensitivity Reactions

For the purposes of this study, a hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both during infusion of investigational product (but does not meet the definition of anaphylaxis as described in Section 4.5.6.1).

Anaphylactic Reactions

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, such as investigational product.

For the purposes of this study, MedImmune is providing the following definition as a simple and rapid means to make the diagnosis of anaphylaxis during infusion with investigational product. This definition was a product of a symposium convened by the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network (Sampson et al, 2006).

In adults, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips, tongue and/or uvula) AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
- Reduced BP (see #3 below for definition) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

- Involvement of the skin-mucosal tissue (eg, generalized hives, itch, flush, swollen lips, tongue and/or uvula).
- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
- Reduced BP (see #3 below for definition) or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

Reduced BP after exposure to known allergen for that subject (minutes to several hours); for adults a systolic BP of less than 90 mm Hg or greater than 30% decrease from that subject's baseline BP (taken at or immediately prior to start of the infusion), whichever BP is lower.

See Section 4.5.6.1 for infusion related event categorization and accompanying table for suggested guidelines for treatment.

6.1.3.6 Vasculitis

For the purposes of this study, vasculitis is defined as an inflammatory disorder involving the vasculature and characterized by typical clinical signs/symptoms (along with clinical laboratory testing, or other diagnostic testing and pathology findings) consistent with the diagnosis. Underlying causes should be identified, such as systemic inflammatory syndromes, wherever possible.

6.2 Assessment of Safety Parameters

6.2.1 Assessment of Severity

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

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

6.2.2 Assessment of Relationship

6.2.2.1 Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered “not related” to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

6.2.2.2 Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

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

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

6.3 Recording of Safety Parameters

6.3.1 Recording of Adverse Events and Serious Adverse Events

Adverse events will be recorded on the CRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the

event meets criteria of an SAE and therefore requires immediate notification to MedImmune Patient Safety. See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 for guidelines for assessment of severity and relationship, respectively. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

6.3.2 Recording of Adverse Events of Special Interest

Both serious and nonserious AESIs will be captured at any time during the subject's participation in the study.

6.3.2.1 Hepatic Function Abnormality

Nonserious and serious events of hepatic function abnormality (as defined in Section 6.1.3.1) should be recorded in the CRF according to the definitions of AE and SAE (Section 6.1.1 and Section 6.1.2, respectively):

- If the underlying diagnosis for the hepatic function abnormality is known, the diagnosis should be recorded as an AE/SAE per Section 6.3.1.
- If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE per Section 6.3.1.

6.3.2.2 Other Adverse Events of Special Interest

Nonserious and serious events of new or reactivated TB infection, herpes zoster infection, malignancy, infusion, hypersensitivity or anaphylactic reactions, and vasculitis (as defined in Section 6.1.3.2 to Section 6.1.3.6) should be recorded in the CRF according to the definitions of AE and SAE (Section 6.1.1 and Section 6.1.2, respectively).

6.4 Reporting Requirements for Safety Parameters

6.4.1 Study Reporting Period and Follow-up for Adverse Events

The reporting period for AEs is the period immediately following the time that written informed consent is obtained until the end of subject participation in the study.

Nonserious AEs will only be captured during the first year of the subject's participation in the study, but will be followed to resolution until the end of subject participation in the study. Nonserious AEs that result in interruption of investigational product and/or discontinuation from the study will be captured at any time during the subject's participation in the study.

6.4.2 Reporting of Serious Adverse Events

6.4.2.1 Study Reporting Period and Follow-up 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 subject participation in the study. After submitting an initial SAE report for a subject (to MedImmune Patient Safety), the investigator is required to follow the subject proactively and provide further information on the subject's condition to MedImmune Patient Safety.

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 must be reported to MedImmune Patient Safety.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

6.4.2.2 Notifying the 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 complete the SAE Report Form and fax it to MedImmune Patient Safety.

MedImmune contact information:

Patient Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878
Fax: +1 301 398 4205

The sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements (see Section 6.4.2.3). The sponsor 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 submit additional information requested by the sponsor as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE. When additional

information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

6.4.2.3 Safety Reporting to Investigators, Institutional Review Boards or Independent Ethics Committees, and Regulatory Authorities

The sponsor is responsible for reporting all applicable SAEs to regulatory authorities, investigators, and IRBs/IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current risk/benefit assessment of an investigational product or that would be sufficient to consider changes in the administration of the investigational product or in the overall conduct of the study.

For all investigators located in the European Economic Area, the sponsor will be responsible for reporting suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities including the European Medicines Agency (EMA), investigators, and IRBs/IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. The SUSARs will be submitted within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations.

For all other investigators, the sponsor will prepare an expedited report for all SAEs that are unexpected and potentially related to the investigational product, and copies will be distributed to all concerned regulatory authorities, investigator(s), and IRBs/IECs according to applicable laws and regulations. The investigational site also will forward a copy of all expedited reports to the site's applicable IRB/IEC. Investigators must also submit safety information provided by the sponsor to the IRB/IEC as detailed in Section 10.1 and Section 10.2.

6.4.3 Other Events Requiring Immediate Reporting

6.4.3.1 Overdose

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

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for

contact information). If the overdose results in an AE, the AE must also be recorded on the AE CRF (see Section 6.3.1). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.4.3.2 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 6.1.3) of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the SAE Report Form, even if the event is considered to be nonserious (see Section 6.4.2.2 for contact information). The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local SOC and follow the subject by conducting testing as clinically indicated:

- If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, or is considered attributable to investigational product, dosing of the study subject should be discontinued.
- If ALT or AST is greater than 3 × ULN please refer to Guidance for Abnormal Liver Function Tests Management in Appendix 8.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor. If the etiology of the event remains unconfirmed and/or is considered related to investigational product (see Section 6.2.2.1), a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by a MedImmune safety review committee (see Section 6.5) to determine whether continued dosing of current study subjects and/or study entry should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the committee is required for resumption of subject dosing or study entry in the event that the study is interrupted. Where applicable, regulatory authorities and IRBs/IECs will be notified of any actions taken with the study.

6.4.3.3 Pregnancy

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety or designee using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information).

Subjects who become pregnant during the study period must not receive additional doses of investigational product and will be withdrawn from the study. After obtaining the subject's consent, the pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to MedImmune Patient Safety after outcome.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information). The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

6.5 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 review of SAEs and timely review of AEs and "other events" reported during the study. MedImmune Patient Safety is responsible for the receipt, immediate review, investigation, and follow-up of SAEs and other immediately reportable events (eg, overdose and pregnancies) reported from the clinical study sites.

A MedImmune safety review committee provides safety surveillance, guidance, and oversight for all clinical development studies in which MedImmune has sponsor accountabilities. The Committee is chaired by the Clinical Medical Director and includes appropriate representatives from Patient Safety, Pre-Clinical Development, and Regulatory Affairs. The committee reviews protocol and program-specific safety data and assessed changes to the benefit/risk profile of the molecule during early phases of development. Based on review of safety data, the committee may suspend enrollment or subject dosing in clinical studies, request modification of study documents, or take other actions as deemed necessary.

An independent DSMB is an advisory to the sponsor and will perform evaluations of safety data at specified time points throughout the study in accordance with the DSMB Charter and make recommendations to the sponsor regarding the conduct of the study (see Section 7.6).

7 STATISTICAL CONSIDERATIONS

7.1 General Considerations

Data will be provided in data listings sorted by SID number. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation,

median, minimum, and maximum. Baseline will be defined as the Day 1 value of this OLE study prior to investigational product administration. Details of endpoint analyses will be described in the Statistical Analysis Plan.

7.2 Analysis Populations

The Safety Population includes all subjects who receive any amount of investigational product. Demographics, safety endpoints, IM, PD, and disease activity will be summarized based on the Safety Population. Additional analysis populations may be defined as needed.

7.3 Endpoints

7.3.1 Primary Endpoint

The primary objective of this study is to evaluate the long-term safety and tolerability of IV MEDI-546 in adult subjects with moderately-to-severely active SLE. The safety and tolerability of MEDI-546 will be assessed primarily by summarizing treatment-emergent AEs (TEAEs) and treatment-emergent SAEs (TESAEs). Other variables used for the safety assessments will include serum chemistry, hematology, urinalysis, vital signs, physical examination, ECG, and concomitant medications.

All TEAEs and TESAEs will be summarized by system organ class and preferred terms, by severity and relationship to investigational product. No formal statistical testing will be performed. Other safety variables as well as their changes from baseline (if applicable) will be summarized descriptively.

7.3.2 Secondary Endpoint

The secondary objective of this study is to evaluate the IM of MEDI-546. Immunogenicity results will be analyzed by summarizing the number and percentage of subjects who develop detectable ADAs. The titer of ADAs will also be summarized. The association of ADA titers with AEs, PK, SLEDAI-2K, and PD markers will also be evaluated.

7.3.3 Exploratory Endpoints

[redacted]

[redacted]

[redacted]

[redacted]

7.4 Interim Analysis

Although no formal interim analyses of the extension period data are planned, analyses of the accumulating data during the extension period may be performed to assess the ongoing safety and risk/benefit of the study treatment and to assist with Phase 3 planning. The final analysis of extension period data will take place after the last on-study subject completes the extension period follow-up visit or discontinues from the study.

7.5 Sample Size and Power Calculations

[redacted]

7.6 Data Safety Monitoring Board

An independent DSMB is an advisory to the sponsor and will perform evaluations of safety data at specified time points throughout the study in accordance with the DSMB Charter (see Appendix 5) and make recommendations to the sponsor regarding the conduct of the study. At any time during the study, as well as on an ad hoc basis, the DSMB will also review any safety data assessed by the medical monitor to be medically relevant.

8 DIRECT ACCESS TO SOURCE DOCUMENTS

The study will be monitored by the sponsor or designee on a regular basis throughout the study period. During monitoring visits, the investigator 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, ICFs, treatment notes, laboratory reports, pharmacy records, radiographs, recorded data from automated instruments, 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.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Data Collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and dated ICFs, progress notes, hospital charts, nurse's notes, diary cards or other worksheets provided to subjects, laboratory reports, ECG strips, etc.

Subject demographics and key/essential disease baseline characteristics thought to affect outcome, ie, stratification variables and other prognostic factors may be collected, as available, for all subjects who provide written informed consent. For subjects who provided informed consent and were not entered into the study, 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), may also be collected.

9.2 Study Monitoring

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

The investigator and institutions involved in the study will permit study-related monitoring and provide direct access to all study records and facilities. Adequate time and space for monitoring visits should be made by the investigator or other investigator site staff.

The monitor will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter, to ensure that the study is conducted

and documented in accordance with the protocol, GCP, and applicable regulations. The monitor will assess subject enrollment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto validated data collection instruments (paper CRF or electronic data screen) against original source documents; the continued acceptability of the facilities and qualifications of the site staff; and the occurrence of AEs/SAEs. All aspects of the study will be carefully monitored for compliance with the protocol, applicable regulatory requirements, GCP, and the site's standard operating procedures.

The monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that corrective action is taken to resolve any problems noted in the course of the monitoring, and that the preventative measures are put into place to prevent recurrence of issues. In cases where compliance is not achieved, shipment(s) of investigational product to the investigator will be discontinued and study participation by that investigator will be terminated.

9.3 Audit and Inspection of the Study

During and after the study, the sponsor or its representative may conduct audits of any data and any facility participating in the study. The investigator and institutions involved in the study will permit such study-related audits and provide direct access to all study records and facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigator should promptly notify the sponsor. The investigator agrees to cooperate fully with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records. The investigator will forward to the sponsor a copy of any inspection records received.

10 ETHICS

10.1 Regulatory Considerations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable

laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC that approves this study to be conducted in its territory. Good Clinical Practice is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

Per GCP, 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 MedImmune Patient Safety or designee, and the investigator will keep the IRB/IEC informed as to the progress of the study.

The investigator will explain the nature of the study and will inform the subject that participation is voluntary and that the subject can withdraw or be withdrawn from the study at any time. Written informed consent will be obtained from each subject prior to the Day 1 procedures to determine if study eligibility criteria are met. A copy of the signed consent form(s) will be given to every subject, and the original(s) will be maintained with the subject's records.

10.2 Institutional Review Board or Independent Ethics Committee

A list of IRB/IEC members or a Statement of GCP Compliance 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 ICF(s), 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 investigator of ICF changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study (as applicable according to local regulations); 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.

10.3 Informed Consent

Freely given informed consent will be obtained and documented for all subjects under this protocol (or a subject's legal representative, if the subject is unable to provide informed consent) in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC.

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 consent form(s) generated by the investigator must be approved by the IRB/IEC and be acceptable to the sponsor. 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(s) approved by the IRB/IEC and signed and dated by the subject or the subject's legal 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 ICF(s) must be kept on file by the investigator for possible inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The subject or the subject's legal representative should receive a copy of the signed and dated written ICF(s) 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.

10.4 Withdrawal of Consent for Continued Study Participation

Data and Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any data collected prior to that time may still be given to and used by

the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

Samples Obtained for Future Research

Samples obtained for future research will be labeled with a sample identification number but will not be labeled with personal identifiers such as the subject's name. A file linking this sample identification number with the SID number will be kept in a secure place at the sponsor with restricted access. If the subject withdraws consent for participating in the future research, this link will allow the sponsor to locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her urine or sera samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

11 DATA HANDLING AND RECORD KEEPING

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a subject's identification number or coded number. All study records, source medical records, and code sheets or logs linking a subject's name to an SID number will be kept in a secure location. Study records such as CRFs 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 specified in the ICF(s) (eg, necessary for

monitoring by regulatory authorities or the sponsor of the clinical study). The investigator must also comply with all applicable privacy regulations (eg, HIPAA 1996, EU Data Protection Directive 95/46/EC).

The study site (and the Principal Investigator) will retain the essential documents specified in the ICH GCP (eg, source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with MedImmune/AstraZeneca. However this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by MedImmune/AstraZeneca, and the specific period and method of retention will be separately discussed between the study site and MedImmune/AstraZeneca. MedImmune/AstraZeneca should notify the head of the study site in writing when the study-related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

12 FINANCING AND INSURANCE

Financing and insurance are addressed in the individual site contracts.

13 PUBLICATION POLICY

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

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15 SUMMARY OF PROTOCOL AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

Protocol Amendment 1, 12Feb2013

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Major changes to the protocol are summarized below.

1. Section 1.2.3 (Summary of Clinical Experience) was revised to remove the explanation regarding the last day of Study CD-IA-MEDI-546-1013 and the first day of Study CD-IA-MEDI-546-1145. This explanation has been moved to Section 3.1 (Overview of Study Design) and clarified.
2. Section 3.1 (Overview of Study Design) was revised to include the explanation that once subjects complete treatment and follow-up in Study CD-IA-MEDI-546-1013 (through Day 422), signed the ICF, and met all study eligibility criteria, they may be enrolled in this OLE study. The start of this OLE study (defined as the day [Day 1] the subject receives their first dose of open-label MEDI-546) should occur within 28 days of the Day 422 visit of Study CD-IA-MEDI-546-1013 or at the discretion of the medical monitor if the start of this OLE study occurs outside the 28-day window.
3. Section 3.1 (Overview of Study Design), Section 3.2 (Estimated Duration of Subject Participation) and Section 4.5.3 (Treatment Regimen) were revised to reduce the duration of the study to 2 years.
4. Figure 3.1-1 (Study Flow Diagram) and Table 5.1-1 (Schedule of Study Procedures for the Treatment Period) was revised to reduce the duration of the study to 2 years.
5. Section 3.4.1 (Rationale for Study Design) was updated to remove the reference to subjects at least 18 years of age. It is assumed that subjects in this study will be at least 18 years of age, as subjects had participated in Study CD-IA-MEDI-546-1013, which had an inclusion criterion of “age 18-65 years at the time of screening”.
6. Section 4.2.1 (Inclusion Criteria) inclusion criterion #3 was clarified to state that females of childbearing potential who are sexually active with a nonsterilized male partner must use 2 methods of effective contraception for 28 days prior to Day 1, and must agree to continue using such precautions for 85 days after the final dose of investigational product.
7. Section 4.2.1 (Inclusion Criteria) inclusion criterion #4 was clarified to state that nonsterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception from Day 1 for 85 days after receipt of the final dose of investigational product.
8. Section 4.2.1 (Inclusion Criteria) inclusion criterion #5 was clarified to state that subjects must be willing to forgo other forms of experimental treatment (and not just experimental treatments for SLE) during the study.
9. Section 4.2.3 (Withdrawal Criteria) was clarified so that subjects who are permanently discontinued from receiving investigational product (and who have not withdrawn consent, are not lost to follow-up or have not enrolled in another clinical study) will complete the follow-up period (beginning with Visit 28/Early Discontinuation Visit) 28

days (± 7 days) after the last dose of investigational product. Two subsequent follow-up visits will also be completed 59 and 85 days (± 7 days) after the last dose of investigational product as per the schedule of study procedures.

10. Section 4.5.6 (Monitoring of Dose Administration) was updated to remove the reference that temperature should be taken orally.
11. Table 5.1-1 (Schedule of Study Procedures for the Treatment Period) was revised to reduce the duration of the study to 2 years; to include a note that for the Day 1 assessment of ECG, if an assessment was performed on Day 396 of Study CD-IA-MEDI-546-1013, then the data can also be used for Day 1 of this study; to move the lipid profile collection to Week 4; to include a note that subjects will be required to fast for at least 8 hours prior to the lipid profile assessment and that if a subject has not fasted, the assessment should be performed under fasted conditions at the next visit; to state that the urine biomarker collection is optional; and to remove the Clinical Evaluation Questionnaire assessment.
12. Table 5.1-2 (Schedule of Study Procedures for the 85-day Follow-up Period) was updated to include new visit numbers (Visits 28, 29 and 30); to include the Early Discontinuation Visit procedures (ie, same as Visit 28); to include a note that subjects will be required to fast for at least 8 hours prior to the lipid profile assessment; to state that the urine biomarker collection is optional; and to remove the Clinical Evaluation Questionnaire assessment.
13. Table 5.1-2 (Schedule of Study Procedures for the 85-day Follow-up Period) and Section 5.1.3.1 (28 Days after the Last Dose [± 7 Days]: First Safety Follow-up Visit or Early Discontinuation Visit [Visit 28]) were revised to remove the SLICC assessment from Visit 28/EDV.
14. Section 5.1.2.1 (Week 0; Day 1: First Infusion [Visit 1]) was revised to remove the lipid profile assessment.
15. Section 5.1.2.1 (Week 0; Day 1: First Infusion [Visit 1]), Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 100: Second through Twenty-sixth Infusion [Visits 2 to 26]), Section 5.1.3.1 (28 Days after the Last Dose [± 7 Days]: First Safety Follow-up Visit or Early Discontinuation Visit [Visit 28]), Section 5.1.3.2 (59 Days after the Last Dose [+/- 7 Days]: Second Safety Follow-up Visit [Visit 29]), Section 5.1.3.3 (85 Days after the Last Dose [± 7 Days]: Third Safety Follow-up Visit [Visit 30]) and Section 5.2.4 (Tuberculosis Testing) were modified to remove the Clinical Evaluation Questionnaire assessment. Section 5.2.13 (Adverse Events of Special Interest) was also modified to remove the Clinical Evaluation Questionnaire, as the investigator is required to assess for AESIs using medical or scientific judgment.
16. Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 100: Second through Twenty-sixth Infusion [Visits 2 to 26]) was updated to include the lipid profile assessment (Week 4 only). Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 100: Second through Twenty-sixth Infusion [Visits 2 to 26]) and Section 5.1.2.5 (Every 48 Weeks; Weeks 48 and 96 [Visits 13 and 25]) were updated to include a note that subjects will be required to fast for at least 8 hours prior to this assessment. If a subject has not fasted, the assessment should be performed under fasted conditions at the next visit.
17. Section 5.1.2.3 (Every 12 Weeks; Weeks 12, 24, 36, 48, 60, 72, 84 and 96 [Visits 4, 7, 10, 13, 16, 19, 22 and 25]), Section 5.1.3.1 (28 Days after the Last Dose [± 7 Days]: First Safety Follow-up Visit or Early Discontinuation Visit [Visit 28]) and Section 5.1.3.3 (85

Days after the Last Dose [± 7 Days]: Third Safety Follow-up Visit [Visit 30]) and Section 5.2.5 (Clinical Laboratory Tests) were updated to state that the urine biomarker collection was optional.

18. Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 100: Second through Twenty-sixth Infusion [Visits 2 to 26]), Section 5.1.2.3 (Every 12 Weeks; Weeks 12, 24, 36, 48, 60, 72, 84 and 96 [Visits 4, 7, 10, 13, 16, 19, 22 and 25]), Section 5.1.2.4 (Every 24 Weeks; Weeks 24, 48, 72 and 96 [Visits 7, 13, 19 and 25]), Section 5.1.2.5 (Every 48 Weeks; Weeks 48 and 96 [Visits 13 and 25]), Section 5.1.2.6 (Week 104; Last Treatment Visit [Visit 27]), Section 5.1.3.1 (28 Days after the Last Dose [± 7 Days]: First Safety Follow-up Visit or Early Discontinuation Visit [Visit 28]), Section 5.1.3.2 (59 Days after the Last Dose [+/- 7 Days]: Second Safety Follow-up Visit [Visit 29]) and Section 5.1.3.3 (85 Days after the Last Dose [± 7 Days]: Third Safety Follow-up Visit [Visit 30]) were revised to reduce the duration of the study to 2 years.
19. Section 5.1.4 (Unscheduled Visit) was added to describe procedures for an unscheduled study visit.
20. Section 5.2.6 (Optional Urine Biomarker Testing) was revised to include additional information on the collection and analysis of optional urine biomarker samples.
21. Section 5.2.12.1 (Systemic Lupus Erythematosus Disease Activity Index-2000) was updated to include a statement that anyone assessing the SLEDAI-2K at the sites must have had appropriate training prior to conducting the SLEDAI-2K.
22. Table 5.2.15-1 (Estimated Volume of Blood to be Collected per Visit) was revised to reduce the amount of blood that would be collected during the study, given that the duration of the study was reduced to 2 years.
23. Section 6.3.2 (Recording of Adverse Events of Special Interest) was clarified to state where nonserious and serious AESIs should be recorded.

Protocol Amendment 2, 01Apr2013

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. Major changes to the protocol are summarized below.

1. Section 2.3 (Exploratory Objectives) [redacted].
2. Section 4.2.3 (Withdrawal Criteria) was revised to clarify how an increase in OCS treatment is managed in the study.
3. Table 5.1-1 (Schedule of Study Procedures for the Treatment Period) was modified to include the following assessments: SF-36v2 was added to Visits 1, 7, 13, 19, 25 and 27; HBV DNA PCR TaqMan, QFT-GIT test, immunology profile, urinalysis, urine β-HCG, and Investigator Flare Question(s) were added to Visit 27.
4. Table 5.1-2 (Schedule of Study Procedures for the 85-day Follow-up Period) was modified to include the SF-36v2 assessment to Visit 30.
5. Section 5.1.2.1 (Week 0; Day 1: First Infusion [Visit 1]), Section 5.1.2.4 (Every 24 Weeks; Weeks 24, 48, 72 and 96 [Visits 7, 13, 19 and 25]), Section 5.1.2.6 (Week 104; Last Treatment Visit [Visit 27]) and Section 5.1.3.3 (85 Days after the Last

Dose [+/- 7 Days]: Third Safety Follow-up Visit [Visit 30]) were revised to include the SF-36v2 assessment.

6. Section 5.1.2.1 (Week 0; Day 1: First Infusion [Visit 1]), Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 100: Second through Twenty-sixth Infusion [Visits 2 to 26]), Section 5.1.2.6 (Week 104; Last Treatment Visit [Visit 27]), Section 5.1.3.1 (28 Days after the Last Dose [+/-7 Days]: First Safety Follow-up Visit or Early Discontinuation Visit [Visit 28]), Section 5.1.3.2 (59 Days after the Last Dose [+/-7 Days]: Second Safety Follow-up Visit [Visit 29]), Section 5.1.3.3 (85 Days after the Last Dose [+/- 7 Days]: Third Safety Follow-up Visit [Visit 30]), Section 5.1.4 (Unscheduled Visit), Section 5.2.14 (SLE Flares and Increase in SLE Disease Activity), and Section 6.1.1 (Adverse Events) were clarified: assessment of worsening and/or flare of SLE disease activity should be performed using the SLE Increase in Disease Activity CRF.
7. Table 5.1-1 (Schedule of Study Procedures for the Treatment Period), Table 5.1-2 (Schedule of Study Procedures for the 85-day Follow-up Period), Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 100: Second through Twenty-sixth Infusion [Visits 2 to 26]), Section 5.1.2.6 (Week 104; Last Treatment Visit [Visit 27]), Section 5.1.3.1 (28 Days after the Last Dose [+/-7 Days]: First Safety Follow-up Visit or Early Discontinuation Visit [Visit 28]), Section 5.1.3.2 (59 Days after the Last Dose [+/-7 Days]: Second Safety Follow-up Visit [Visit 29]), Section 5.1.3.3 (85 Days after the Last Dose [+/- 7 Days]: Third Safety Follow-up Visit [Visit 30]), Section 5.1.4 (Unscheduled Visit), Section 6.1.1 (Adverse Events), Section 6.4.1 (Study Reporting Period and Follow-up for Adverse Events) were modified to include a description of how nonserious AEs that result in interruption of investigational product and/or discontinuation from the study would be collected. This addition to the protocol was made to be compliant with the United States Food and Drug Administration draft guidance "Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations."
8. Section 5.1.2.6 (Week 104; Last Treatment Visit [Visit 27]) was revised to include the following assessments: SF-36v2, HBV DNA PCR TaqMan, QFT-GIT test, immunology profile, urinalysis, urine β-HCG, and Investigator Flare Question(s).
9. Section 5.2.15 (Patient-reported Outcomes) and Section 5.2.15.1 (Short Form-36 Version 2) were added to the protocol to describe the SF-36v2 assessment.
10. Section 6.1.3 (Adverse Events of Special Interest) was modified to remove the description of the AESIs, as this information is provided in the following subsections: Section 6.1.3.1 (Hepatic Function Abnormality), Section 6.1.3.2 (New or Reactivated TB Infection), Section 6.1.3.3 (Herpes Zoster Infection), Section 6.1.3.4 (Malignancy), Section 6.1.3.5 (Infusion, Hypersensitivity, and Anaphylactic Reactions), and Section 6.1.3.6 (Vasculitis).
11. Section 6.1.3 (Adverse Events of Special Interest) and Section 6.3.2 (Recording of Adverse Events of Special Interest) were clarified to state that both serious and nonserious AESIs will be captured at any time during the subject's participation in the study.
12. Section 6.1.3.5 (Infusion, Hypersensitivity, and Anaphylactic Reactions) was modified to include the following subsections: Section 6.1.3.5.1 (Infusion Reactions), Section 6.1.3.5.2 (Hypersensitivity Reactions), and Section 6.1.3.5.3 (Anaphylactic Reactions).

13. Section 6.1.3.6 (Vasculitis) was modified to remove the last sentence in the paragraph, as AESIs of vasculitis that are associated with the subject's underlying SLE will be collected.
14. Section 6.3.2 (Recording of Adverse Events of Special Interest) was modified to include recording information for nonserious and serious events of hepatic function abnormality in Section 6.3.2.1 (Hepatic Function Abnormality) and serious and nonserious events of new or reactivated TB infection, herpes zoster infection, malignancy, infusion, hypersensitivity or anaphylactic reactions, and vasculitis in Section 6.3.2.2 (Other Adverse Events of Special Interest).
15. Section 7.3.3 (Exploratory Endpoints) [redacted]
16. Section 14 (References) was modified to include Ware et al, 2008 to the reference list.
17. Appendix 7 (Short Form-36 Version 2) was added to include an example of the SF-36v2 in the protocol.

Protocol Amendment 3, 26Mar2014

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

1. Cover page was updated to change the medical monitor from Stephen Yoo, MD, Senior Director, Clinical Development to Warren Greth, MD, MSc, Senior Director, Clinical Development.
2. Figure 3.1-1 (Study Flow Diagram) was updated to change duration of IV infusion to "approximately 60 minutes". Note however that MEDI-546 should not be administered over a period of less than 55 minutes. If a subject has a history of infusion reactions, MEDI-546 administration may be lengthened per the investigator's discretion.
3. Section 4.2.3 (Withdrawal Criteria), Section 4.5.2 (Other Study Medications), Section 4.5.2.1 (Corticosteroids), and Section 4.6.1 (Permitted Non-SLE Concomitant Medications) was modified to state that OCS medication taken > 40 mg/day of prednisone (or equivalent) for greater than 14 days, dosing with study medication must be withheld until OCS medication can be tapered to ≤ 40 mg/day. The change was made to allow OCS medication to be tapered to 40 mg/day (and not just below 40 mg/day).
4. Section 4.5.1 (Investigational Products), Section 4.5.4 (Investigational Product Dose Preparation), Section 4.5.4.1 (Dose Calculation), Section 4.5.4.2 (Investigational Product Inspection), and Section 4.5.4.3 (Dose Preparation Steps) were modified to include information on a new formulation of MEDI-546 Drug Product (ie, 150 mg/mL). Table 4.5.1-1 (Identification of Investigational Products) was also modified to include information on a new formulation of MEDI-546 Drug Product (ie, 150 mg/mL).
5. Section 4.5.4.1 (Dose Calculation) was modified to add Table 4.5.4.1-1 (Dose Calculation for MEDI-546 Drug Product for IV Infusion).
6. Section 4.5.4.3 (Dose Preparation Steps) was modified to add Table 4.5.4.3-1 (Dose Preparation for MEDI-546). Text was also added to describe the type of syringes to be used and the number of needle sticks that could be made into the IV bag.

7. Section 4.5.5 (Treatment Administration), third bullet was modified to state that the dose of MEDI-546 must be prepared using aseptic technique and that the total in-use storage time from needle puncture of the first vial of MEDI-546 for investigational product preparation to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C-8°C (36°F to 46°F). The fourth and fifth bullets were modified to state that the entire contents of the IV bag should be administered using an infusion pump over approximately 60 minutes. MEDI-546 should not be administered over a period of less than 55 minutes. If a subject has a history of infusion reactions, MEDI-546 administration may be lengthened per the investigator's discretion. The second sub-bullet of the seventh bullet was modified to state that an infusion with a start time of 12:00PM would have duration of infusion recorded as 60 minutes (a time of 1:00 PM).
8. Section 4.5.5 (Treatment Administration), Section 4.5.6 (Monitoring of Dose Administration), Section 5.1.2.1 (Week 0; Day 1: First Infusion [Visit 1]), Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 100: Second through Twenty-sixth Infusion [Visits 2 to 26]), and Section 5.2.3 (Vital Signs) were revised to include windows (ie, [± 5]) for vital sign assessments.
9. Section 5.1 (Schedule of Study Procedures) was modified to state that if Day 1 of this study occurred on the same day as Day 422 (+ 28 days) of Study CD-IA-MEDI-546-1013, then many of the procedures and samples only need to be collected one time and will be utilized for both studies. If Day 1 of this study occurs 28 days after Day 422 of Study CD-IA-MEDI-546-1013, then Day 1 procedures and samples of this study will need to be collected.
10. Table 5.1-1 (Schedule of Study Procedures for the Treatment Period) was revised to denote those study procedures that should be conducted on the same day of investigational product administration on Day 1.
11. Table 5.1-1 (Schedule of Study Procedures for the Treatment Period) and Table 5.1-2 (Schedule of Study Procedures for the 85-day Follow-up Period) were clarified to state that serum collection for proteomics/biomarkers was optional. Section 5.1.2.1 (Week 0; Day 1: First Infusion [Visit 1]), Section 5.1.2.3 (Every 12 Weeks; Weeks 12, 24, 36, 48, 60, 72, 84 and 96 [Visits 4, 7, 10, 13, 16, 19, 22 and 25]), Section 5.1.2.4 (Every 24 Weeks; Weeks 24, 48, 72 and 96 [Visits 7, 13, 19 and 25]), Section 5.1.2.6 (Week 104; Last Treatment Visit [Visit 27]), Section 5.1.3.1 (28 Days after the Last Dose [+/- 7 Days]): First Safety Follow-up Visit or Early Discontinuation Visit [Visit 28]), and Section 5.1.3.3 (85 Days after the Last Dose [+/- 7 Days]): Third Safety Follow-up Visit [Visit 30]) were also clarified to state that the serum sample collection for proteomics/biomarkers was optional.
12. Section 5.1.2.1 (Week 0; Day 1: First Infusion [Visit 1]) was reorganized to indicate assessments that need to be completed before using data from Study CD-IA-MEDI-546-1013, assessments that need to be completed on the same day as investigational product dosing, and assessments where data from Day 422 [+ 28 days] of Study CD-IA-MEDI-546-1013 can be used for this study.
13. Section 5.2.4 (Tuberculosis Testing) was modified to add information for subjects who may have had recent contact with anyone with active TB or who show signs or symptoms of active TB. Also added information for when a subject should be discontinued from the study due to active TB or discontinuation/noncompliance with latent TB treatment.

14. Section 5.2.5 (Clinical Laboratory Tests) was modified to include information that any female subject who is postmenopausal based on documented results from the serum follicle-stimulating hormone test in any previous study (including Study CD-IA-MEDI-546-1013) will not require urine HCG tests in this study. Any female subject who feels that they have had a change in status to postmenopausal at any point during this study can request a serum follicle-stimulating hormone test. If the results show that the subject is postmenopausal, then the subject will not require any further urine HCG tests.
15. Section 5.2.9 (Optional Proteomics/Biomarkers) was modified to add that serum for proteomics/biomarkers will only be collected from subjects who provide written consent for this procedure.
16. Section 6.4.3.2 (Hepatic Function Abnormality) and Section 6.5 (Safety Management During the Study) were revised to remove reference to the the MedImmune Safety Monitoring Committee, as this committee no longer exists. A MedImmune safety review committee, which includes, but is not limited to, appropriate representatives from Patient Safety, Clinical Development, and Regulatory Affairs, will review the protocol-specific safety data.
17. Appendix 1 (Signatures) was modified to remove signature sheets for Stephen Yoo, MD, Liangwei Wang, PhD, and Theodore Phillips, as their signatures are no longer required, per change in the sponsor's standard operating procedure for protocols. Added signature sheet for Jorn Drappa, MD, whose signature is now required, per change in the sponsor's standard operating procedure for protocols.

Protocol Amendment 4, 12Feb2015

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

1. Study Abstract (Study Design) and Section 3.1 (Overview of Study Design) - clarified that subjects in this study will be adult male or female subjects with chronic, moderately-to-severely active SLE who were previously treated with investigational product (MEDI-546 or placebo) and completed Study CD-IA-MEDI-546-1013 through treatment and follow-up (with the exception of those subjects in the regions of Donetsk and Lugansk in the Ukraine, where the political situation necessitated a suspension of study activities).
2. Study Abstract (Study Design, Treatment Regimen), Section 1.3 (Research Hypothesis), Section 3.1 (Overview of Study Design), Figure 3.1-1 (Study Flow Diagram), Section 3.4.1 (Rationale for Study Design), Section 3.4.2 (Rationale for MEDI-546 Dose), Section 4.5.3 (Treatment Regimen), Section 4.5.4.1 (Dose Calculation), Table 4.5.4.1-1 (Dose Calculation for MEDI-546 Drug Product for IV Infusion), and Section 5.1 (Schedule of Study Procedures) - changed dose of MEDI-546 from 1000 to 300 mg as the efficacy and safety data from Study CD-IA-MEDI-546-1013 indicated that the 300 mg dose had a more favorable benefit:risk profile than the 1000 mg dose for subjects with chronic, moderately-to-severely active SLE.
3. Study Abstract (Study Design), Section 3.1 (Overview of Study Design), Figure 3.1-1 (Study Flow Diagram), and Section 4.5.5 (Treatment Administration) - changed IV

infusion time from approximately 60 minutes to at least 30 minutes as the efficacy and safety data from Study CD-IA-MEDI-546-1013 indicated that the 300 mg dose had a more favorable benefit:risk profile than the 1000 mg dose for subjects with chronic, moderately-to-severely active SLE.

4. Study Abstract (Study Design, Treatment Regimen), Section 3.1 (Overview of Study Design), Figure 3.1-1 (Study Flow Diagram), and Section 4.5.3 (Treatment Regimen) - changed the duration of investigational product administration from 2 to 3 years. This change was made to collect more long-term safety data with MEDI-546.
5. Study Abstract (Study Design), Section 3.1 (Overview of Study Design) and Section 3.4.2 (Rationale for MEDI-546 Dose) - removed sentence that stated that as additional MEDI-546 data became available, if another dose is determined to be the optimal dose, the protocol would be amended. This change was made based on efficacy and safety data from Study CD-IA-MEDI-546-1013 that indicated that the 300 mg dose had a more favorable benefit:risk profile than the 1000 mg dose for subjects with chronic, moderately-to-severely active SLE.
6. Study Abstract (Sample Size and Power Calculations), Section 1.2.3 (Summary of Clinical Experience), and Section 7.5 (Sample Size and Power Calculation) - updated sections to state that a total of 307 subjects have been randomized in Study CD-IA-MEDI-546-1013.
7. Section 1.2.2 (Summary of Nonclinical Experience) - updated findings from the 9-month repeated-dose toxicity study to state that even though the arteritis findings in male animals may be a consequence of species-specific immunogenicity and its relevance to human safety is unknown, the possibility of other factors than production of antibodies to MEDI-546 cannot be ruled out. Also updated findings to the ePPND study to state that the number of stillbirths was comparable to the control group and the testing facility's historical incidence data and the growth and development of the infants were within normal limits for infant cynomolgus monkeys, including immune assessments keyhole limpet hemocyanin immunization IgM and IgG titer values, peripheral blood immunophenotyping, hematology analyses, and lymphoid organ histopathology (spleen, thymus, and lymph nodes).
8. Section 1.2.3 (Summary of Clinical Experience) - revised summary of Study MI-CP180 for brevity; updated summary to state that an interim analysis of Study CD-IA-MEDI-546-1013 had been conducted; and added a summary for Study D3461C00002, a Phase 2, multicenter, open-label, dose-escalation study to evaluate the safety and tolerability of MEDI-546 in adult Japanese subjects with active SLE.
9. Section 3.2 (Estimated Duration of Subject Population) - updated the duration of study participation based on the extension of the study from 2 to 3 years.
10. Section 3.4.2 (Rationale for MEDI-546 Dose) - updated that rationale for the MEDI-546 dose and reduced infusion time in the OLE study. Based on the analysis of both efficacy and safety data from Study CD-IA-MEDI-546-1013, the Sponsor has determined that the 300 mg dose has a more favorable benefit-risk profile than the 1000 mg dose for subjects with chronic, moderately-to-severely active SLE. Population modeling has demonstrated clinically meaningful benefit at 300 mg, with no incremental benefit at 1000 mg and also has predicted inadequate PK exposure and suboptimal efficacy at doses lower than 300 mg. In addition, as the dose of 1000 mg has been administered repeatedly over

60 minutes at a rate of 16.7 mg/min with no increased frequency of infusion related reactions, administering 300 mg over 30 minutes at a rate of 10 mg/min will not result in any increased risk to the subject for infusion related reactions. It should be noted that the DSMB has not made any recommendations to modify this study (including any changes in dose) or Study CD-IA-MEDI-546-1013, based on an ongoing review of safety data from both studies.

11. Section 4.2.1 (Inclusion Criteria) - modified Inclusion Criterion 2 to state that subjects must have qualified for and received investigational product (MEDI-546 or placebo) and completed the treatment period plus the follow-up period (through Day 422) in Study CD-IA-MEDI-546-1013. Subjects who discontinued from Study CD-IA-MEDI-546-1013 are not eligible for this study, unless active participation was solely prevented by local governmental instability due to political unrest and all other inclusion and exclusion criteria were met. This criterion was modified because subjects in the regions of Donetsk and Lugansk in the Ukraine, where the political situation necessitated a suspension of study activities, may have been unable to complete all of the visits in Study CD-IA-MEDI-546-1013.
12. Section 4.2.3 (Withdrawal Criteria) - clarified Criterion 8 to state that "Receipt of any of the following medications (other than MEDI-546 administered as per protocol) any time from the last MEDI-546 dose in Study CD-IA-MEDI-546-1013 to 85 days post last MEDI-546 dose Study CD-IA-MEDI-546-1145..." would result in permanent discontinuation of investigational product.
13. Section 4.2.3 (Withdrawal Criteria), Section 4.5.2 (Other Study Medications), Section 4.5.2.1 (Corticosteroids), and Section 4.6.1 (Permitted Non-SLE Concomitant Medications) - clarified that for subjects who have an increase in OCS treatment above a total dose > 40 mg/day for a dosing period > 14 days, dosing with MEDI-546 may be continued, unless there is a safety concern. Also added the statement that frequent steroid use above Study CD-IA-MEDI-546-1013 baseline for SLE disease control (> 2 times every 6 months, higher doses [> 40 mg/day], and/or longer duration than permitted by the protocol) after 12 months of open-label MEDI-546 should result in discontinuation of MEDI-546 administration for failure to achieve a favorable benefit:risk profile.
14. Section 4.5.2.2 (Slow-acting Immunosuppressants) - removed "antimalarials" as there were no antimalarials on the list.
15. Section 4.5.3 (Treatment Regimen) - clarified that subjects will receive MEDI-546 300 mg administered as an IV infusion Q4W starting at Day 1 (Week 0) or the visit following approval of this amendment (for those subjects who have already been dosed in this study) for up to 3 years or until the sponsor discontinues development of MEDI 546 for SLE, whichever comes first.
16. Table 4.5.4.1-1(Dose Calculation for MEDI-546 Drug Product for IV Infusion) - changed volume for IV infusion based on the new dose (300 mg) of MEDI-546.
17. Section 4.5.4.2 (Investigational Product Inspection) - changed the description of MEDI-546 from "clear, colorless" to "clear, colorless to slightly yellow liquid" to be consistent with the current formulation of the investigational product.
18. Table 4.5.4.3-1 (Dose Preparation for MEDI-546) - changed volume of saline removed from IV infusion bag, volume of MEDI-546 drug product added to IV infusion bag,

number of vials to be used, and recommended type of syringe to be used, based on the new dose (300 mg) of MEDI-546.

19. Section 4.5.6 (Monitoring of Dose Administration) and Section 5.2.3 (Vital Signs) - clarified that vital signs will be measured until stable and the subject is ready for discharged as judged by the investigator.
20. Table 5.1-1 (Schedule of Study Procedures for the Treatment Period) - added additional weeks (Weeks 108-156) and visits (Visits 27-40) to the treatment period to extend the treatment period by an additional year; listed out week and visit numbers for the Q4W column for clarity; removed duplicate line for assessment of Cushingoid features; added ECG assessments, which were inadvertently removed during a previous amendment, to Day 1, Q48W, and LTV; clarified that HBV DNA should be < 29 IU/mL to be considered undetectable; clarified that QFT-GIT test is to be performed only if it was negative or if it was indeterminate at any visit during Study CD-IA-MEDI-546-1013 and also added QFT-GIT assessments to Q48W and LTV; added Pap smear at Week 144 (Visit 37); clarified that the SLICC referred to the SLICC/ACR Damage Index; clarified that the investigator flare question is to assess worsening and/or flare of SLE disease activity; added that subjects should be evaluated for signs and symptoms of TB using a TB surveillance form at Day 1, Q4W, Q12W, Q24W, Q48W, and LTV.
21. Table 5.1-2 (Schedule of Study Procedures for the 85-day Follow-up Period) - renumbered follow-up visits (to Visits 41-43), which follow the extended treatment period; added that subjects should be evaluated for signs and symptoms of TB using a TB surveillance form at V41, V42, and V43; clarified that the SLICC assessment included ACR; and clarified that the investigator flare question is to assess worsening and/or flare of SLE disease activity.
22. Section 5.1.2.1 (Week 0; Day 1: First Infusion [Visit 1]), Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 152: Second through Thirty-ninth Infusion [Visits 2 to 39]), and Section 5.1.2.6 (Week 156; Last Treatment Visit [Visit 40]) - removed vital signs assessment (formerly Number [No.] 7) as vital signs will be taken before administration of investigational product (within 15 minutes of the beginning of the investigational product infusion; now No. 16); clarified that ECGs are required at Day 1 if not done at Day 396 of Study CD-IA-MEDI-546-1013; moved assessment for Cushingoid features from No. 21 to No. 8 (and added that if this assessment was performed on Day 365 of Study CD-IA-MEDI-546-1013, then data can also be used for Day 1 of this study); clarified that for all remaining assessments, if Day 1 of this study occurs on the same day as Day 422 (+ 28 days) of Study CD IA MEDI-546-1013, then the procedures and samples can be collected one time and can be utilized for both studies, and that if Day 1 of this study does not occur on the same day as Day 422 (+ 28 days) of Study CD-IA-MEDI-546-1013, then the procedures and samples should be collected at Day 1; moved assessment for physical examination from No. 17 to No. 9; and combined collection of all predose blood samples (formerly No. 9 and No. 19) under No. 10.
23. Section 5.1.2.1 (Week 0; Day 1: First Infusion [Visit 1]), Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 152: Second through Thirty-ninth Infusion [Visits 2 to 39]), Section 5.1.2.6 (Week 156; Last Treatment Visit [Visit 40]), Section 5.1.3.1 (28 Days after the Last Dose [± 7 Days]): First Safety Follow-up Visit or early Discontinuation Visit [Visit 41]), Section 5.1.3.2 (59 Days after the Last Dose [± 7 Days]: Second Safety Follow-up Visit

[Visit 42]), Section 5.1.3.3 (85 Days after the Last Dose [± 7 Days]: Third Safety Follow-up Visit [Visit 43]), and Section 5.1.4 (Unscheduled Visit) - clarified that in addition to assessing worsening and/or flare of SLE disease activity using the SLE Increase in Disease Activity CRF, complete the CRF for SLE related AEs that are not serious, if applicable.

24. Section 5.1.2.1 (Week 0; Day 1: First Infusion [Visit 1]), Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 152: Second through Thirty-ninth Infusion [Visits 2 to 39]), Section 5.1.2.6 (Week 156; Last Treatment Visit [Visit 40]), Section 5.1.3.1 (28 Days after the Last Dose [± 7 Days]): First Safety Follow-up Visit or early Discontinuation Visit [Visit 41]), Section 5.1.3.2 (59 Days after the Last Dose [± 7 Days]: Second Safety Follow-up Visit [Visit 42]), Section 5.1.3.3 (85 Days after the Last Dose [± 7 Days]: Third Safety Follow-up Visit [Visit 43]), and Section 5.1.4 (Unscheduled Visit) - added procedure that subjects should be evaluated for signs and symptoms of TB using a TB surveillance form.
25. Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 152: Second through Thirty-ninth Infusion [Visits 2 to 39]), Section 5.1.2.6 (Week 156; Last Treatment Visit [Visit 40]), and Section 5.2.5 (Clinical Laboratory Tests) - clarified for hepatitis B virus DNA PCR TaqMan assessment, subjects with isolated hepatitis B core antibody positivity during Study CD IA MEDI 546-1013 or at any time for the duration of this study will be tested monthly for HBV DNA. To remain eligible for this study, the subject's HBV DNA levels must remain undetectable as per the central lab (ie, < 29 IU/mL HBV DNA detected).
26. Section 5.1.2.2 (Every 4 Weeks; Weeks 4 to 152: Second through Thirty-ninth Infusion [Visits 2 to 39]) - renumbered individual weeks (Weeks 4 to 152), infusions (second through thirty-ninth), and visits (Visits 2-39) for clarity and consistency; changed "Week 100" to "Week 152" due to the extension of the treatment period by an additional year; removed "if indicated" from "Take vital signs (BP, pulse, respiration, and temperature, if indicated)", as temperature should always be taken after administration of investigational product, and added that vital signs should be taken "...until the subject is stable and ready for discharge (as judged by the investigator)"; and removed vital signs assessment (No. 2) since vitals are taken during administration of investigational product (No. 7).
27. Section 5.1.2.3 (Every 12 Weeks; Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144 [Visits 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, and 37]) - added weeks (Weeks 108, 120, 132, and 144) and visits (Visits 28, 31, 34, and 37) to Q12W assessments due to the extension of the treatment period by an additional year; added immunogenicity assessment at Week 36; and removed SLICC/ACR Damage Index assessment since the frequency of this assessment is better suited for every 24 weeks (see Section 5.1.2.4).
28. Section 5.1.2.4 (Every 24 Weeks; Weeks 24, 48, 72, 96, 120 and 144 [Visits 7, 13, 19, 25, 31, and 37]) - added weeks (Weeks 120 and 144) and visits (Visits 31 and 37) to Q24W assessments due to the extension of the treatment period by an additional year; clarified that only collection of predose blood samples are to be performed every 24 Weeks (Q24W) starting at Week 72; and added SLICC/ACR Damage Index assessment as it is more appropriate to evaluate this tool at 6-month intervals.
29. Section 5.1.2.5 (Every 48 Weeks; Weeks 48, 96, and 144 [Visits 13, 25, and 37]) - added week (Week 144) and visit (Visit 37) to Q48W assessments due to the extension of the treatment period by an additional year and added Pap smear assessment for females only at Week 144 (Visit 37) as additional safety surveillance.

30. Section 5.1.2.6 (Week 156; Last Treatment Visit [Visit 40]) - renumbered week (Week 156) and visit (Visit 40) due to the extension of the treatment period by an additional year; added procedures for administering investigational product and assessing for AEs/SAEs/AESIs, which had been inadvertently omitted; added step (No. 10) for administration of investigational product and taking vital signs during administration of investigational product. Added performance of SLEDAI-2K for consistency with the schedule of study procedures.
31. Section 5.1.3.1 (28 Days after the Last Dose [+/- 7 Days]: First Safety Follow-up Visit or Early Discontinuation Visit [Visit 41]) - renumbered follow-up visit due to the extension of the treatment period by an additional year.
32. Section 5.1.3.2 (59 Days after the Last Dose [+/- 7 Days]: Second Safety Follow-up Visit [Visit 42]) - renumbered follow-up visit due to the extension of the treatment period by an additional year.
33. Section 5.1.3.3 (85 Days after the Last Dose [+/- 7 Days]: Third Safety Follow-up Visit [Visit 43]) - renumbered follow-up visit due to the extension of the treatment period by an additional year.
34. Section 5.2.1 (Medical History) - clarified that only new events or worsening of previous events that occur between Day 422 of Study CD IA-MEDI-546-1013 and prior to signing the informed consent of Study CD-IA-MEDI-546-1145 should be recorded in the Medical History CRF and removed text regarding non-SLE medical history being captured for the 6 months prior to study; non-SLE medical history would be captured in the source documents.
35. Section 5.2.2 (Physical Examination, ECG, Weight, Cushingoid Features and Pap Smear) - clarified that any medically significant changes from the Study CD-IA-MEDI-546-1013 Day 396 ECG will be recorded as an AE. Details regarding the use of a Pap smear were added to this section.
36. Section 5.2.4 (Tuberculosis Testing) - clarified QFT-GIT testing, including what should be done for TB surveillance and/or treatment for indeterminate and positive results.
37. Section 5.2.13 (Adverse Events of Special Interest) - removed statement that subjects will be evaluated for signs and symptoms of TB at every visit, as this is now stated in Section 5.2.4 (Tuberculosis Testing).
38. Section 5.2.14 (SLE Flares and Increase in SLE Disease Activity) - clarified that the SLE Increase in Disease Activity CRF does not need to be completed for SAEs of SLE Increase in Disease Activity.
39. Table 5.2.16-1 (Estimated Volume of Blood to be Collected per Visit) - updated blood volumes due to the additional TB testing at the other study visits and extension of the treatment period by an additional year.
40. Section 6.1.1 (Adverse Events) - Added text to clarify that only laboratory abnormalities resulting in clinical sequelae should be recorded as AEs.
41. Section 6.1.3.1 (Hepatic Function Abnormality) and Section 6.4.3.2 (Hepatic Function Abnormality) - added that if ALT or AST is greater than 3 × ULN, refer to Guidance for Abnormal Liver Function Tests Management in Appendix 8.
42. Section 6.1.3.2 (New or Reactivated and Latent TB Infection) - Added language defining latent TB infection.

43. Section 6.2.1 (Assessment of Severity) - corrected the definition of Grade 4 (life threatening) AEs/SAEs to remove reference to disabilities, which was previously inadvertently added to this definition.
44. Section 6.5 (Safety Management During the Study) - clarified the members of the MedImmune safety review committee.
45. Appendix 8 (Guidance for Abnormal Liver Function Tests) - added appendix for guidance for abnormal liver function tests management.

Appendix 1 Signatures

Sponsor Signature(s)

A Phase 2, Open-label Extension Study to Evaluate Long-term Safety of MEDI-546 in Adults with Systemic Lupus Erythematosus

I agree to the terms of this protocol.

Signature and date: [electronic signature appended]

[redacted]

Signature of Coordinating Investigator

A Phase 2, Open-label Extension Study to Evaluate Long-term Safety of MEDI-546 in Adults with Systemic Lupus Erythematosus

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available or applicable) _____

Signature of Principal Investigator

A Phase 2, Open-label Extension Study to Evaluate Long-term Safety of MEDI-546 in Adults with Systemic Lupus Erythematosus

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available)_____

Appendix 2 General Guidance for Determination of Major Surgery

The goal of this guidance is to maximize the risk/benefit for each subject entering this study. An important aspect to this goal is taking into account all relevant history, including recent surgeries and/or injuries which could influence the safety of the subject potentially being exposed to an additional immunomodulatory medication or could bias the efficacy endpoints of the trial.

Given the advancement and availability of surgical techniques, major surgery is in the judgment of the investigator and his/her evaluation of the following criteria, regardless of the specific surgical procedure:

1. Has the subject completely recovered (mentally, emotionally, and physically) from the surgery and is not receiving additional medications related to the prior surgery (ie, antibiotics)?
2. Has the subject completed all follow-up visits related to the surgery, including ancillary services such as physical and/or occupational therapy?
3. Has the subject resumed all of their prior activities?
4. Has the subject returned to his/her baseline medications for SLE and non-SLE indications?

Appendix 3 Restricted Medications

Medication	Discontinuation Prior to Signing of Informed Consent Form	Medication	Discontinuation Prior to Signing of Informed Consent Form
Abatacept (CTLA 4 Ig)	24 weeks	Immunosuppressants	Washout Time
Adalimumab	12 weeks	Infliximab	12 weeks
Alefacept	12 weeks	Intravenous Globulin	4 weeks
AMG 623	48 weeks	IPP-201101	12 weeks
Anakinra	12 weeks	Leflunomide	36 weeks
Atacicept (TACI-Ig)	12 weeks	Lenalidomide	8 weeks
Belimumab	48 weeks	Memantine	4 weeks
Biologics (eg, IFN)	Washout Time	Natalizumab	24 weeks
Certolizumab pegol	24 weeks	Ocrelizumab	48 weeks
Cyclophosphamide	24 weeks	Pimecrolimus	4 weeks
Cyclosporine	4 weeks	Plasmapheresis	24 weeks
Danazol	4 weeks	Retinoids	4 weeks
Dapsone	4 weeks	Rituximab	48 weeks
Eculizumab	12 weeks	Sulfasalazine	4 weeks
Efalizumab	12 weeks	Sirolimus	4 weeks
Epratuzumab	24 weeks	Tacrolimus	4 weeks
Etanercept	4 weeks	Thalidomide	8 weeks
Golimumab	12 weeks	Tocilizumab	12 weeks

Appendix 4 Vasculitic Syndromes Excluded from the Study

Subjects with a history of, or current diagnosis of the following vasculitis syndromes, are excluded from participating in the study. Vasculitis due to SLE is allowed in the study.

- Behçet's Disease
- Buerger's Disease
- Central Nervous System Vasculitis
- Churg Strauss Syndrome
- Cryoglobulinemia
- Giant Cell Arteritis
- Henoch-Schönlein Purpura
- Kawasaki Disease
- Microscopic Polyangiitis
- Polyarteritis Nodosa
- Polymyalgia Rheumatica
- Takayasu's Arteritis
- Wegener's Granulomatosis

Appendix 5 Data and Safety Monitoring Board Membership

The DSMB is a multidisciplinary group, independent of MedImmune, consisting of two clinicians in the field of Rheumatology, one clinician in Infectious Disease, and one Biostatistician who, collectively, have experience with SLE and in the conduct and monitoring of randomized clinical trials; the Biostatistician will be a non-voting member.

Membership Requirements

- DSMB members will not act as investigators or sub-investigators for this study and will have no study involvement outside their role on the DSMB
- Data must be treated with confidentiality
- Members must have no financial interest in MedImmune or competitors that would be expected to bias their participation
- Members cannot have a conflict of interest that materially may influence their judgment

Responsibilities and Function of the DSMB

The DSMB is established to provide an independent review and assessment of the accumulating safety data and to further safeguard the interests and safety of the participating subjects. The primary role of the DSMB is to make a recommendation to MedImmune regarding the safety of the study based on analysis of available data.

MedImmune is jointly responsible with the DSMB for safeguarding the interests of participating subjects and for the conduct of the study. The medical monitor must notify the DSMB regarding any new safety information related to the investigational product and development program (eg, toxicology information, potential safety signals, etc), other related products under development by the sponsor or another organization, or any other issues that might affect the DSMB's review of this study. The MedImmune medical monitor may ask, if required, for an ad hoc DSMB meeting.

Review of Safety Summary Data

The DSMB is an advisory to the sponsor and will review summary tables of selected safety data (ie, laboratory values and adverse events). Adverse events of special interest will also be reviewed including new or reactivation of TB infections, herpes zoster infections, malignancy, infusion, hypersensitivity, or anaphylactic reactions, and vasculitis.

Periodic Review of the Data

The DSMB will meet periodically and review aggregate data on the adverse events and laboratory assessments in summary tables and listings.

The DSMB will use a priori defined and, when appropriate, ad hoc analyses to assess safety. The DSMB will utilize all available study data when forming any recommendation to discontinue the study.

The DSMB will be responsible for ensuring the timely review of the accumulated safety data. Based on the reviews and assessments of the data, the DSMB will notify the MedImmune medical monitor (or designee) when safety concerns lead to a recommendation to alter the conduct of the study.

Reporting of DSMB

The chairman of the DSMB is responsible for providing a summary of the recommendations after each meeting to the designated personnel at MedImmune.

The summary will clearly communicate recommendations, which will include:

1. Study can continue as planned
2. Additional safety data are needed
3. Study must be suspended
4. Study must be permanently discontinued
5. Study must be modified such as:

- Changes in enrollment criteria
- Changes in safety rules
- Changes in stopping rules
- Changes in dose

Appendix 6 Oral Corticosteroid Guidance

Oral corticosteroid doses up to 40 mg/day of prednisone or equivalent are permitted at study entry. Examples of equivalent doses are provided in the table below. Based on the opinion of the investigator, OCS doses should be tapered throughout the entire study as permitted by the protocol. Oral corticosteroid tapering must not occur until after all assessments have been completed and investigational product has been administered.

Examples of Equivalent Doses of Oral Prednisone

Oral Prednisone and Equivalents	**Equivalent Dose**			
Oral Prednisone	**10 mg**	**20 mg**	**30 mg**	**40 mg**
Cortisone	50 mg	100 mg	150 mg	200 mg
Hydrocortisone	40 mg	80 mg	120 mg	160 mg
Methylprednisolone	8 mg	16 mg	24 mg	32 mg
Prednisolone	10 mg	20 mg	30 mg	40 mg
Triamcinolone	8 mg	16 mg	24 mg	32 mg

If a subject experiences an increase in disease activity secondary to tapering of OCS, the daily OCS dose may be returned to the last dose that was used immediately prior to the most recent OCS dose taper. If the subject does not re-achieve an improvement in disease activity, then the daily OCS dose may be increased to the dose administered at Day 1.

If the subject re-achieves an improvement in disease activity, then further daily OCS dose tapering can resume with a smaller reduction of the daily OCS dose, at the discretion of the investigator. However, if the subject does not re-achieve an improvement in disease activity, then the investigator may continue to follow the subject expectantly to determine if the subject's disease activity will stabilize similar to that at Day 1, will improve over time, or worsen significantly compared to Day 1 requiring a change in background medications.

It is up to the investigator to determine at a given visit what oral prednisone or equivalent dose reduction, if any, is desirable.

Example of OCS Tapering Schedule

Visit	Initial Dose of Oral Prednisone or Equivalent			
	40 mg	**30 mg**	**20 mg**	**10 mg**
Day 29	30 mg	25 mg	15 mg	10 mg
Day 43	25 mg	20 mg	10 mg	10 mg
Day 57	15 mg	15 mg	10 mg	7.5 mg
Day 71	10 mg	10 mg	7.5 mg	7.5 mg
Day 85	7.5 mg	7.5 mg	7.5 mg	7.5 mg

Appendix 7 Short Form-36 Version 2

Protocol MI-CP_ _ _
Visit _ _ _
Subj Initials _ _ _

For Subject Completion ONLY
CONFIDENTIAL

SID _ _ _ _ _ _ _
Date _ _/ _ _ _/ _ _ _ _
(DD/ MON/ YYYY)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

Protocol MI-CP_ _ _
Visit _ _ _
Subj Initials _ _ _

For Subject Completion ONLY
CONFIDENTIAL

SID _ _ _ _ _ _ _
Date _ _/ _ _ _/ _ _ _ _
(DD/ MON/ YYYY)

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c Lifting or carrying groceries	☐1	☐2	☐3
d Climbing several flights of stairs	☐1	☐2	☐3
e Climbing one flight of stairs	☐1	☐2	☐3
f Bending, kneeling, or stooping	☐1	☐2	☐3
g Walking more than a mile	☐1	☐2	☐3
h Walking several hundred yards	☐1	☐2	☐3
i Walking one hundred yards	☐1	☐2	☐3
j Bathing or dressing yourself	☐1	☐2	☐3

Protocol MI-CP_ _ _
Visit _ _ _
Subj Initials _ _ _

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SID _ _ _ _ _ _ _
Date _ _/ _ _ _/ _ _ _ _
(DD/ MON/ YYYY)

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

Protocol MI-CP_ _ _ For Subject Completion ONLY SID _ _ _ _ _ _ _
Visit _ _ _ CONFIDENTIAL Date _ _/_ _ _/_ _ _ _
Subj Initials _ _ _ (DD/ MON/ YYYY)

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

Protocol MI-CP_ _ _
Visit _ _ _
Subj Initials _ _ _

For Subject Completion ONLY
CONFIDENTIAL

SID _ _ _ _ _ _ _
Date _ _/ _ _ _/ _ _ _ _
(DD/ MON/ YYYY)

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

Protocol MI-CP_ _ _ For Subject Completion ONLY SID _ _ _ _ _ _ _
Visit _ _ _ CONFIDENTIAL Date _ _/_ _ _/_ _ _ _
Subj Initials _ _ _ (DD/ MON/ YYYY)

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

Appendix 8 Guidance for Abnormal Liver Function Tests Management

This guidance is based on the July 2009 Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation.

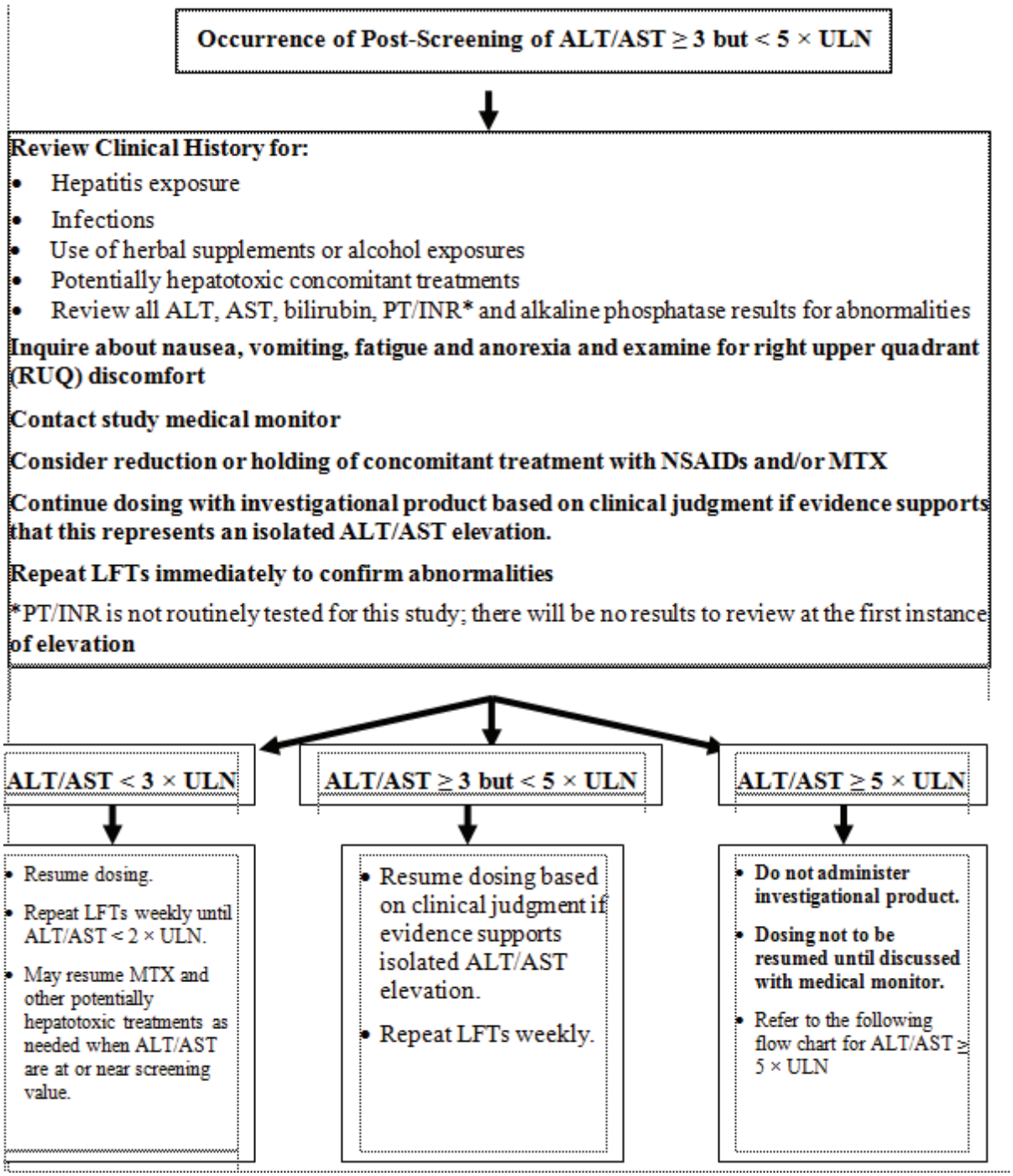
Section IV of the US FDA document deals with the clinical evaluation of and monitoring of drug-induced liver injury, and this protocol-specific guidance has adopted the recommendations on detection of drug-induced liver disease, confirmation of abnormal ALT/AST with regard to retesting, follow-up observation, advice on appropriate history gathering and advice on the need for obtaining additional laboratory tests and consultations as needed. MedImmune has adopted a conservative approach to holding administration of investigational product based on abnormal liver function tests (LFTs) until a full understanding of the event has been understood by the principle investigator and the medical monitor. This understanding is required so that the principle investigator, in consultation with the medical monitor, can reach a decision as to whether dosing can be continued or whether it is advisable to stop investigational product permanently. The US FDA document acknowledges there is no published consensus on how this decision should be made but this protocol-specific guidance requires involvement of the medical monitor at any early stage of clinically significant increases in ALT/AST to provide additional information on accumulating clinical experience of MEDI-546 as well as input from the investigator regarding the nature of the subject and other factors that may be relevant. This approach will provide the balance necessary to permit learning about the investigational product while maximizing safety concerns to minimize the potential for functional liver impairment and damage. There are 2 separate parts to the guidance to detect clinically significant liver injury depending on whether the subject entered the study with normal or mildly elevated (up to 2 × ULN) ALT/AST or on more severe abnormalities in subjects with ALT/AST > 2 × ULN at baseline.

For the purpose of this document, LFTs will be AST, ALT, total bilirubin, and alkaline phosphatase.

The decision to include subjects in this clinical trial with baseline LFT abnormalities is supported by the US FDA guidance.

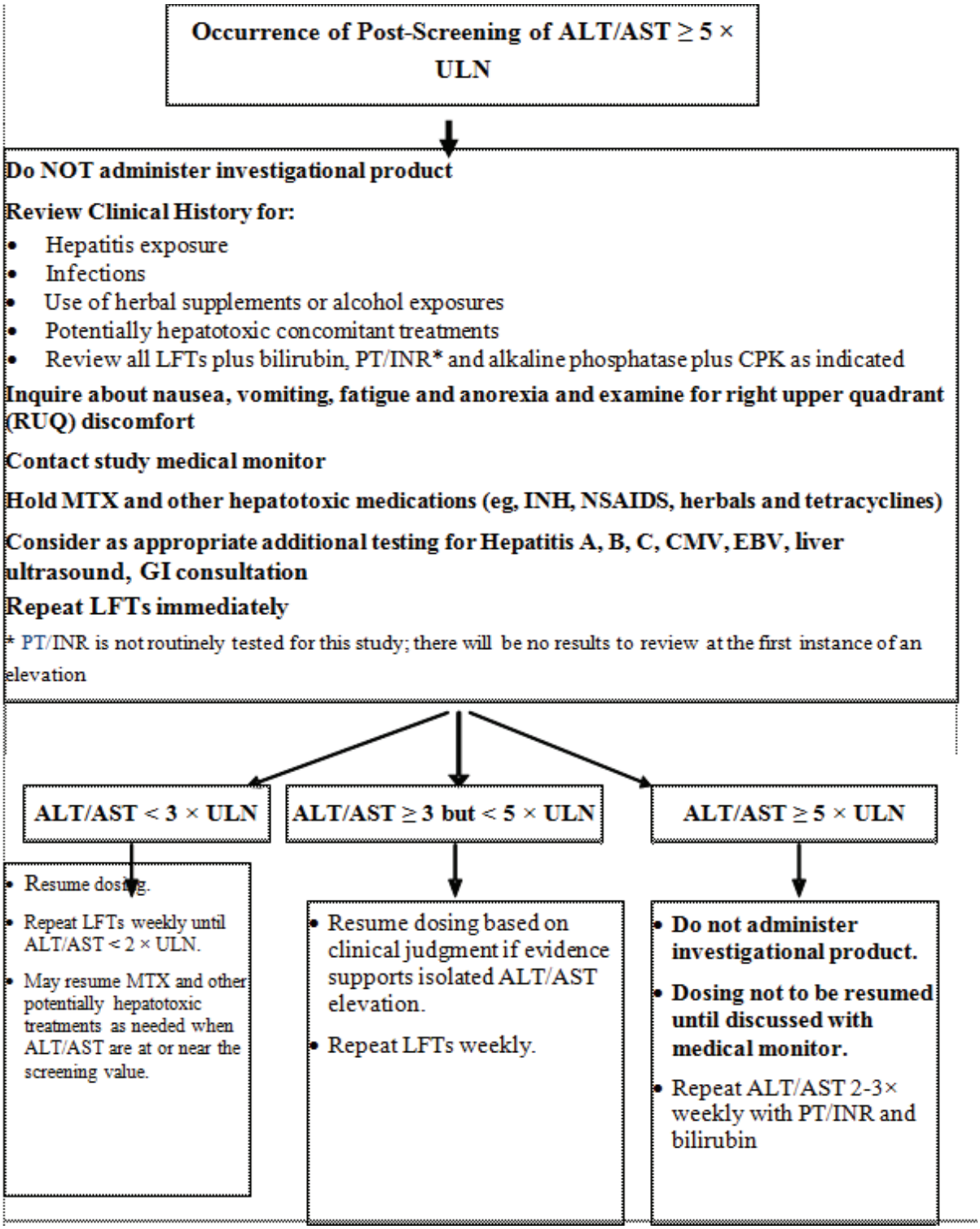
Copies of the document “Guidance of Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation” can be located at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Guidance for abnormal LFTs that develop post-screening in subjects with ALT/AST ≤ 2 × ULN at screening due to liver involvement by SLE in the opinion of the investigator:



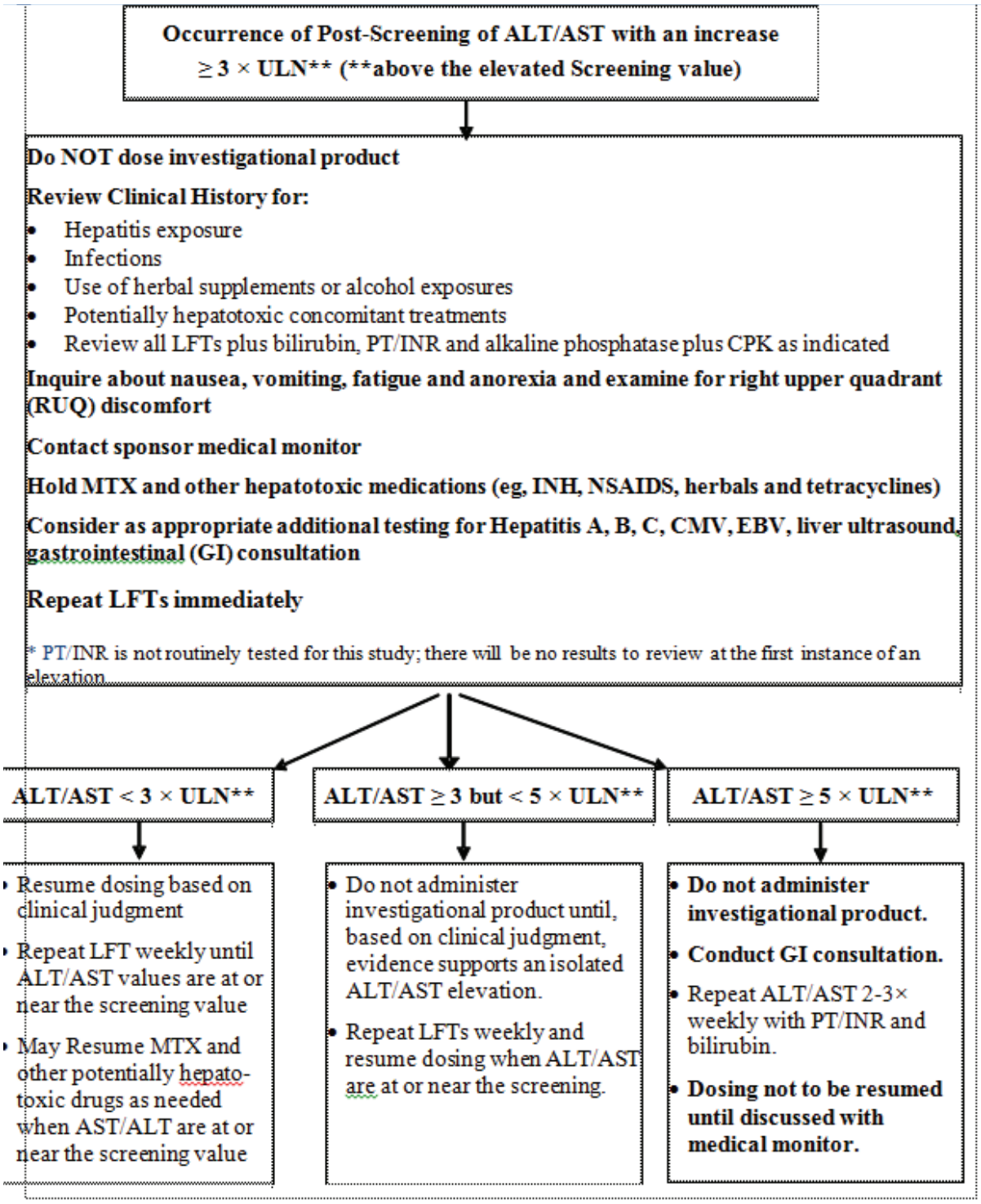
ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalization ratio; LFT = liver function test; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; PT = prothrombin time; RUQ = right upper quadrant; SLE = systemic lupus erythematosus; ULN = upper limit of normal

Guidance for abnormal LFTs that develop post-screening in subjects with ALT/AST ≤ 2 × ULN at screening due to liver involvement by SLE in the opinion of the investigator:



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; CPK = creatinine phosphokinase; EBV = Epstein-Barr virus; GI = gastrointestinal; INH = isoniazid; INR = international normalization ratio; LFT = liver function test; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; PT = prothrombin time; RUQ = right upper quadrant; SLE = systemic lupus erythematosus; ULN = upper limit of normal

Guidance for abnormal LFTs that develop post-screening in subjects with ALT/AST > 2 × ULN at screening due to liver involvement by SLE in the opinion of the investigator:



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; CPK = creatinine phosphokinase; EBV = Epstein-Barr virus; GI = gastrointestinal; INH = isoniazid; INR = international normalization ratio; LFT = liver function test; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drugs; PT = prothrombin time; RUQ = right upper quadrant; SLE = systemic lupus erythematosus; ULN = upper limit of normal

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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.