A PHASE IB, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF MULTIPLE INTRAVENOUS DOSES OF MEDI-545, A FULLY HUMAN ANTI-INTERFERON-ALPHA MONOCLONAL ANTIBODY, IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Study Agent: MEDI-545

MedImmune Protocol Number: MI-CP152

IND Number: IND 12751

Manufacturer: MedImmune
[redacted]
Phone: [redacted]
Fax: [redacted]

Sponsor: MedImmune

Medical Monitor: [redacted]
Associate Director, Clinical Development
MedImmune
Phone: [redacted]
Fax: [redacted]

Study Monitor: MedImmune

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

Signature_____ Date_____

Printed Name_____

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine aminotransferase
ANAM	Automated Neuropsychological Assessment Metrics
ANA	Antinuclear antibody
AST	Aspartate aminotransferase
AUC_{τ}	Area under the concentration curve within a dosing interval
$AUC_{ss, \tau}$	Area under the curve within a dosing interval at steady state
BILAG	British Isles Lupus Assessment Group
BUN	Blood urea nitrogen
CL_{ss}	Total body clearance at steady state
C_{max}	Peak concentration
$C_{ss, max}$	Peak concentration within a dosing interval at steady state
$C_{ss, min}$	Trough concentration at steady state
CTMM	Clinical Trial Material Manager
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
MHAQ	Modified Health Assessment Questionnaire
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HSV	Herpes simplex virus
IFN	Interferon
Ig	Immunoglobulin
IgG1κ	Immunoglobulin G1 kappa
IM	Immunogenicity
IV	Intravenous
IVP	Intravenous push
IVRS	Interactive voice response system
LFA	Lupus Foundation of America
LFT	Liver function test
Mab	Monoclonal antibody
mRNA	Messenger ribonucleic acid
MRT	Mean residence time
NCI CTCAE V3.0	National Cancer Institute's Common Terminology Criteria for Adverse Events Version 3.0
NSAID	Nonsteroidal anti-inflammatory drug
OBGYN	Obstetrician/gynecologist

pDC	Plasmacytoid dendritic cells
PID	Patient identification number
PGA	Physician global assessment
PK	Pharmacokinetic(s)
RNA	Ribonucleic acid
RNP	Ribonucleoprotein
SAE	Serious adverse events
SC	Subcutaneous
SELENA	Safety of Estrogens in Lupus Erythematosus
SF-36	Short Form 36 Health Survey
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SMC	Safety Monitoring Committee
SSA	Sjogren's Syndrome A
$T_{1/2}$	Terminal phase half-life
T_{max}	Time to peak concentration
$T_{ss, max}$	Time to peak concentration at steady state
TB	Tuberculosis
ULN	Upper limit of normal
Vd_{ss}	Steady state volume of distribution
Vd_z	Terminal phase volume of distribution
λz	Terminal phase elimination rate constant

TABLE OF CONTENTS

STUDY ABSTRACT

TITLE:

A Phase 1b, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety and Tolerability of Multiple Intravenous doses of MEDI-545, a Fully Human Anti-interferon-alpha Monoclonal Antibody, in Patients With Systemic Lupus Erythematosus

RATIONALE:

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that affects multiple organs and can substantially reduce patients' quality of life and increase mortality. Constitutional symptoms, polyarthritis, discoid and photosensitive skin rashes, glomerulonephritis, proteinuria, renal insufficiency, cognitive impairment, psychoses, seizures, neutropenia, lymphopenia, thrombocytopenia, coagulation abnormalities, serositis, and oral ulcers are among the myriad disease manifestations. Current treatment options for moderately to severely active SLE include potent immunosuppressive drugs with unfavorable long-term adverse effects. Recent research data suggest a potential role of type I interferon (IFN) in disease pathogenesis of SLE; thus, IFN inhibition may be efficacious in the treatment of this disease.

MEDI-545 is a fully human $IgG_1\kappa$ MAb that binds to and neutralizes a majority of the subtypes of human IFN-α. In preclinical studies of MEDI-545 in cynomolgus monkeys, no treatment-related toxicological findings except transient, localized reactions at the injection sites were observed. This included a repeated-dose toxicity study in which MEDI-545 was administered intravenously every 2 weeks for 27 weeks (a total of 14 injections). No antibodies against MEDI-545 were detected in immunogenicity (IM) studies in cynomolgus monkeys.

MEDI-545 has been or is being investigated in 5 clinical studies in patients with SLE, psoriasis, or myositis. Two studies are complete, a single-dose intravenous (IV) study in patients with SLE (MI-CP126) and a single-dose IV study in patients with psoriasis (MI-CP145). Three studies are ongoing, a multiple-dose IV study in patients with SLE (MI-CP152), a multiple-dose IV study in patients with myositis (MI-CP151), and a multiple-dose subcutaneous (SC) study in patients with SLE (MI-CP179). The first clinical trial of MEDI-545, MI-CP126, was a randomized, double-blind, placebo-controlled, single-dose, dose-escalation study with an open-label extension evaluating the safety and tolerability of single IV doses of MEDI-545 ranging from 0.3 to 30.0 mg/kg. A total of 67 patients were treated in the study, including 50 patients (17 in the placebo group and 33 in the MEDI-545 group) in the blinded phase and 17 patients in the open-label extension. Single-dose administration of IV MEDI-545 at doses ranging from 0.3 to 30.0 mg/kg to patients with mild to moderate SLE was well tolerated in this study. There were no deaths, no related serious adverse events (SAEs), and no adverse events (AEs) that resulted in discontinuation of study drug reported in either the blinded phase or open-label extension. The pattern and type of AEs were generally consistent with the underlying conditions of this patient population. No dose effect was observed for safety considerations, and most AEs were associated with the system organ classes of Investigations and Musculoskeletal and Connective

Tissue Disorders. The most common AEs in > 10% of patients in the MEDI-545 group were blood bicarbonate decreased, blood glucose decreased, systemic lupus erythematosus flares, hemoglobin decreased, protein urine present, diarrhea, headache, nausea, and arthralgia.. The majority of AEs were Grade 1 (mild) in severity. Viral reactivation events occurred at a low frequency in both the placebo and MEDI-545 groups during the study. All but one event was Grade 1 in severity. MEDI-545 mean serum concentrations following IV administration exhibited a bi-phasic decline with a shallow initial distribution phase followed by a prolonged terminal elimination phase. In both the blinded phase and open-label extension, MEDI-545 pharmacokinetics (PK) was linear and dose proportional over the dose ranges tested. Mean maximum observed concentration (C_{max}) and area under the curve (AUC) increased proportionally with dose. In the blinded phase, mean half-life ($T_{1/2}$) ranged between 15.4 and 23.5 days (excluding the 1.0 mg/kg dose group), and mean CL ranged between 143 and 197 mL/day. In the open-label extension, mean $T_{1/2}$ ranged between 19.8 and 28.0 days, and mean clearance (CL) ranged between 147 and 184 mL/day. Both mean $T_{1/2}$ and CL values indicate that the target IFN-α does not seem to influence MEDI-545 PK. The low volumes of distribution, about 3 to 7 L, indicate limited distribution of MEDI-545 systemically. There was no detectable antibody response to MEDI-545 (defined as a titer with a dilution value of ≥1:10) seen for any patient at any time point for the blinded phase and open-label extension. A dose-dependent neutralization of type I IFN gene signature was noted following single IV administration of MEDI-545 at doses ranging from 0.3 to 30.0 mg/kg. Assessment of clinical outcome using standard SLE evaluation methods (ie, British Isles Lupus Assessment Group, Safety of Estrogens in Lupus Erythematosus, Systemic Lupus Erythematosus Disease Activity Index, and physician global assessment) suggested improvement of disease by MEDI-545 in the blinded phase of the study. Clinical outcomes in the open-label extension were similar to those in the MEDI-545 group reported in the blinded phase. After the study reporting period for SAEs had ended, a report of angiosarcoma of the left breast was reported for a patient that had participated in the MI-CP126 study. The patient had received a single 1.0 mg/kg dose of MEDI-545. Thirteen months after receipt of the single dose of MEDI-545, a left breast mass was detected and further investigated. The mass was determined to be an angiosarcoma.

MI-CP145 was a Phase 1, multicenter, randomized, double-blind, placebo-controlled, dose-escalation study of single-dose IV MEDI-545 (0.3, 1.0, 3.0, 10.0, or 30.0 mg/kg) in 40 adult patients with chronic plaque psoriasis. A total of 36 patients received MEDI-545 or placebo in this study. This study was discontinued after the first patient in the 30.0 mg/kg dose cohort had an SAE of anaphylactic reaction (infusion reaction) during administration of study drug and was hospitalized for 3 days. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug in that patient. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies, that tryptase levels 10 hours after the event were normal, that the drug product met quality standards, and that when this anaphylactic event occurred, the patient was receiving drug at a relatively high rate of infusion. After thorough review, the Medical Monitor judged this event to be an infusion reaction and the Safety Monitoring Committee (SMC) concurred. Single-dose administration of IV MEDI-545 at doses ranging from 0.3 to 10.0 mg/kg to patients with chronic plaque psoriasis was well tolerated in this study. There were no deaths reported in the study. One patient randomized to the MEDI-545 30 mg/kg treatment group, discontinued investigational product due to a serious anaphylactic reaction. There were no other SAEs or AEs that resulted in discontinuation of

investigational product. One other patient had an SAEs of myocardial infarction, which was judged by the investigator as not related to MEDI-545. No dose effect was observed, and most AEs were associated with the system organ class of Investigations. The most common AEs in > 10% of patients in the MEDI-545group were nasopharyngitis, white blood cell count increase, back pain, pain in extremity, and headache. MEDI-545 mean serum concentrations following IV administration exhibited a bi-phasic decline with a shallow initial distribution phase followed by a prolonged terminal elimination phase. MEDI-545 PK was linear and dose proportional over the dose range of 0.3 to 10.0 mg/kg. Mean C_{max} and AUC increased proportionally with dose from 14.9 µg/mL following 0.3 mg/kg to 338 µg/mL after 10.0 mg/kg, except for a high individual value of 1447 µg/mL in the 3.0 mg/kg dose cohort. Dose proportionality was also observed for $AUC_{(0-t)}$ and AUC over the dose range of 0.3 mg/kg to 10.0 mg/kg. Mean $T_{1/2}$ was about 21 days across the different doses; mean CL ranged between 115 and 194 mL/day across dose groups. Both mean $T_{1/2}$ and CL values indicate that the target IFN-α does not seem to influence MEDI-545 PK. The low volumes of distribution, about 3 to 6 L, and the similarity of mean Vd_{ss} and mean Vd_z values indicate limited distribution of MEDI-545. There was no detectable antibody response to MEDI-545 (defined as a titer with a dilution value of ≥1:10) seen for any patient at any time point, using a drug tolerant assay. There were no primary or secondary efficacy variables in this study; however, exploratory analyses were conducted to evaluate the potential effects of MEDI-545 on neutralization of type I interferon gene signature, clinical response, inflammatory histological features in skin biopsies, and patient-reported outcomes. The effects of MEDI-545 on neutralization of type I interferon gene signature showed no difference in inhibition of gene signature in involved skin at either Study Day 14 or Study Day 28. Changes in target lesions were similar between the placebo and MEDI-545 group as were the changes in PASI score, PASI 50 responses, and PGA. In addition, the patient-reported outcomes showed little or no differences in the assessments of VAS, DLQI, SF36, and BDI.

MI-CP151 is a Phase 1b, multicenter, multinational, randomized, double-blind, placebo-controlled study to evaluate the safety of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) in 40 adult patients with dermatomyositis (DM) or polymyositis (PM). In this study, MEDI-545 or placebo is initially administered every 2 weeks for 12 weeks (7 doses) followed 2 weeks later by MEDI-545 every 2 weeks for another 12 weeks (7 doses) for a total of 26 weeks (14 doses). The study is ongoing, and data remain blinded to treatment assignment. As of 02/Nov/2009, 51 patients have been dosed in MI-CP151. The majority of AEs are mild or moderate in severity. The most common AE (incidence > 10%) is headache. There is one viral reactivation AE (Grade 2 herpes zoster ophthalmic). There are no deaths reported in MI-CP151. Nine of the 51 patients (17.6%) have SAEs. For 1 patient, the SAE (hyponatremia) was judged by the investigator as related to study drug.

The current study, MI-CP152, is a dose-escalation study to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) in 148 adult patients with SLE. In this study, MEDI-545 is being administered every 2 weeks for a total of 14 doses over 26 weeks. The planned starting dose of MEDI-545 (0.3 mg/kg) in MI-CP152 is less than one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated administrations every 2 weeks for 27 weeks). The first 12 randomized patients in each dose cohort will provide safety data for dose escalation; the additional patients planned (20 each in Dose Cohorts 1 through 3 and 40 in Dose Cohort 4) are intended to increase safety data and provide adequate numbers of

patients for exploratory analyses of effect of MEDI-545 on the inhibition of type I IFN gene signature. On 28/Sep/2007, one patient in MI-CP152 experienced an SAE of Grade 3 hypersensitivity reaction characterized by chills, rigors, swollen hands, hives, moderate hypotension and several bouts of diarrhea following the fifth dose of MEDI-545 (1.0 mg/kg), which resolved the same day. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug. The patient was discharged home several hours after the infusion. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies and that when this event occurred, the patient was receiving drug at a relatively high rate of infusion. After thorough review, the Medical Monitor judged this event to be an infusion reaction. Study MI-CP152 was stopped on 10/Oct/2007 due to an SAE of anaphylactic reaction associated with Grade 4 hypotension in MI-CP145 and resumed in January 2008.

A review of the safety data from both MI-CP145 and MI-CP152 concluded the aforementioned SAEs of an infusion reaction in each study were most likely due to MEDI-545 administered at a high rate of infusion, approximately 92 and 75 mg per minute for these 2 patients weighing 92 and 122 kg, respectively. As a result of this determination it was decided to decrease the likelihood of future events such as these by limiting the potential for administration of these high rates of MEDI-545 infusion by decreasing the maximum dose of MEDI-545 permitted and mandating a minimum period of administration. Consequently, the MI-CP152 and the MI-CP151 protocols were amended to reduce the starting dose of MEDI-545 from 1.0 to 0.3 mg/kg, reduce the highest dose of MEDI-545 from 30.0 to 10.0 mg/kg, and set the infusion volume and time to 100 mL over at least 60 minutes

In the interest of potential safety, a decision was made to eliminate Dose Cohort 5 that allowed infusion to be administered over 30 minutes. While it would be desirable from a convenience standpoint for the patient to decrease the length of study medication infusion time to 30 minutes, it is likely that any infusion reaction of an allergic nature, while uncommon, could potentially have more severe manifestations than might be expected if the infusion was administered at a more rapid rate. It is not apparent that the overall incidence of these uncommon reactions will be diminished in those patients in Dose Cohort 4 with the 60 minute infusion time being utilized, but the potential severity of those events could be reduced. Thus, it was felt that the benefit of utilizing a 30-minute length of infusion versus the 60-minute length of infusion did not outweigh the potential safety risk and the overall drug administration to the patient remains the same. The additional 20 patients added to Dose Cohort 4 will provide additional experience with the duration of infusion that will be employed in any additional planned studies.

As of 02/Nov/2009, 183 patients have been dosed in the current study, MI-CP152. This study is ongoing, and data remain blinded to treatment assignment. The majority of AEs are mild or moderate in severity. The most common AEs (incidence >10%) are urinary tract infection, nasopharyngitis, lymphocyte count decreased, blood potassium decreased, nausea, diarrhoea, systemic lupus erythematosus flares, arthralgia, and headache. Viral reactivation AEs occurred in 10 patients. There have been 5 deaths in the study, four of which were judged by the investigator as unrelated to study drug. One death was due to multiple drug overdose, another due to congestive heart failure and another patient died in screening due to sepsis before receiving study drug. There was one death due to herpes encephalitis. The study drug was unblinded for this patient and the patient was receiving placebo. Finally one patient died due to liver failure, this

event was judged by the investigator as being related to study drug, however the sponsor considers the event to be related to a blood infection and low blood pressure. This patient also took herbal medicines. The possibility exists that use of herbal medicines combined with MEDI-545 may increase a risk of unexpected liver problems. SAEs occurred in 31 of the 183 patients (37.3%), with 8 patients having related SAEs. One patient had a diagnosis of lymphoma that occurred after the patient received 2 doses of study drug, although signs and symptoms of lymphoma were present before any study drug was given.
. A third study of MEDI-545 in patients with SLE (MI-CP179) is evaluating the safety and tolerability of multiple SC dose schedules of MEDI-545 and/or placebo. In this study, a total of 80 patients will be randomized in a 1:1:2:2:2 ratio to receive 1 of 5 treatment arms of MEDI-545 or placebo as follows: (1) SC MEDI-545 100 mg once; SC Placebo × 12 doses on other weeks; (2) SC MEDI-545 100 mg every 4 weeks × 4 doses; SC Placebo × 9 doses on other weeks; (3) SC MEDI-545 100 mg every 2 weeks × 7 doses; SC Placebo × 6 doses on other weeks; (4) SC MEDI-545 100 mg every week × 13 doses; and (5) SC Placebo every week × 13 doses. As of 02/Nov/2009, 74 patients have been dosed in MI-CP179. The majority of AEs are mild or moderate in severity. The most common AEs (incidence > 10%) are upper respiratory tract infection and nausea. There are no viral reactivation AEs. There was one case of breast cancer (angiosarcoma) that was judged by the investigator as being not related to study drug. There are no deaths reported in MI-CP179. Five of the 74 patients (6.8%) had SAEs. Two SAEs (cellulitis and pneumonia) were judged by the investigator as related to study drug.

OBJECTIVES:

Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of multiple IV doses of MEDI-545 in adult patients with SLE.

Secondary Objectives

The secondary objectives of the study are to evaluate the pharmacokinetic (PK) and Immunogenicity (IM) of multiple IV doses of MEDI-545 in adult patients with SLE.

Exploratory Objectives

Exploratory objectives are to:
1. Evaluate the effect of MEDI-545 on the expression of type I IFN-inducible genes;
2. Evaluate the effect of MEDI-545 on other potential disease mechanisms in SLE;
3. Evaluate the effect of MEDI-545 on disease activity; and
4. Evaluate the effect of MEDI-545 on patient-reported outcomes in this patient population.

DESIGN:

This is a multicenter, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and tolerability of multiple IV doses of MEDI-545 in adult patients with SLE.

Approximately 30 to 40 international sites (USA, Canada, Brazil, Argentina, and Chile) will participate in this study.

A total of 148 evaluable patients are planned for the study; this excludes the 22 patients who were treated prior to 10/Oct/2007. Four escalating doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo will be tested using an infusion time of at least 60 minutes. Dose Cohorts 1 through 3 will include 32 patients each; while Dose Cohort 4 will include 52 patients. All patients will be randomized in a 3:1 ratio, using central randomization (without regard to site) and stratified by the level of type I IFN-inducible gene signature (low/undetectable versus high), to receive either MEDI-545 or placebo (ie, 24 patients each in Dose Cohorts 1 through 3 will receive MEDI-545 and 8 patients will receive placebo and 39 patients in Dose Cohort 4 will receive MEDI-545 and 13 patients will receive placebo).

Patients are considered evaluable if they receive the first 4 doses of study drug (MEDI-545 or placebo) and complete the required evaluations, or if they discontinue study drug administration before the fourth dose for safety reasons. Nonevaluable patients may be replaced to maintain a size of at least 32 patients each in Dose Cohorts 1 through 3 and 52 patients in Dose Cohort 4. Data from all patients will be included in safety analyses. A dose cohort may be expanded by up to 4 additional patients if eligible patients are already in screening at the time 32 patients in Dose Cohorts 1 through 3 or 52 patients in Dose Cohort 4 have been randomized into the dose cohort.

MEDI-545 or placebo will be administered as an IV infusion for at least 60 minutes) once every 2 weeks for 26 weeks, for a total of 14 doses. Study drug administration will start on Study Day 0 and continue through Study Day 182. Patients will be generally maintained on the same stable dose of SLE treatment as baseline through Study Day 196. SLE treatment may be adjusted as clinically indicated after Study Day 196 through Study Day 350. The follow-up period ends on Study Day 350.

Patients who were treated with study drug prior to 10/Oct/2007 were followed for safety reasons according to the schedule of patient evaluations from Study Day 238 through Study Day 350 as described in Table 4. Decisions regarding dose escalation will be made by the Medical Monitor based on the review of all cumulative, blinded safety information which includes the safety data through Study Day 42 from the first 12 randomized patients in the preceding lower dose cohort.

Patients who participate in this study may have the option of entering a long-term safety study (MI-CP212). This includes both MEDI-545 and placebo patients, including the patients who were treated in MI-CP152 prior to 10/Oct/2007, but excludes patients who discontinued from previous MEDI-545 clinical studies for safety reasons. Patients must complete the treatment period and follow up through Day 266 of this study to participate in MI-CP212. Patients must also qualify for the long-term safety study (following written informed consent), as per the MI-CP212 protocol inclusion and exclusion criteria. If patients qualify, they will receive open-label MEDI-545. Patients may be treated for approximately 3 years and may be followed for an additional 3 months following the last dose of IV MEDI-545.

PATIENT POPULATION:

The patients in this study will be male or female adults with active SLE despite standard of care.

Inclusion Criteria:

Patients must meet *all* of the following criteria:

1. Male or female adults ≥ 18 years of age at the time of the first dose of study drug;
2. Written informed consent obtained from the patient or the patient's legal representative;
3. Meet at least 4 of the 11 revised American College of Rheumatology (ACR) classification criteria for SLE (see Appendix A) (ACR, 1999);
4. Have positive antinuclear antibody (ANA) test at ≥ 1:80 serum dilution in the past or at screening (prior positive ANA test must be documented via a lab report);
5. Have at least one system with a score of A or two systems with a score of B on the British Isles Lupus Assessment Group (BILAG) index at screening, or have a Safety of Estrogens in Lupus Erythematosus (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score ≥ 6;
6. Sexually active women, unless surgically sterile (including tubal ligation) or at least 2 years post-menopausal, must use an effective method of avoiding pregnancy (including oral, injectable, transdermal, or implanted contraceptives, intrauterine device, diaphragm with spermicide, cervical cap, abstinence, or sterile sexual partner) in addition to the use of condoms (male or female condoms with spermicide) from screening through the end of the study. Cessation of birth control after this point should be discussed with a responsible physician. Sexually active men, unless surgically sterile, must likewise practice two effective methods of birth control (condom with spermicide or abstinence) and must use such precautions from Study Day 0 through the end of the study;
7. Ability to complete the study period, including follow-up period through Study Day 350; and
8. Willing to forego other forms of experimental treatment during study.

Exclusion Criteria:

Patients must have *none* of the following:

1. Have received MEDI-545 within 120 days prior to screening or have either detectable levels of MEDI-545 or anti-MEDI-545 antibodies (positive at > 1:10 serum dilution) in serum at screening;
2. History of allergy or reaction to any component of the study drug formulation;
3. Have received prednisone > 20 mg/day (or an equivalent dose of another oral corticosteroid) within 14 days before randomization/entry;
4. Have received the following dosages of medications within 28 days before randomization/entry: hydroxychloroquine > 600 mg/day, mycophenolate mofetil > 3 g/day, methotrexate > 25 mg/week, azathioprine > 3 mg/kg/day, cyclophosphamide, cyclosporine, or thalidomide;
5. Have received leflunomide >20 mg/day in the 6 months prior to Study Day 0;
6. Have received fluctuating doses of antimalarials, mycophenolate mofetil, methotrexate, leflunomide, or azathioprine within 28 days before randomization/entry or fluctuating doses

of nonsteroidal anti-inflammatory drugs or oral corticosteroids within 14 days before randomization/entry;

7. Treatment with any investigational drug therapy within 28 days before randomization/entry into the study, B cell-depleting therapies within 12 months before randomization/entry, or biologic therapies within 30 days or 5 half-lives of the biologic agent, whichever is longer, before randomization/entry into the study;
8. In the investigator's opinion, evidence of clinically significant active infection, including ongoing, chronic infection, within 28 days before randomization/entry;
9. A history of severe viral infection, as judged by the investigators, including severe infections of either cytomegalovirus or the herpes family such as disseminated herpes, herpes encephalitis, ophthalmic herpes;
10. Herpes zoster infection within 3 months before randomization/entry;
11. Evidence of infection with hepatitis B or C virus, or human immunodeficiency virus (HIV)-1 or HIV-2, or active infection with hepatitis A, as determined by results of testing at screening;
12. Vaccination with live attenuated viruses within 28 days before randomization/entry;
13. Pregnancy (women, unless surgically sterile or at least 2 years post-menopausal, must have a negative serum pregnancy test within 28 days before receiving the study drug and a negative urine pregnancy test on days of study drug administration before receiving the study drug);
14. Breastfeeding or lactating women;
15. History of primary immunodeficiency;
16. History of alcohol or drug abuse < 1 year prior to randomization/entry;
17. History of cancer (except basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy > 1 year prior to randomization/entry);
18. History of active tuberculosis (TB) infection;
19. History of latent tuberculosis infection or newly positive TB skin test (reaction defined as ≥ 10 mm in diameter if not on systemic immunosuppressive medication or ≥ 5 mm if on systemic immunosuppressive medication) without completion of an appropriate course of treatment or with ongoing prophylactic therapy;
20. Elective surgery planned from the time of screening through Study Day 196;
21. At screening blood tests (within 28 days before randomization/entry), any of the following:
    - Aspartate aminotransferase (AST) > 2 × upper limit of normal range (ULN), unless caused by SLE, as determined by the investigator
    - Alanine aminotransferase (ALT) > 2 × ULN, unless caused by SLE, as determined by the investigator
    - Creatinine > 4.0 mg/dL (> 354 μmol/L)
    - Neutrophils < 1,500/μL (< 1.5×10^9/L)
    - Platelet count < 50,000/ μL (< 50×10^9/L)
22. History of any disease, evidence of any current disease (other than SLE), any finding upon physical examination, or any laboratory abnormality that, in the opinion of the investigator or medical monitor, may compromise the safety of the patient in the study or confound the analysis of the study; or
23. Any employee of the research site who is involved with the conduct of the study.

TREATMENT:

A total of 148 evaluable patients are planned for the study; this excludes the 22 patients who were treated prior to 10/Oct/2007. Four escalating doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo will be tested using an infusion time of at least 60 minutes Dose cohorts 1 through 3 will include 32 patients each; while Dose Cohort 4 will include 52 patients. All patients will be randomized in a 3:1 ratio to receive either MEDI-545 or placebo (ie, 24 patients each in Dose Cohorts 1 through 3 will receive MEDI-545 and 8 patients will receive placebo and 39 patients in Dose Cohort 4 will receive MEDI-545 and 13 will receive placebo). MEDI-545 or placebo will be administered every 2 weeks as an IV infusion for 26 weeks, for a total of 14 doses.

Dose Cohort	N[a]	Treatment	Infusion Time
1	32	MEDI-545 0.3 mg/kg (n=24): Placebo (n=8)	60 minutes
2	32	MEDI-545 1.0 mg/kg (n=24): Placebo (n=8)	60 minutes
3	32	MEDI-545 3.0 mg/kg (n=24): Placebo (n=8)	60 minutes
4	52	MEDI-545 10.0 mg/kg (n=39): Placebo (n=13)	60 minutes

a. A dose cohort may be expanded by up to 4 additional patients if eligible patients are already in screening at the time 32 patients each in Dose Cohorts 1 through 3 or 52 patients in Dose Cohort 4 have been randomized into the dose cohort.

PATIENT EVALUATION AND FOLLOW-UP:

Screening evaluations include medical history, physical examination, BILAG/SELENA-SLEDAI assessments, electrocardiogram (ECG), chest x-ray (or chest x-ray with two views [anterior-posterior and lateral] or computed tomography (CT) scan performed within the previous 6 months), tuberculosis (TB) skin test, blood tests for hepatitis A, B, C, HIV-1 and HIV-2, serum and urine β human chorionic gonadotropin (βHCG) for women (unless surgically sterile or 2 years after menopause), AEs/SAEs, serum chemistry panel (including Na, K, Cl, bicarbonate, blood urea nitrogen, creatinine, AST, ALT, bilirubin, alkaline phosphatase, and random glucose), complete blood count (CBC) with differential and platelets, autoantibodies and complement levels, and urinalysis. In addition, whole blood samples are taken to analyze levels of messenger RNA (mRNA) for type I IFN-inducible gene expression; the results are used for randomization stratification. In patients who have received MEDI-545 previously, serum levels of MEDI-545 and antibodies to MEDI-545 at screening will be measured. A negative urine βHCG for women (unless surgically sterile or 2 years after menopause) on all study days is required before study drug administration.

Safety assessments include AE and SAE evaluation, physical examination, vital signs, serum chemistry panel, CBC with differential and platelets, serum for safety biomarkers in any patient who has a Grade 1 or higher infusion reaction (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies), urinalysis, and viral cultures and titers via oropharyngeal swabs for herpes simplex virus (HSV)-1 and HSV-2; vaginal swabs (women) for HSV-1, HSV-2, and human papillomavirus (HPV); and blood tests for Epstein Barr virus and cytomegalovirus.

MEDI-545 serum concentrations and anti-MEDI-545 antibodies will be measured to assess PK and IM profiles of MEDI-545.

Clinical disease activity is assessed using the following indicators: requirement of rescue oral, IV, intra-articular, or intramuscular corticosteroids or other potential disease modifying therapies to treat SLE during the treatment period, changes from baseline in SLE treatment during the follow-up period, BILAG scores, SELENA-SLEDAI score, flares, active joint count, physician global assessment, photographs of skin lesions (optional, if present), and renal function. In addition, autoantibodies and complement levels in blood will be measured.

Patient-reported outcomes are measured using the following instruments: Patient global assessment, Automated Neuropsychological Assessment Metrics tests (this test is optional and is only being done at selected North American sites), modified health assessment questionnaire, Beck Depression Index (this test is only being done at North American sites), the Krupp Fatigue Severity score, work productivity questionnaire, and the Short Form 36 Health Survey.

Exploratory analyses will be performed to investigate the effects of MEDI-545 on the levels of type I IFN-inducible gene expression in whole blood through analyses of RNA gene expression signatures. Other exploratory tests will examine the effect of MEDI-545 B cell subsets and other potential SLE biomarkers.

ASSESSMENT OF ENDPOINTS:

There will be 2 patient populations analyzed in this study. The primary patient population will include up to 164 patients who receive study drug (excluding patients who received study drug prior to 10/Oct/2007). The secondary patient population will include only the 22 patients who received study drug prior to 10/Oct/2007.

The safety and tolerability of MEDI-545 will be assessed primarily by summarizing treatment-emergent AEs/SAEs and by assessing changes in viral cultures and titers, including oropharyngeal swabs for HSV-1 and HSV-2; vaginal swabs for HSV-1, HSV-2, and HPV; and peripheral blood test (using polymerase chain reaction testing) for Epstein Barr Virus and cytomegalovirus. The occurrence of treatment-emergent AEs and SAEs will be summarized from the first administration of study drug through Study Day 350. Treatment-emergent AEs and SAEs will be summarized by system organ class and preferred terms, by severity, and by relationship to study drug. For the primary population, treatment-emergent AEs and SAEs will be summarized for placebo, each of the MEDI-545 dose cohorts, and for all MEDI-545 doses combined. No formal statistical testing will be performed to compare treatment groups. Other variables used for the safety assessments include serum chemistry, CBC with differential and platelets, and urinalysis. These variables as well as their changes from baseline will be summarized descriptively.

The secondary endpoints of this study are the PK and IM of multiple IV doses of MEDI-545. PK parameters such as maximum serum concentration, half-life, area under the concentration curve, clearance, and volume of distribution will be estimated. All PK parameters will be estimated by noncompartamental analysis. IM results will be analyzed by summarizing the

number and percentage of SLE patients who develop detectable anti-MEDI-545 antibodies by treatment and dose cohort. PK and IM results will be analyzed separately for the primary and secondary patient populations.

The inhibition of Type I IFN gene expression in whole blood will be summarized for MEDI-545 and placebo-treated patients. Data for B cell subsets, other potential SLE biomarkers, measures of disease activity including flares and changes in concomitant SLE medications, and patient-reported outcomes will be summarized in a similar manner.

1 INTRODUCTION

1.1 Background

Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease (American College of Rheumatology [ACR], 1999). The disease includes constitutional symptoms and signs and musculoskeletal, mucocutaneous, renal, pulmonary, cardiac, hematologic, and neuropsychiatric manifestations. In addition, serological abnormalities include antinuclear antibodies (ANA); antibodies to double-stranded (ds) DNA, Smith (Sm) antigen, ribonucleoprotein (RNP), Ro/Sjogren's Syndrome A (SSA) and La/SSB antigens and cardiolipin; and low complement levels.

The prevalence of SLE in the United States is approximately 40 to 50 cases per 100,000 people (Lawrence, 1998). Reported incidence of new cases varies from 2 to 8 per 100,000 people per year (Hochberg, 1985). SLE may occur at any age in men or women, but predominantly affects women of childbearing years (Cooper, 1998; Lahita, 1999). About 20% of patients develop lupus before 16 years of age, 65% between 16 and 65 years, and 15% after the age of 65 years. For lupus patients of all ages, the overall female-to-male ratio is about 9:1 or 10:1.

More than half of SLE patients have evidence of chronic damage to one or more organ systems, which is a major contributor to the mortality and morbidity associated with SLE (Petri, 2001). The most common manifestations of SLE are fatigue (74%–100%), arthritis or arthralgia (83%–95%), skin involvement (80%– 91%), fever (40%–80%), weight loss (44%–60%), renal disease (34%–73%), gastrointestinal involvement (38%–44%), pulmonary involvement (24%–98%), cardiac involvement (20%–46%), lymphadenopathy (21%–50%), splenomegaly (9%–20%), hepatomegaly (7%–25%), and central nervous system involvement (25%–75%) (von Feldt, 1995). Central nervous system involvement, reflected in functional and cognitive impairment, affects a large number of patients. Psychosis and convulsions occur in 5%–52% and 2%–20% of patients, respectively, over the course of the disease (von Feldt, 1995).

SLE patients typically have periods of waxing and waning disease activities. Periods of increased disease activity are referred to as flares. It is not known what causes SLE flares. Evidence suggests that in populations of patients followed at academic centers, the median disease flare rate is on average 0.6 flares per year or more (von Feldt, 1995; Ho, 2001).

SLE reduces the quality of life in many patients (Dobkin, 1999). Instruments that measure health-related quality of life include the Arthritis Impact Measurement Scales, the Short Form 36 Health Survey (SF-36), SF-20 Health Survey, and the Health Assessment Questionnaire (HAQ). The Clinical Activity Index, the Systemic Lupus Activity Measure, the Safety of Estrogens in Lupus Erythematosus (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and the British Isles Lupus Activity Group (BILAG) scores (Dobkin, 1999) measure disease activity of lupus. Disability is increased in SLE patients. During periods of active disease, patients often suffer from fatigue that significantly affects their daily activities. Two of three lupus patients report a complete or partial loss of their income because they are unable to work. One in 3 patients has been temporarily disabled by the disease, and one in 4 patients currently receives disability payments (Lupus Foundation of America, 2007).

Mortality of lupus patients has remained higher than that of the general population despite advances in treatment. In a study of the Olmsted County, MN population, the standardized mortality rate ratio of lupus patients compared with the general population was 2.70 (95% confidence interval: 1.65-4.18) between 1950 and 1992 (Uramoto, 1999). The U.S. Centers for Disease Control and Prevention issued a report in May 2002, which indicated that deaths attributed to lupus increased over a 20-year period, particularly among African American women between 45 and 64 years of age. However, it is not clear if the rise is the result of an actual increase in lupus mortality or better identification and reporting of deaths due to complications of the disease. Two of the most common causes of death in people with lupus are overwhelming infection and kidney failure.

There is substantial unmet medical need in the treatment of SLE. Despite the fact that SLE can be a serious and life-threatening illness, no new therapy has been approved for SLE treatment in four decades (Wallace, 2003). Many agents currently used to treat SLE, such as azathioprine, cyclophosphamide, and mycophenolate, have not been approved for the disease. Treatments for mild SLE include nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics for fever, arthralgia, and arthritis; and topical sunscreens to minimize photosensitivity. Antimalarial agents (eg, hydroxychloroquine) and corticosteroids may be added to control arthralgia, arthritis, and rashes. Patients with moderate-to-severe disease activity are treated with corticosteroids, and steroid-sparing agents including azathioprine, cyclophosphamide, or mycophenolate mofetil. It is often difficult to taper patients with moderate or severe disease completely off corticosteroids, which cause long-term morbidity and may contribute to early cardiovascular mortality (Urowitz, 1976; Petri, 2001). Even low-dose prednisone, if used as a long-term treatment, carries increased risk for side effects (Petri, 2001).

Interferons (IFNs) are classified into type I and type II (Theofilopoulos, 2005). Type I IFNs include IFN-α (13 subtypes) and IFNs β, ω, and κ. Evidence suggests that type I IFNs have a role in SLE (Crow, 2003; Kirou, 2005; Dall'era, 2005; Baechler, 2003; Baechler, 2004). Type I IFNs stimulate the maturation of plasmacytoid dendritic cells (pDCs) and the generation and function of natural killer cells, T cells, and B cells. Treatment with IFN-α has been associated with the development of SLE autoantibodies and clinical features of the disease (Niewold, 2005; Ioannou, 2000). In murine models of SLE, type I IFN receptor deficiency appears to protect against lupus (Santiago-Raber, 2003; Kono, 2003). IFN-α activity is elevated in the sera of SLE patients (Ytterberg, 1982; Bengtsson, 2000; Dall'era, 2005; Hua, 2006). IFN levels are strongly associated with SLE disease activity (Bengtsson, 2000; Dall'era, 2005). Patients with high anti-dsDNA antibody titers, lupus nephritis, and progressive skin rashes have high serum levels of type I IFN (Bengtsson, 2000). In addition, patients with acute skin involvement tend to have elevated IFN in blood and skin (Dall'era, 2005). Increased expression of genes induced by type I interferons (know as the gene expression signature) is prominent in peripheral blood mononuclear cells in approximately 60% of SLE patients and is associated with greater disease activity (Baechler, 2003; Bennett, 2003; Crow, 2003; Kirou, 2004; Kirou, 2005; Feng, 2006). Skin biopsies from both the affected and unaffected skin of patients with SLE also show increased type I IFN gene signature (Blomberg, 2001; Farkas, 2001). Proteins induced by IFN are increased in patients with active central nervous system symptoms (Okamoto, 2004). These data support the hypothesis that inhibiting type I IFN may reduce disease activity in SLE.

1.2 Description of MEDI-545

MEDI-545 is a fully human $IgG_1\kappa$ MAb that binds to and neutralizes a majority of the subtypes of human IFN-α. MEDI-545 is composed of two identical heavy chains and two identical light chains, with an overall molecular weight of approximately 147 kD. The observed intact mass and peptide map are consistent with the expected protein, based on the DNA sequence. MEDI-545 has N-linked biantennary complex and high mannose type oligosaccharides attached to the heavy chain.

The biological activity of MEDI-545 is quantified relative to reference standard using a luciferase reporter gene bioassay. This bioassay measures the inhibition of IFN-α-induced luciferase expression caused by the binding of MEDI-545 to IFN-α.

1.3 Preclinical Experience with MEDI-545

In preclinical experiments, MEDI-545 has been shown to exhibit: 1) a high potency for neutralization of a broad spectrum of IFN-α subtypes in Daudi cell proliferation assays; 2) reversal of IFN-α–induced cell surface and soluble marker expression in peripheral blood mononuclear cells from healthy donors; and 3) high affinity for antigen as measured by surface plasmon resonance (Biacore®) analysis.

MEDI-545 cross-reacts with cynomolgus monkey IFN-α and neutralizes the biological activity of a subset of recombinant cynomolgus monkey IFN-α, but with reduced potency compared to human IFN-α. In contrast, MEDI-545 does not cross-react with rodent IFN-α. Based on these results, the cynomolgus monkey represents a suitable model to investigate the pharmacological toxicity of MEDI-545. Toxicology studies conducted in cynomolgus monkeys following single or multiple intravenous (IV) and subcutaneous (SC) doses of MEDI-545 show that IV or SC delivery of MEDI-545 is well tolerated with no adverse findings.

In a non-GLP (Good Laboratory Practice) single IV dose pharmacokinetics and immunogenicity study, 4 cynomolgus monkeys received a single IV dose of 50 mg/kg MEDI-545. There was no control group or necropsy in this study. There were no treatment-related adverse effects in study end points that included clinical pathology and immunophenotyping. The only clinical signs noted were transient, localized reactions at the injection site following dose. In a subsequent non-GLP study, 2 cynomolgus monkeys received bolus IV injection (over 4-5 minutes) of 100 mg/kg MEDI-545 and were monitored for 2 days for adverse signs related to bolus IV administration. There was no control group or necropsy in this study and no notable findings following MEDI-545 bolus IV administration.

In a GLP study with single IV dose administration (0, 50 and 100 mg/kg MEDI-545), moderate, transient elevations in aspartate transaminase (AST) and alanine transaminase (ALT) were observed in some of the monkeys, but there were no corresponding histomorphologic changes. Additionally, the mild changes in AST and ALT were fully reversible. These transient mild changes in enzymes without liver histopathology were not considered adverse in nature and were not evident in the subsequent six month repeat IV dose toxicity study. Transient erythema at the injection site was observed in some monkeys following dose administration. The no-observable-

adverse-effect level (NOAEL) for the single-dose toxicity study was determined to be 100 mg/kg, the highest dose tested.

In an initial GLP repeated IV dose study, animals received bolus injections of MEDI-545 (1, 5, or 50 mg/kg) twice weekly for 2 weeks for a total of 4 doses. There were no treatment-related effects on systemic toxicity, mortality, body weights, clinical pathology parameters, or macroscopic or microscopic tissue findings. The NOAEL for this study was determined to be 50 mg/kg/dose, the highest dose tested. In the second repeated-dose study, animals received IV administration of MEDI-545 (0, 10, or 100 mg/kg) every 2 weeks for 27 weeks (14 doses in total). Toxicity was assessed based on survival, clinical observations, body weight, physical examinations, dermal scoring, ophthalmic examinations, electrocardiogram (ECG) examinations, clinical pathology, organ weights, and macroscopic and microscopic pathology. Due to the lack of adverse findings, the NOAEL for MEDI-545 when administered once every 2 weeks via IV injection to cynomolgus monkeys for 27 weeks was determined to be 100 mg/kg, the highest dose tested.

Following single-dose SC administration of MEDI-545 (10, 30, and 100 mg/kg), toxicity was assessed based on mortality, clinical observation, dermal irritation, body weight, ophthalmologic, electrocardiographic, blood pressure, clinical pathology, organ weight, and macroscopic and microscopic pathology data. Immunogenicity assay results found no anti-MEDI-545 antibody detected at any time point for any animal. As there were no treatment-related adverse effects in any parameters assessed, the NOAEL for this study was determined to be at least 100 mg/kg, the highest dose tested.

A repeated SC dose study was intended to bridge to existing repeat IV dose nonclinical safety data. Cynomolgus monkeys received SC injections of a control article or 10 or 100 mg/kg MEDI-545 weekly for 4 weeks for a total of 4 doses. Toxicity was assessed based on survival, clinical observations, body weight, physical examinations, dermal scoring, ophthalmic examinations, ECG examination, blood pressure, clinical pathology, organ weights, and macroscopic and microscopic pathology. All animals survived until their scheduled sacrifice. No adverse treatment-related findings occurred in any of the parameters assessed. The NOAEL for the repeated-dose SC toxicity study was determined to be at least 100 mg/kg, the highest dose tested.

Results from the toxicokinetics data collected in the 6 month repeat IV dose study showed that after the last dose (Dose 14) the mean half-life was 499 hours (21 days and 547 hours (23 days for the 10 and 100 mg/kg groups, respectively). There were no anti-MEDI-545 antibodies detected in any of the IV monkey studies. Comparison of toxicokinetics at the 100 mg/kg SC dose from the single SC dose study and the single IV dose study demonstrated satisfactory bioavailability by the SC route. The SC C_{max} was 1576.3 μg/mL compared to the 2235 μg/mL for IV. Half-life was comparable (278 hours for SC vs. 368 hours for IV) as was $AUC_{(0-\infty)}$ (513753 μg*hr/mL for SC and 492508 μg*hr/mL for IV). There were no anti-MEDI-545 antibodies detected in the single SC dose study. Toxicokinetics analysis in the repeat SC dose study after the last dose (Dose 4) showed a mean half-life of 352 hours (14.7 days) and 368 hours (15.33 days) for the 10 and 100 mg/kg dose groups, respectively. Immunogenicity assay results showed evidence of anti-MEDI-545 antibody at Study Day 106 (Recovery Phase Day 78)

in one high-dose male and one control female (he control animal's positive assay outcome could be a result of the immunogenicity assay's expected 5% false positive rate).

In tissue cross-reactivity studies, MEDI-545 did not bind to any of the human or cynomolgus monkey tissues tested.

Human type I IFNs include 13 subtypes of IFN-α, and there is no clear 1:1 correspondence between human IFN-α subtypes and those in other mammalian species. The specific roles of IFN-α subtypes in host defense against viral infections and in the pathogenesis of SLE in humans are unknown. Given the lack of direct correspondence between human and other mammalian IFN-α subtypes, animal models may not usefully predict the possible clinical effects of MEDI-545 in naturally occurring infections in patients with SLE. As such, the most appropriate way to evaluate the effect of MEDI-545 on viral infections is by careful clinical monitoring in humans.

Further details of current preclinical information on MEDI-545 can be found in the investigator's brochure.

1.4 Clinical Experience with MEDI-545

MEDI-545 has been or is being investigated in 5 clinical studies in patients with SLE, psoriasis, or myositis. Two studies are complete, a single-dose IV study in patients with SLE (MI-CP126) and a single-dose IV study in patients with psoriasis (MI-CP145). Three studies are ongoing, a multiple-dose IV study in patients with SLE (MI-CP152), a multiple-dose IV study in patients with myositis (MI-CP151), and a multiple-dose SC study in patients with SLE (MI-CP179). The first clinical trial was a Phase 1 study (MI-CP126) in patients with SLE. MI-CP126 was a randomized, double-blind, placebo-controlled, single-dose, dose-escalation study with an open-label extension to evaluate the safety and tolerability of single IV doses of MEDI-545 ranging from 0.3 to 30.0 mg/kg. A total of 67 patients were treated in the study, including 50 patients (17 in the placebo group and 33 in the MEDI-545 group) in the blinded phase and 17 patients in the open-label extension.

Single-dose administration of IV MEDI-545 at doses ranging from 0.3 to 30.0 mg/kg to patients with mild to moderate SLE was well tolerated in this study. There were no deaths, no related SAEs, and no AEs that resulted in discontinuation of study drug reported in either the blinded phase or open-label extension. The pattern and type of AEs were generally consistent with the underlying conditions of this patient population. No dose effect was observed for safety considerations, and most AEs were associated with the system organ classes of Investigations and Musculoskeletal and Connective Tissue Disorders. The most common adverse events in > 10% of patients in the MEDI-545 group were blood bicarbonate decreased, blood glucose decreased, systemic lupus erythematosus flares, hemoglobin decreased, protein urine present, diarrhea, headache, nausea, and arthralgia. The majority of AEs were Grade 1 (mild) in severity. Viral reactivation events occurred at a low frequency in both the placebo and MEDI-545 groups during the study. All but one event was Grade 1 in severity. MEDI-545 mean serum concentrations following IV administration exhibited a bi-phasic decline with a shallow initial distribution phase followed by a prolonged terminal elimination phase. In both the blinded phase

and open-label extension, MEDI-545 PK was linear and dose proportional over the dose ranges tested. Mean C_{max} and AUC increased proportionally with dose. In the blinded phase, mean $T_{1/2}$ ranged between 15.4 and 23.5 days (excluding the 1.0 mg/kg dose group), and mean CL ranged between 143 and 197 mL/day. In the open-label extension, mean $T_{1/2}$ ranged between 19.8 and 28.0 days, and mean CL ranged between 147 and 184 mL/day. Both mean $T_{1/2}$ and CL values indicate that the target IFN-α does not seem to influence MEDI-545 PK. The low volumes of distribution, about 3 to 7 L, indicate limited distribution of MEDI-545 systemically. There was no detectable antibody response to MEDI-545 (defined as a titer with a dilution value of ≥1:10) seen for any patient at any time point for the blinded phase and open-label extension. A dose-dependent neutralization of type I IFN gene signature was noted following single IV administration of MEDI-545 at doses ranging from 0.3 to 30.0 mg/kg. Assessment of clinical outcome using standard SLE evaluation methods (ie, BILAG/SELENA-SLEDAI, and PGA) suggested improvement of disease by MEDI-545 in the blinded phase of the study. Clinical outcomes in the open-label extension were similar to those in the MEDI-545 group reported in the blinded phase. After the study reporting period for serious adverse events had ended, a report of angiosarcoma of the left breast was reported for a patient that had participated in the MI-CP126 study. The patient had received a single 1.0 mg/kg dose of MEDI-545. Thirteen months after receipt of the single dose of MEDI-545, a left breast mass was detected and further investigated. The mass was determined to be an angiosarcoma.

MI-CP145 was a Phase 1, multicenter, randomized, double-blind, placebo-controlled, dose-escalation study of single-dose IV MEDI-545 (0.3, 1.0, 3.0, 10.0, or 30.0 mg/kg) in adult patients with chronic plaque psoriasis. A total of 36 patients received MEDI-545 or placebo in this study. This study was discontinued after the first patient in the 30.0 mg/kg dose cohort had an SAE of anaphylactic reaction (infusion reaction) during administration of study drug and was hospitalized for 3 days. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug in that patient. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies, that tryptase levels 10 hours after the event were normal, that the drug product met quality standards, and that when this anaphylactic event occurred, the patient was receiving drug at a relatively high rate of infusion. After thorough review, the Medical Monitor judged this event to be an infusion reaction and the Safety Monitoring Committee (SMC) concurred. Single-dose administration of IV MEDI-545 at doses ranging from 0.3 to 10.0 mg/kg to patients with chronic plaque psoriasis was well tolerated in this study. There were no deaths reported in the study. One patient randomized to the MEDI-545 30 mg/kg treatment group, discontinued investigational product due to a serious anaphylactic reaction. There were no other SAEs or AEs that resulted in discontinuation of investigational product. One other patient had an SAEs of myocardial infarction, which was judged by the investigator as not related to MEDI-545. No dose effect was observed, and most AEs were associated with the system organ class of Investigations. The most common AEs in > 10% of patients in the MEDI-545 group were nasopharyngitis, white blood cell count increase, back pain, pain in extremity, and headache. MEDI-545 mean serum concentrations following IV administration exhibited a bi-phasic decline with a shallow initial distribution phase followed by a prolonged terminal elimination phase. MEDI-545 PK was linear and dose proportional over the dose range of 0.3 to 10.0 mg/kg. Mean C_{max} and AUC increased proportionally with dose from 14.9 µg/mL following 0.3 mg/kg to 338 µg/mL after 10.0 mg/kg, except for a high individual

value of 1447 µg/mL in the 3.0 mg/kg dose cohort. Dose proportionality was also observed for $AUC_{(0-t)}$ and AUC over the dose range of 0.3 mg/kg to 10.0 mg/kg. Mean $T_{1/2}$ was about 21 days across the different doses; mean CL ranged between 115 and 194 mL/day across dose groups. Both mean $T_{1/2}$ and CL values indicate that the target IFN-α does not seem to influence MEDI-545 PK. The low volumes of distribution, about 3 to 6 L, and the similarity of mean Vd_{ss} and mean Vd_z values indicate limited distribution of MEDI-545. There was no detectable antibody response to MEDI-545 (defined as a titer with a dilution value of ≥1:10) seen for any patient at any time point, using a drug tolerant assay. There were no primary or secondary efficacy variables in this study; however, exploratory analyses were conducted to evaluate the potential effects of MEDI-545 on neutralization of type I interferon gene signature, clinical response, inflammatory histological features in skin biopsies, and patient-reported outcomes. The effects of MEDI-545 on neutralization of type I interferon gene signature showed no difference in inhibition of gene signature in involved skin at either Study Day 14 or Study Day 28. Changes in target lesions were similar between the placebo and MEDI-545 group as were the changes in PASI score, PASI 50 responses, and PGA. In addition, the patient-reported outcomes showed little or no differences in the assessments of VAS, DLQI, SF36, and BDI.

MI-CP151 is a Phase 1b, multicenter, multinational, randomized, double-blind, placebo-controlled study to evaluate the safety of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) in 40 adult patients with dermatomyositis (DM) or polymyositis (PM). In this study, MEDI-545 or placebo is initially administered every 2 weeks for 12 weeks (7 doses) followed 2 weeks later by MEDI-545 every 2 weeks for another 12 weeks (7 doses) for a total of 26 weeks (14 doses). The study is ongoing, and data remain blinded to treatment assignment. As of 02/Nov/2009, 51 patients have been dosed in MI-CP151. The majority of AEs are mild or moderate in severity. The most common AE (incidence > 10%) is headache. There is one viral reactivation AE (Grade 2 herpes zoster ophthalmic). There are no deaths reported in MI-CP151. Nine of the 51 patients (17.6%) have SAEs. For 1 patient, the SAE (hyponatremia) was judged by the investigator as related to study drug.

The current study, MI-CP152, is a dose-escalation study to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) in approximately 148 adult patients with SLE. In this study, MEDI-545 is being administered every 2 weeks for a total of 14 doses over 26 weeks. The planned starting dose of MEDI-545 (0.3 mg/kg) in MI-CP152 is less than one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated IV administrations every 2 weeks for 26 weeks). The first 12 randomized patients in each of the 4 dose cohorts will provide safety data for dose escalation; the additional patients planned (20 each in Dose Cohorts 1 through 3 and 40 in Dose Cohort 4) are intended to increase safety data and provide adequate numbers of patients for exploratory analyses of effect of MEDI-545 on the inhibition of type I IFN gene signature. On 28/Sep/2007, one patient in MI-CP152 experienced an SAE of Grade 3 hypersensitivity reaction characterized by chills, rigors, swollen hands, hives, moderate hypotension and several bouts of diarrhea following the fifth dose of MEDI-545 (1.0 mg/kg), which resolved the same day. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies and that when this event occurred, the patient was receiving drug at a relatively high rate of infusion. After thorough review, the Medical Monitor judged this event to be an infusion reaction. This study was stopped on

10/Oct/2007 due to an SAE of anaphylactic reaction associated with Grade 4 hypotension in MI-CP145; it was restarted in January 2008.

A review of the safety data from both MI-CP145 and MI-CP152 concluded the aforementioned SAEs of an infusion reaction in each study were most likely due to MEDI-545 administered at a high rate of infusion, approximately 92 and 75 mg per minute for these 2 patients weighing 92 and 122 kg respectively. As a result of this determination it was decided to decrease the likelihood of future events such as these by limiting the potential for administration of these high rates of MEDI-545 infusion by decreasing the maximum dose of MEDI-545 permitted and mandating a minimum period of administration. Consequently, the MI-CP152 and the MI-CP151 protocols were amended to reduce the starting dose of MEDI-545 from 1.0 to 0.3 mg/kg, reduce the highest dose of MEDI-545 from 30.0 to 10.0 mg/kg, and set the infusion volume and time to 100 mL over at least 60 minutes.

In the interest of potential safety, a decision has been made to eliminate Dose Cohort 5 that allowed infusion to be administered over 30 minutes. While it would be desirable from a convenience standpoint for the patient to decrease the length of study medication infusion time to 30 minutes it is likely that any infusion reaction of an allergic nature, while uncommon, could potentially have more severe manifestations than might be expected if the infusion was administered at a more rapid rate. It is not apparent that the overall incidence of these uncommon reactions will be diminished in those patients in Dose Cohort 4 with the 60-minute infusion time being utilized but the potential severity of those events could be reduced. Thus, it was felt that the benefit of utilizing a 30-minute length of infusion versus the 60-minute length of infusion did not outweigh the potential safety risk and the overall drug administration to the patient remains the same. The additional patients added to Dose Cohort 4 will provide additional experience with the duration of infusion that will be employed in any additional planned studies

As of 02/Nov/2009, 183 patients have been dosed in the current study, MI-CP152. This study is ongoing, and data remain blinded to treatment assignment. The majority of AEs are mild or moderate in severity. The most common AEs (incidence >10%) are urinary tract infection, nasopharyngitis, lymphocyte count decreased, blood potassium decreased, nausea, diarrhoea, systemic lupus erythematosus flares, arthralgia, and headache. Viral reactivation AEs occurred in 10 patients. There have been 5 deaths in the study, four of which were judged by the investigator as unrelated to study drug. One death was due to multiple drug overdose, another due to congestive heart failure and another patient died in screening due to sepsis before receiving study drug. There was one death due to herpes encephalitis. The study drug was unblinded for this patient and the patient was receiving placebo. Finally one patient died due to liver failure, this event was judged by the investigator as being related to study drug, however the sponsor considers the event to be related to a blood infection and low blood pressure. This patient also took herbal medicines. The possibility exists that use of herbal medicines combined with MEDI-545 may increase a risk of unexpected liver problems. SAEs occurred in 31 of the 183 patients (37.3%), with 8 patients having related SAEs. One patient had a diagnosis of lymphoma that occurred after the patient received 2 doses of study drug, although signs and symptoms of lymphoma were present before any study drug was given.

A third study of MEDI-545 in patients with SLE (MI-CP179) is evaluating the safety and tolerability of multiple SC dose schedules of MEDI-545 and/or placebo. In this study, a total of 80 patients will be randomized in a 1:1:2:2:2 ratio to receive 1 of 5 treatment arms of MEDI-545 or placebo as follows: (1) SC MEDI-545 100 mg once; SC Placebo × 12 doses on other weeks; (2) SC MEDI-545 100 mg every 4 weeks × 4 doses; SC Placebo × 9 doses on other weeks; (3) SC MEDI-545 100 mg every 2 weeks × 7 doses; SC Placebo × 6 doses on other weeks; (4) SC MEDI-545 100 mg every week × 13 doses; and (5) SC Placebo every week × 13 doses. Two patients have been dosed in this study as of 13/Aug/2008. As of 02/Nov/2009, 74 patients have been dosed in MI-CP179. The majority of AEs are mild or moderate in severity. The most common AEs (incidence > 10%) are upper respiratory tract infection and nausea. There are no viral reactivation AEs. There was one case of breast cancer (angiosarcoma) that was judged by the investigator as being not related to study drug. There are no deaths reported in MI-CP179. Five of the 74 patients (6.8%) had SAEs. Two SAEs (cellulitis and pneumonia) were judged by the investigator as related to study drug.

Further details of current clinical information on MEDI-545 can be found in the investigator's brochure.

1.5 Rationale for Study

SLE is a systemic autoimmune disease that affects multiple organs and can substantially reduce patients' quality of life and increase mortality. Constitutional symptoms, polyarthritis, discoid and photosensitive skin rashes, glomerulonephritis, proteinuria, renal insufficiency, cognitive impairment, psychoses, seizures, neutropenia, lymphopenia, thrombocytopenia, coagulation abnormalities, serositis, and oral ulcers are among the myriad disease manifestations. Current treatment options for moderately to severely active SLE include potent immunosuppressive drugs with unfavorable long-term adverse effects. Recent research data suggest a potential role of type I IFN in disease pathogenesis of SLE; thus, IFN inhibition may be efficacious in the treatment of this disease.

MEDI-545 is a fully human immunoglobulin IgG1κ monoclonal antibody that binds to and neutralizes majority of the subtypes of human IFN-α and therefore may be potentially effective as a treatment for SLE. In preclinical studies of MEDI-545 in cynomolgus monkeys, no treatment-related toxicological findings except transient, localized reactions at the injection sites were observed. No antibodies against MEDI-545 were detected in IM studies in cynomolgus monkeys with IV administration; and the IM assay results showed evidence of anti-MEDI-545 antibody in one high-dose male and one control female with SC administration.

MEDI-545 was investigated in patients with SLE (MI-CP126) and psoriasis (MI-CP145) and is currently under investigation in patients with myositis (MI-CP151) and SLE (MI-CP179 and MI-CP152). Studies MI-CP126 and MI-CP145 evaluated the safety and tolerability of single IV administration of MEDI-545, and studies MI-CP151 and MI-CP152 are evaluating the safety and tolerability of multiple IV administration of MEDI-545. Study MI-CP179 is evaluating the safety and tolerability of multiple SC dose schedules of MEDI-545 and/or placebo. Two SAEs have occurred with MEDI-545 that were judged to be related to IV infusion of MEDI-545 at relatively rapid rates. Otherwise, MEDI-545 has had an acceptable safety profile.

Dose-dependent inhibition of type I IFN gene signature in whole blood and skin has been observed, and evidence suggesting clinical activity of MEDI-545 was observed in MI-CP126.

The current study, MI-CP152, is a dose-escalation study to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) in approximately 148 adult patients with SLE. In this study, MEDI-545 is being administered every 2 weeks for a total of 14 doses over 26 weeks. The planned starting dose of MEDI-545 (0.3 mg/kg) in MI-CP152 is less than one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated IV administrations every 2 weeks for 26 weeks). The first 12 randomized patients in each dose cohort will provide safety data for dose escalation; the additional patients planned (20 each in Dose Cohorts 1 through 3 and 40 in Dose Cohort 4) are intended to increase safety data and provide adequate numbers of patients for exploratory analyses of effect of MEDI-545 on the inhibition of type I IFN gene signature. On 28/Sep/2007, one patient in MI-CP152 experienced an SAE of Grade 3 hypersensitivity reaction characterized by chills, rigors, swollen hands, hives, moderate hypotension and several bouts of diarrhea following the fifth dose of MEDI-545 (1.0 mg/kg), which resolved the same day. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies and that when this event occurred, the patient was receiving drug at a relatively high rate of infusion, $\geq$ 0.75 mg/min. After thorough review, the Medical Monitor judged this event to be an infusion reaction. This study was stopped on 10/Oct/2007 due to an SAE of anaphylactic reaction associated with Grade 4 hypotension in MI-CP145 and restarted in January 2008.

A review of the safety data from both MI-CP145 and MI-CP152 concluded the aforementioned SAEs of an infusion reaction in each study were most likely due to MEDI-545 administered at a high rate of infusion, approximately 92 and 75 mg per minute for these 2 patients weighing 92 and 122 kg respectively. As a result of this determination it was decided to decrease the likelihood of future events such as these by limiting the potential for administration of these high rates of MEDI-545 by decreasing the maximum dose of MEDI-545 permitted and mandating a minimum period of administration. Consequently, the MI-CP152 and the MI-CP151 protocols were amended to reduce the starting dose of MEDI-545 from 1.0 to 0.3 mg/kg, reduce the highest dose of MEDI-545 from 30.0 to 10.0 mg/kg, and set the infusion volume and time to 100 mL over at least 60 minutes.

In the interest of potential safety, a decision has been made to eliminate Dose Cohort 5 that allowed infusion to be administered over 30 minutes. While it would be desirable from a convenience standpoint for the patient to decrease the length of study medication infusion time to 30 minutes it is likely that any infusion reaction of an allergic nature, while uncommon, could potentially have more severe manifestations than might be expected if the infusion was administered at a more rapid rate. It is not apparent that the overall incidence of these uncommon reactions will be diminished in those patients in Dose Cohort 4 with the 60-minute infusion time being utilized but the potential severity of those events could be reduced. Thus, it was felt that the benefit of utilizing a 30-minute length of infusion versus the 60-minute length of infusion did not outweigh the potential safety risk and the overall drug administration to the patient remains

the same. The additional patients added to Dose Cohort 4 will provide additional experience with the duration of infusion that will be employed in any additional planned studies.

As of 02/Nov/2009, 183 patients have been dosed in the current study, MI-CP152. This study is ongoing, and data remain blinded to treatment assignment. The majority of AEs are mild or moderate in severity. The most common AEs (incidence >10%) are urinary tract infection, nasopharyngitis, lymphocyte count decreased, blood potassium decreased, nausea, diarrhoea, systemic lupus erythematosus flares, arthralgia, and headache. Viral reactivation AEs occurred in 10 patients. There have been 5 deaths in the study, four of which were judged by the investigator as unrelated to study drug. One death was due to multiple drug overdose, another due to congestive heart failure and another patient died in screening due to sepsis before receiving study drug. There was one death due to herpes encephalitis. The study drug was unblinded for this patient and the patient was receiving placebo. Finally one patient died due to liver failure, this event was judged by the investigator as being related to study drug, however the sponsor considers the event to be related to a blood infection and low blood pressure. This patient also took herbal medicines. The possibility exists that use of herbal medicines combined with MEDI-545 may increase a risk of unexpected liver problems. SAEs occurred in 31 of the 183 patients (37.3%), with 8 patients having related SAEs. One patient had a diagnosis of lymphoma that occurred after the patient received 2 doses of study drug, although signs and symptoms of lymphoma were present before any study drug was given.

2 STUDY OBJECTIVES AND OVERVIEW

2.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of multiple IV doses of MEDI-545 in adult patients with SLE.

2.2 Secondary Objectives

The secondary objectives of the study are to evaluate the PK and IM of multiple IV doses of MEDI-545 in adult patients with SLE.

2.3 Exploratory Objectives

Exploratory objectives are to:

1. Evaluate the effect of MEDI-545 on the expression of type I IFN-inducible genes;
2. Evaluate the effect of MEDI-545 on other potential disease mechanisms in SLE;
3. Evaluate the effect of MEDI-545 on disease activity; and
4. Evaluate the effect of MEDI-545 on patient-reported outcomes in this patient population.

2.4 Overview

2.4.1 Design

This is a multicenter, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and tolerability of multiple IV doses of MEDI-545 in adult patients with SLE. Approximately 30 to 40 international sites (USA, Canada, Brazil, Argentina, and Chile) will participate in this study.

A total of 148 evaluable patients are planned for the study; this excludes the 22 patients who were treated prior to 10/Oct/2007. Four escalating doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo will be tested using an infusion time of at least 60 minutes. Dose Cohorts 1 through 3 will include 32 patients each; while Dose Cohort 4 will include 52 patients. All patients will be randomized in a 3:1 ratio, using central randomization (without regard to site) and stratified by the level of type I IFN-inducible gene signature (low/undetectable versus high), to receive either MEDI-545 or placebo (ie, 24 patients each in Dose Cohorts 1 through 3 will receive MEDI-545 and 8 patients will receive placebo and 39 patients in Dose Cohort 4 will receive MEDI-545 and 13 patients will receive placebo).

Patients are considered evaluable if they receive the first 4 doses of study drug (MEDI-545 or placebo) and complete the required evaluations, or if they discontinue study drug administration before the fourth dose for safety reasons. Nonevaluable patients will be replaced to maintain a size of at least 32 patients each in Dose Cohorts 1 through 3 and 52 patients in Dose Cohort 4. Data from all patients will be included in the safety analyses. A dose cohort may be expanded by up to 4 additional patients if eligible patients are already in screening at the time 32 patients in Dose Cohorts 1 through 3 or 52 patients in Dose Cohort 4 have been randomized into the dose cohort.

MEDI-545 or placebo will be administered once every 2 weeks as an IV infusion (for at least 60 minutes for 26 weeks, for a total of 14 doses. Study drug administration will start on Study Day 0 and continue through Study Day 182. Patients will be generally maintained on the same stable dose of SLE treatment as baseline through Study Day 196. SLE treatment may be adjusted as clinically indicated after Study Day 196 through Study Day 350. See Section 3.3.5 for details on concomitant medications. The follow-up period ends on Study Day 350.

Decisions regarding dose escalation will be made by the Medical Monitor based on the review of all cumulative, blinded safety information, which includes the safety data through Study Day 42 from the first 12 randomized patients in the preceding lower dose cohort. Detailed dose escalation criteria are described in Section 4.9.
The study schema is presented in Figure 1.

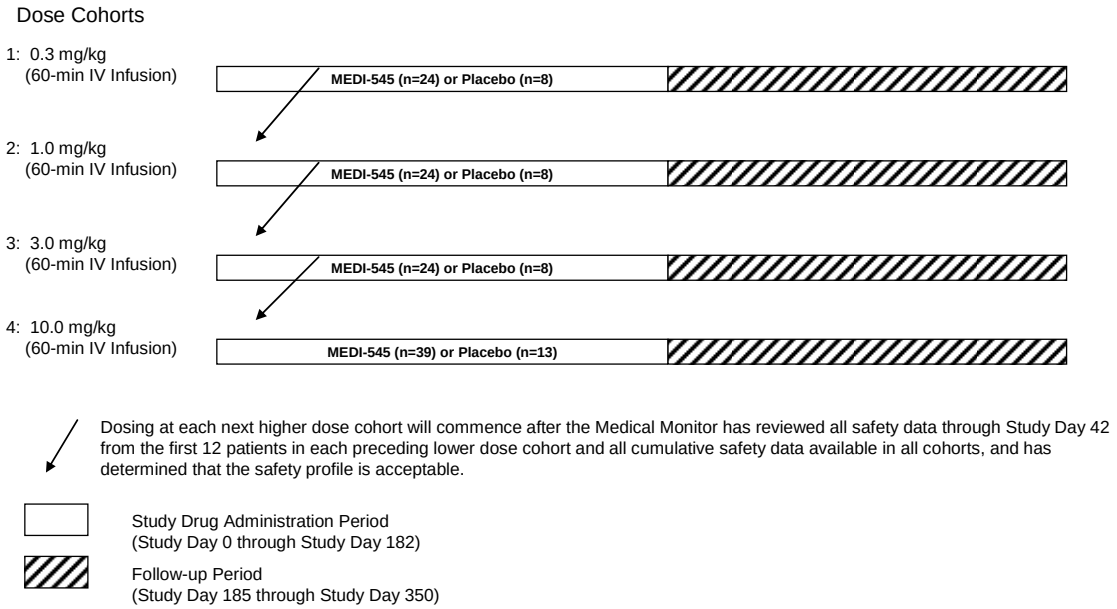


Figure 1 Study Schema

Patients who were treated with study drug prior to 10/Oct/2007 were followed for safety reasons according to the schedule of patient evaluations from Study Day 238 through Study Day 350 as described in Table 4.

Patients who participate in this study may have the option of entering a long-term safety study (MI-CP212). This includes both MEDI-545 and placebo patients, including the patients who were treated in MI-CP152 prior to 10/Oct/2007, but excludes patients who discontinued from previous MEDI-545 clinical studies for safety reasons. Patients must complete the treatment period and follow up through Day 266 of this study to participate in MI-CP212. Patients must also qualify for the long-term safety study (following written informed consent), as per the MI-CP212 protocol inclusion and exclusion criteria. If patients qualify, they will receive open-label MEDI-545. Patients may be treated for approximately 3 years and may be followed for an additional 3 months following the last dose of IV MEDI-545.

2.4.2 Patient Evaluations and Follow-Up

Screening evaluations include medical history, physical examination, BILAG/SELENA-SLEDAI assessments, ECG, chest x-ray (or chest x-ray with two views [anterior-posterior and lateral] or computed tomography (CT) scan performed within the previous 6 months), TB skin test, blood tests for hepatitis A, B, C, human immunodeficiency virus (HIV)-1 and HIV-2, serum and urine βHCG for women (unless surgically sterile or 2 years after menopause), AEs/SAEs, serum chemistry (including Na, K, Cl, bicarbonate, blood urea nitrogen [BUN], creatinine, AST, ALT, bilirubin, alkaline phosphatase, and random glucose), CBC with differential and platelets, autoantibody and complement levels, and urinalysis. In addition, whole blood samples are taken to analyze levels of messenger mRNA for type I IFN-inducible gene expression; the results are used for randomization stratification. In patients who have received MEDI-545 previously, serum levels of MEDI-545 and antibodies to MEDI-545 at screening will be measured. A negative urine βHCG for women (unless surgically sterile or 2 years after menopause) on all study days is required before study drug administration.

Safety assessments include AE and SAE evaluation, physical examination, vital signs, serum chemistry panel, CBC with differential and platelets, serum for safety biomarkers in any patient with a Grade 1 or higher infusion reaction (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies), urinalysis, and viral cultures and titers via oropharyngeal swabs for herpes simplex virus (HSV)-1 and HSV-2; vaginal swabs (women) for HSV-1, HSV-2, and human papillomavirus (HPV); and blood tests for Epstein Barr virus (EBV) and cytomegalovirus.

MEDI-545 serum concentrations and anti-MEDI-545 antibodies will be measured to assess PK and IM profiles of MEDI-545.

Clinical disease activity is assessed using the following indicators: requirement of rescue oral, IV, intra-articular, or intramuscular corticosteroids or other potential disease modifying therapies to treat SLE during the treatment period, changes from baseline in SLE treatment during the follow-up period, BILAG scores, SELENA-SLEDAI score, flares, active joint count, physician global assessment, photographs of skin lesions (optional, if present), and renal function. In addition, autoantibodies and complement levels in blood will be measured.

Patient-reported outcomes are measured using the following instruments: patient global assessment, Automated Neuropsychological Assessment Metrics (ANAM) tests (this test is optional and is only being done at selected North American sites), modified Health Assessment Questionnaire (MHAQ), Beck Depression Index (performed only at North American sites), the Krupp Fatigue Severity score, work productivity questionnaire, and the SF-36.

Exploratory analyses will be performed to investigate the effects of MEDI-545 on the levels of type I IFN-inducible gene expression in whole blood through analyses of RNA gene expression signatures. Other exploratory tests will examine the effect of MEDI-545 B cell subsets and other potential SLE biomarkers.

3 STUDY PROCEDURES

3.1 Patient Selection

The patients in this study will be male or female adults with active SLE despite standard of care.

The patient will be counseled by an investigator (physician) or qualified designee who will address the questions and concerns of the patient and secure written informed consent for participation in the study. Written informed consent will be obtained prior to conducting study procedures.

3.1.1 Inclusion Criteria

Patients must meet *all* of the following criteria:

1. Male or female adults ≥ 18 years of age at the time of the first dose of study drug;
2. Written informed consent obtained from the patient or the patient's legal representative;
3. Meet at least 4 of the 11 revised ACR classification criteria for SLE (see Appendix A) (ACR, 1999);
4. Have positive ANA test at ≥ 1:80 serum dilution in the past or at screening (prior positive ANA test must be documented via a lab report);
5. Have at least one system with a score of A or two systems with a score of B on the BILAG index at screening, or have a SELENA-SLEDAI score ≥ 6;
6. Sexually active women, unless surgically sterile (including tubal ligation) or at least 2 years post-menopausal, must use an effective method of avoiding pregnancy (including oral, injectable, transdermal, or implanted contraceptives, intrauterine device, diaphragm with spermicide, cervical cap, abstinence, or sterile sexual partner) in addition to the use of condoms (male or female condoms with spermicide) from screening through the end of the study. Cessation of birth control after this point should be discussed with a responsible physician. Sexually active men, unless surgically sterile, must likewise practice two effective methods of birth control (condom with spermicide or abstinence) and must use such precautions from Study Day 0 through the end of the study.
7. Ability to complete the study period, including follow-up period through Study Day 350; and
8. Willing to forego other forms of experimental treatment during study.

3.1.2 Exclusion Criteria

Patients must have *none* of the following:

1. Have received MEDI-545 within 120 days prior to screening or have either detectable levels of MEDI-545 or anti-MEDI-545 antibodies (positive at > 1:10 serum dilution) in serum at screening;
2. History of allergy or reaction to any component of the study drug formulation;
3. Have received prednisone > 20 mg/day (or an equivalent dose of another oral corticosteroid) within 14 days before randomization/entry;
4. Have received the following dosages of medications within 28 days before randomization/entry: hydroxychloroquine > 600 mg/day, mycophenolate mofetil > 3 g/day,

methotrexate > 25 mg/week, azathioprine > 3 mg/kg/day, cyclophosphamide, cyclosporine, or thalidomide;
5. Have received leflunomide >20 mg/day in the 6 months prior to Study Day 0;
6. Have received fluctuating doses of antimalarials, mycophenolate mofetil, methotrexate, leflunomide, or azathioprine within 28 days before randomization/entry or fluctuating doses of NSAIDs or oral corticosteroids within 14 days before randomization/entry;
7. Treatment with any investigational drug therapy within 28 days before randomization/entry into the study, B cell-depleting therapies within 12 months before randomization/entry, or biologic therapies within 30 days or 5 half-lives of the biologic agent, whichever is longer, before randomization/entry into the study;
8. In the investigator's opinion, evidence of clinically significant active infection, including ongoing, chronic infection, within 28 days before randomization/entry;
9. A history of severe viral infection, as judged by the investigators, including severe infections of either cytomegalovirus or the herpes family such as disseminated herpes, herpes encephalitis, ophthalmic herpes;
10. Herpes zoster infection within 3 months before randomization/entry;
11. Evidence of infection with hepatitis B or C virus, or HIV-1 or HIV-2, or active infection with hepatitis A, as determined by results of testing at screening;
12. Vaccination with live attenuated viruses within 28 days before randomization/entry;
13. Pregnancy (women, unless surgically sterile or at least 2 years post-menopausal, must have a negative serum pregnancy test within 28 days before receiving the study drug and a negative urine pregnancy test on days of study drug administration before receiving the study drug);
14. Breastfeeding or lactating women;
15. History of primary immunodeficiency;
16. History of alcohol or drug abuse < 1 year prior to randomization/entry;
17. History of cancer (except basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy > 1 year prior to randomization/entry);
18. History of active TB infection;
19. History of latent TB infection or newly positive TB skin test (reaction defined as ≥ 10 mm in diameter if not on systemic immunosuppressive medication or ≥ 5 mm if on systemic immunosuppressive medication) without completion of an appropriate course of treatment or with ongoing prophylactic therapy;
20. Elective surgery planned from the time of screening through Study Day 196;
21. At screening blood tests (within 28 days before randomization/entry), any of the following:
    - AST > 2 × upper limit of normal range (ULN), unless caused by SLE, as determined by the investigator,
    - ALT > 2 × ULN unless caused by SLE, as determined by the investigator,
    - Creatinine > 4.0 mg/dL (> 354 μmol/L)
    - Neutrophils < 1,500/ μL (< 1.5×10^9/L)
    - Platelet count < 50,000/ μL (< 50×10^9/L)
22. History of any disease, evidence of any current disease (other than SLE), any finding upon physical examination, or any laboratory abnormality that, in the opinion of the investigator or medical monitor, may compromise the safety of the patient in the study or confound the analysis of the study; or
23. Any employee of the research site who is involved with the conduct of the study.

3.2 Randomization/Entry

3.2.1 Patient Randomization/Entry Procedures and Treatment Allocation

Patients will be screened by investigators or qualified designees to assess eligibility for randomization into the study. A master log will be maintained of all consented patients and will document all screening failures, including the reason for screening failure.

An interactive voice response system (IVRS) will be used for assignment of the patient identification number (PID), randomization to a particular treatment, and assignment of study drug kit numbers. A patient is considered randomized into the study upon receipt from the IVRS of the PID. A block randomization schema using a 3:1 MEDI-545-to-placebo ratio and stratified by the level of expression of mRNA for type I IFN-inducible genes (low/undetectable versus high) will be used. Whole blood samples will be collected during screening and type I IFN-inducible gene expression will be determined. Central randomization will be applied without regard to site.

The randomization procedures are:

- Investigator or qualified designee confirms the patient meets all eligibility criteria and has signed an informed consent form;
- MedImmune calls the IVRS before Study Day 0 to provide the results of type I IFN gene signature in the patient;
- The IVRS notifies the investigator or qualified designee that the patient may be randomized into the study;
- The Investigator or qualified designee calls the IVRS on Study Day 0 and provides at a minimum the initials, date of birth, and body weight of the patient;
- The IVRS randomly assigns a treatment (MEDI-545 or placebo) to the patient along with a PID and blinded study drug kit number to be used for that patient; and
- A confirmatory fax or e-mail with this information is sent to the investigator or qualified designee.

Patients will receive either MEDI-545 or placebo in a blinded manner on Study Day 0. Patients are considered evaluable if they receive the first 4 doses of study drug (MEDI-545 or placebo), or if their discontinuation of study drug administration before the fourth dose is due to safety reasons. In each of the 4 dose cohorts, if one of the first patients is randomized but not treated, or not evaluable (or needs to be replaced for other reasons), the treatment assignment for this replaced patient will be used for the next patient enrolled in this cohort as a replacement. If more patients are to be replaced, the replaced patient's treatment assignment will be used in order of enrollment. A dose cohort may be expanded by up to 4 additional patients if eligible patients are already in screening at the time 32 patients in Dose Cohorts 1 through 3 or 52 patients in Dose Cohort 4 have been randomized into the dose cohort.

Decisions relating to dose escalation will be made by the Sponsor based on review of blinded cumulative safety data by the Medical Monitor (see Section 4.9). A Safety Monitoring Committee (SMC) will independently review cumulative safety surveillance data and the Medical Monitor's decisions on dose escalation, throughout the study and make recommendations regarding the study progression. The SMC can stop study entry and dosing as

they deem necessary. Additional details are given in Section 4.8. The sponsor will notify the sites when randomization in each dose cohort is completed and when randomization into the next dose cohort is permitted.

3.2.2 Blinding

This is a double-blind study. All MedImmune and contract personnel associated with this study with the exception of MedImmune Clinical Research and Pharmacy Services (CRPS), including the medical monitor, project management, statistician, site monitors, and data management, will be blinded to the treatment randomization until the study is completed and the database is closed. In addition, the patient and the clinical site staff including the investigators, study nurses, coordinators, and the Clinical Trial Material Manager (CTMM) will also be blinded.

A limited number of MedImmune personnel independent of the project team, who will perform and interpret assays such as gene signature expression analyses or PK/PD analyses, will be unblinded during the conduct of the study. Unblinded MedImmune personnel involved in all interim assessments will not be associated with the clinical conduct of the study and will not reveal the treatment assignment of individual patients to any clinical personnel involved in the study. Only changes to the clinical development plan that affect individuals involved in the clinical conduct of the study will be communicated, ie, the actual results of the interim analyses will not be communicated. In addition, once the last patient of each dose cohort has completed Study Day 28 and the gene expression analyses are completed, an interim analysis of the gene expression data may be reviewed by senior management for the purpose of making clinical development decisions. Additional interim assessments of safety and clinical activity can be made as follows: when at a minimum the 25th patient in Dose Cohort 3 completes Study Day 84; when at a minimum the 20th patient in Dose Cohort 4 completes Study Day 56; and when all patients in Dose Cohort 4 complete Study Day 84 and Study Day 196. These interim assessments are also for the purpose of making clinical development decisions.

Study drug will be supplied to the pharmacy as numbered, blinded kits containing MEDI-545 or placebo vials. The clinical site staff will order study drug from the pharmacy using the site's normal ordering procedures. The CTMM will prepare the study drug from one or more of the appropriate vials (determined by the patient's weight and randomization assignment). Detailed instructions are in the Clinical Trial Material Manual supplied by MedImmune.

If an investigator feels they need to be unblinded to an individual subject's treatment in order to treat an AE, the investigator must contact the medical monitor at MedImmune.

In the event the treatment allocation for a subject becomes known to the investigator, the investigator or designated staff must notify MedImmune immediately.

3.3 Study Drug

3.3.1 Study Drug Supplies and Accountability

The sponsor will provide the investigators with adequate quantities of liquid MEDI-545 and placebo. All study drug will be stored at +2°C to +8°C (36°F to 46°F) and must not be frozen.

MEDI-545 (100 mg/mL): MEDI-545 is supplied as a sterile liquid containing 0.75 mL of MEDI-545 solution at a concentration of 100 mg/mL in a 3 mL single-use glass vial. The solution also contains 25 mM histidine/histidine-HCl, 8% (w/v) trehalose dihydrate, and 0.02% (w/v) polysorbate 80, and has a pH of 6.0.

Placebo: Placebo is supplied as a sterile liquid containing 0.75 mL solution in a 3 mL single use vial. The solution contains 25 mM histidine/histidine-HCl, 8% (w/v) trehalose, and 0.02% (w/v) polysorbate 80, and has a pH of 6.0.

The CTMM is required to maintain accurate drug accountability records. Upon completion of the study, all study drug accountability records will be returned to the sponsor. All unused study drug will be returned to assigned distribution centers as designated by the sponsor.

3.3.2 Treatment Regimens

A total of 148 evaluable patients are planned for the study; this excludes the 22 patients who were treated prior to 10/Oct/2007. A dose cohort may be expanded by up to 4 additional patients (for a maximum of 16 additional patients) if eligible patients are already in screening at the time 32 patients in Dose Cohorts 1 through 3 or 52 patients in Dose Cohort 4 have been randomized into the dose cohort. Four escalating doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo will be tested using an infusion time of at least 60 minutes Dose cohorts 1 through 3 will include 32 patients each; while Dose Cohort 4 will include 52 patients. All patients will be randomized in a 3:1 ratio to receive either MEDI-545 or placebo (ie, 24 patients each in cohorts 1 through 3 will receive MEDI-545 and 8 patients will receive placebo and 39 patients in Dose Cohort 4 will receive MEDI-545 and 13 patients will receive placebo). MEDI-545 or placebo will be administered every 2 weeks as an IV infusion for 26 weeks, for a total of 14 doses.

Dose Cohort	N[a]	Treatment	Infusion Time
1	32	MEDI-545 0.3 mg/kg (n=24): Placebo (n=8)	60 minutes
2	32	MEDI-545 1.0 mg/kg (n=24): Placebo (n=8)	60 minutes
3	32	MEDI-545 3.0 mg/kg (n=24): Placebo (n=8)	60 minutes
4	52	MEDI-545 10.0 mg/kg (n=39): Placebo (n=13)	60 minutes

a. A dose cohort may be expanded by up to 4 additional patients (for a maximum of 16 additional patients), if eligible patients are in screening at the time 32 patients in Dose Cohorts 1 through 3 and 52 patients in Dose Cohort 4 have been randomized into the dose cohort.

See Section 3.2.1 for the definition of evaluable patients and replacement rules. See Section 3.3.5 for concomitant treatment for SLE permitted during the study.

3.3.3 Study Drug Ordering and Preparation

Study drug in blinded kits will be sent to the study sites before randomization. The dose of study drug for IV administration will be prepared by the CTMM using aseptic techniques. Detailed

instructions on study drug preparation can be found in the Clinical Trial Material Manual provided to the study sites.

The volume of study drug administered is calculated on the basis of the patient's weight (in kg) measured on Study Day 0 using the following formula:

$$\text{Dose (mL)} = \frac{\text{Wt (kg)} \times \text{Dose (mg/kg)}}{\text{100 mg/mL}}$$

For example: For an 80-kg patient dosed at 3 mg/kg MEDI-545, the volume of MEDI-545 required for IV administration would be 2.4 mL.

Study drug (MEDI-545 or placebo) for administration must be prepared using aseptic technique. Study drug will be diluted in 0.9% normal saline and the volume of the dilution will be standardized to 100 mL. The study drug will be administered using an infusion pump over 60 minutes as described in Table 1.

Table 1 Summary of Infusion Volume, Duration, and Rate

Dose Cohort	Dose (mg/kg)	Infusion Volume [a] (mL)	Infusion Duration	Infusion Rate (mL/hr)	Maximum Infusion Rate (mg/min)[b]
1	0.3	100	$\geq$ 60 minutes	100	0.6
2	1.0	100	$\geq$ 60 minutes	100	2.0
3	3.0	100	$\geq$ 60 minutes	100	6.0
4	10.0	100	$\geq$ 60 minutes	100	20.0

a. Some study drug will remain in the tubing at the end of the infusion; the remaining study drug should be flushed with 10 mL to 20 mL of normal saline to complete the administration of the entire dose of study medication.
b. The maximum infusion rates (mg/kg/min) are based on 120 kg of body weight.

3.3.4 Administration of Study Drug

The study drug should be dispensed by the pharmacist or qualified designee and administered as an infusion over at least 60 minutes using an infusion pump. Do not ever administer study drug by intravenous push (IVP) or bolus injection. A physician must be present at the infusion site during all administrations of study drug.

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be monitored before infusion (at anytime the day of dosing, prior to infusion), approximately every 15 minutes during infusion, at the end of the infusion (within 10 minutes after the infusion has stopped), and approximately every 30 minutes after completion of the infusion until stable, 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. Blood pressure and heart rate will also be taken prior to discharge from the site on visits in which study drug is administered.

Patients should not be premedicated unless they have had a prior infusion reaction, since the primary objective of this study is to evaluate the expected frequency of safety events and

tolerability of the study drug. However, after a reaction determined to be an infusion reaction has been documented, the investigator may elect to administer prophylactically an anti-histamine or Tylenol for the comfort and safety of the patient prior to subsequent infusions.

Because compatibility of MEDI-545 with IV medications and solutions other than 0.9% Sodium Chloride for Injection, USP, is not known, the study drug solution should not be infused through an IV line in which other solutions or medications are being administered.

Study drug must be administered within 8 hours after preparation. If the dose is not administered within 8 hours, a new dose must be prepared using a new vial as the study drug product contains no bacteriostatic agents.

3.3.4.1 Dose Modification for Toxicity Management: Anaphylaxis and Infusion Reactions

Infusion reactions have been reported with the administration of intravenous gammaglobulin (IVIG) and nearly all approved monoclonal antibodies. Infusion reactions have occurred with the investigational drug MEDI-545. For purposes of this protocol, infusion reactions are defined as anaphylactoid-like AEs related to the infusion of the study drug itself that usually occur within first 24 hours after infusion, especially within minutes to a few hours, and will be distinguished from true anaphylactic reactions by absence of measurable antibodies against the study drug. Infusion reactions are characterized by a complex of signs and symptoms that include flu-like illness, fever, chills/rigors, nausea, urticaria, headache, bronchospasm, angioedema, hypotension, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. For purposes of this protocol, a classification of infusion reactions is given in Table 2, with suggested treatment options. Final treatment is at the discretion of the investigator and should reflect local standard of care.

Table 2 Classification and Suggested Treatments for Infusion Reactions

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

Table 2 Classification and Suggested Treatments for Infusion Reactions

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

If a Grade 1 or higher infusion reaction occurs during or after study drug administration, the patient will remain at the study site for a minimum of 2 hours for observation after resolution of symptoms and undergo the following procedures unless transfer to an emergency or hospital facility is deemed warranted:

- Clinical evaluation, treatment, and stabilization of patient according to standard medical practice, with suggested approaches outlined above;
- Close monitoring of vital signs for example every 5 to 10 minutes for Grade 1 or Grade 2 infusion reactions and every 2 to 5 minutes for Grade 3 or Grade 4 infusion reactions until stable, as judged by the investigator;
- Collect whole blood for assessment of safety biomarkers (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies) for Grade 1 or higher infusion reactions as soon as possible after the event, at 60 minutes after the event, and at discharge; and
- Consider adding prophylactic treatment (ie, acetaminophen and diphenhydramine) prior to the next infusion of study drug.

3.3.4.2 Dose Modification for Toxicity Management: Blood Chemistry Abnormalities

If total bilirubin is > 2 × ULN at the central laboratory:

- Do not administer study drug at next dosing visit.
- Repeat total bilirubin as well as direct and indirect values, liver function tests (LFTs; including AST, ALT, and alkaline phosphatase), evaluate reticulocyte count immediately to confirm abnormalities. Repeat all tests again in 1 week.
  - If bilirubin remains > 2 × ULN (not due to Gilbert's syndrome or hemolysis) do not administer study drug at next dosing visit
  - If bilirubin returns to within normal limits (< ULN), study drug may be administered at next scheduled dosing visit
  - If repeat bilirubin is < 2 × ULN but > ULN; hold dose and discuss with medical monitor.

Study drug will be discontinued in subjects who miss 2 consecutive scheduled doses of study drug due to elevated bilirubin (see Section 4.7).

If ALT or AST is > 3 × ULN refer to Guidance for Abnormal Liver Function Tests in Appendix C.

Study drug will be discontinued in subjects who miss 3 consecutive scheduled doses of study drug due to elevated ALT or AST (see Section 4.7).

As indicated in the Guidance for Abnormal Liver Function Tests (Appendix C), additional laboratory tests may be ordered from Quintiles Laboratory as needed. The LFTs that the guidelines require to be repeated are AST, ALT, total bilirubin and alkaline phosphatase.

Additional tests may be ordered as required by investigators, these tests include: CPK, GGT, INR, PT, albumin, EBV, CMV, hepatitis A antibody, hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody.

3.3.5 Concomitant Medications

All concomitant medications, including herbal products, used by the patient from randomization/entry through Study Day 350 will be recorded on the case report form. Patients may not receive the following concomitant medications from randomization through Study Day 350:

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

The dosage of concomitant analgesics for SLE symptoms may be adjusted as needed throughout the study. The dosages of concomitant NSAIDs, antimalarials, mycophenolate, methotrexate, leflunomide, or azathioprine must remain constant from 28 days before Study Day 0 through Study Day 196, unless disease activity is not controlled by burst and taper corticosteroids, as outlined below. If doses of concomitant NSAIDs, antimalarials, mycophenolate, methotrexate, leflunomide, or azathioprine must be adjusted to control disease activity, this should be discussed with the Medical Monitor first. Dosage of oral corticosteroids should remain unchanged from 14 days before Study Day 0 through Study Day 196, but may be adjusted after Study Day 196 through Study Day 350 (follow-up period), except burst-and taper treatment as described below. No more than 2 courses of burst-and-taper treatment of oral corticosteroids or 2 courses of intramuscular injections of methylprednisolone acetate (Depo-Medrol® injectable suspension) or another corticosteroid with equivalent dose are allowed before Study Day 126. Each course of burst-and-taper of oral corticosteroid must last no more than 14 days, followed by a return to the baseline dose of corticosteroid. The maximum daily dose of oral corticosteroids given during a course must not exceed 40 mg/day prednisone or another corticosteroid with equivalent dose, or intra-articular corticosteroid. The intramuscular injection of methylprednisolone acetate, another corticosteroid with equivalent dose, or intra-articular corticosteroid should not exceed a total of 2 injections and a maximum of 160 mg per course. Between Study Day 142 and Study Day 196, the baseline dosage of oral corticosteroid must be maintained and no burst-and-taper is allowed. In the follow-up period, corticosteroid dosage may be adjusted as clinically warranted.

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

Patients may receive medications to treat AEs, as deemed necessary by the investigator or the patient's physician.

3.4 Schedule of Patient Evaluations

All patients who are assigned a PID and receive any study drug will be followed according to the protocol regardless of the number of doses of study drug received, unless consent for follow-up is withdrawn. The sponsor must be notified of all deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule.

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

Schedules of screening, treatment period, and follow-up procedures are presented in Table 3 (screening and treatment periods) and in Table 4 (follow-up period), followed by a detailed description of each visit.

Table 3 Schedule of Patient Evaluations: Screening and Treatment Periods

Evaluations	Screen[a]	Treatment Period (Study Days)														
		0	14	28	42	56	70	84	98	112	126	140	154	168	182	Disc[b]
Written informed consent	X															
Verify eligibility criteria	X	X														
Medical history	X	X[c]														
Physical examination	X	X[c]						X[c]								X
Body Weight		X[c]													X[c]	
ECG	X							X								X
Chest x-ray	X[d]															
TB skin test	X[e]															
Hepatitis A, B, C; HIV-1, HIV-2	X															
Serum βHCG [f]	X															
Urine βHCG [f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
STUDY DRUG ADMINISTRATION		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
SAFETY ASSESSMENT																
Vital signs [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential, platelets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for safety biomarkers [i]		X														
Urinalysis [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral cultures and titers [k]		X		X		X		X		X		X		X		X
Record concomitant medications		X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DISEASE ACTIVITY																
BILAG/SELENA-SLEDAI assessments	X	X[c]		X		X		X		X		X		X	X	X
Active joint count		X[c]		X[c]		X[c]				X[c]				X[c]		X
Physician global assessment	X	X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]	X[c]	X
Skin photographs (optional) [l]		X[c]		X[c]		X[c]				X[c]				X[c]		X
ANAM tests [m]		X		X		X				X				X		X
Beck Depression Index		X[c]		X[c]		X[c]				X[c]				X[c]		X
Patient global assessment		X[c]		X[c]		X[c]				X[c]				X[c]		X[c]
MHAQ		X[c]		X[c]		X[c]				X[c]				X[c]		X[c]

Evaluations	Screen[a]	Treatment Period (Study Days)														
		0	14	28	42	56	70	84	98	112	126	140	154	168	182	Disc[b]
DISEASE ACTIVITY (Continued)																
Krupp Fatigue Severity score		X[c]		X[c]		X[c]				X[c]				X[c]		X
Work productivity questionnaire		X[c]		X[c]		X[c]				X[c]				X[c]		X
SF-36		X[c]				X[c]				X[c]						X
Renal function [n]	X	X		X		X		X		X		X		X	X	X
Autoantibody & complement levels [o]	X	X		X		X		X		X		X		X	X	X
Serum for IFN-α assays & storage		X		X		X				X				X		X
Whole blood for RNA analysis & storage	X	X		X		X				X						X
Blood sample for flow cytometry [p]		X		X		X				X						X
Blood sample for disease biomarkers		X		X		X				X						X
DNA sample (optional)			X													
PK/IM																
MEDI-545 serum concentration	X[q]	X[r]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[r]	X
Anti-MEDI-545 antibodies	X[q]	X[s]		X[s]		X[s]				X[s]						X

Table 3 Footnotes:

a. Within 28 days prior to Study Day 0.
b. The following evaluations will be performed in patients who discontinue the study prematurely (prior to Study Day 182). If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.
c. Assessments may be performed up to 72 24 hours prior to dosing.
d. A chest x-ray taken within 6 months of screening is considered suitable for screening and need not be repeated; also, a previously obtained chest CT scan, prior to the screening period, can substitute for a chest x-ray if the CT has already been done within the previous 6 months. If the chest x-ray is done, it must be with 2 views (anterior-posterior and lateral)..
e. Do not administer TB skin test if the patient is known to be positive.
f. Women, unless surgically sterile or at least 2 years post-menopausal, must have a negative serum pregnancy test within 28 days before randomization/entry, and a negative urine pregnancy test on Study Day 0 and all subsequent study drug infusion days before receiving the study drug.
g. Vital signs include heart rate, blood pressure, respiratory rate and temperature. Blood pressure should be obtained with the patient in the position to be used for drug administration. Vital signs are obtained before dosing (at anytime the day of dosing, prior to infusion), approximately every 15 minutes during infusion, at the end of the infusion (within 10 minutes after the infusion has stopped), and approximately every 30 minutes after completion of the infusion until stable, as judged by the investigator. Blood pressure and heart rate will also be taken prior to discharge from the site on visits in which study drug is administered.
h. Includes Na, K, Cl, bicarbonate, BUN, creatinine, AST, ALT, bilirubin, alkaline phosphatase, and random glucose.

i. A blood sample for assessment of safety biomarkers (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies) will be collected in all patients at any time prior to study drug administration on Study Day 0 and in any patient with an infusion reaction as soon as possible after the event, 60 minutes after the event, and at discharge (see Section 3.3.4 for details).
j. Includes urine dipstick tests and microscopy for red blood cells and white blood cells.
k. Oropharyngeal swabs (performed by investigator or qualified designee) for HSV-1 and HSV-2; vaginal swabs (self-collected, female patients only, or collected by an MD/OBGYN or qualified medical personnel such as an appropriately trained nurse practitioner, if approved by the sponsor) for HSV-1 and HSV-2, and HPV; and blood samples for EBV and cytomegalovirus tests.
l. Photographs of up to two target skin lesions (if present) are requested but not required for study participation. Photographs will be performed at selected North American sites North American sites only.
m. ANAM tests are optional and will be performed only on English-speaking patients at selected sites in North America.
n. Includes spot morning urine for protein/creatinine ratio and estimated glomerular filtration rate calculated based on the Cockcroft-Gault equation (Cockcroft, 1976).
o. Includes ANA, anti-Ro, anti-La, anti-RNP, anti-Sm, IgG and IgM anti-cardiolipin antibodies, total hemolytic complement, anti-dsDNA, C3, and C4 measurements.
p. Flow cytometry will be performed at selected North American sites.
q. For patients who had previously received MEDI-545 only.
r. Serum samples for MEDI-545 concentrations are collected immediately before study drug administration, immediately after, and 2 hours after the completion of study drug administration.
s. Blood samples should be collected before study drug administration.

Table 4 Schedule of Patient Evaluations: Follow-up Period

Evaluations	Follow-up Period (Study Days)								
	185	189	196	210	238	266	294	322	350[a]
SAFETY ASSESSMENT									
Physical examination			X						X
ECG			X						
Vital signs [b]	X	X	X	X	X	X	X	X	X
Body weight									X
AE/SAE assessment	X	X	X	X	X	X	X	X	X
Serum chemistry [c]			X	X	X	X	X	X	X
CBC with differential & platelet			X	X	X	X	X	X	X
Urinalysis [d]			X	X	X	X	X	X	X
Viral cultures and titers [e]			X		X		X		X
Record concomitant medications			X	X	X	X	X	X	X
Urine βHCG					X				
DISEASE ACTIVITY									
BILAG/SELENA-SLEDAI assessments			X	X	X	X	X	X	X
Active joint count			X		X		X		X
Physician global assessment			X	X	X	X	X	X	X
Skin photographs (optional) [f]			X		X		X		X
Beck Depression Index			X		X		X		X
Patient global assessment			X		X		X		X
MHAQ			X		X		X		X
Krupp Fatigue Severity score			X		X		X		X
Work productivity questionnaire			X		X		X		X
SF-36			X						X
Renal function [g]			X	X	X	X	X	X	X
Autoantibody & complement levels [h]			X	X	X	X	X	X	X
Serum for IFN-α assays & storage			X	X	X		X		X
Whole blood for RNA analysis & storage			X	X	X		X		X
Blood sample for flow cytometry			X		X		X		X
Blood sample for disease biomarkers			X		X		X		X

Evaluations	Follow-up Period (Study Days)								
	185	189	196	210	238	266	294	322	350[a]
PK/IM									
MEDI-545 serum concentration	X	X	X	X	X	X	X	X	X
Anti-MEDI-545 antibodies			X		X		X		X

Table 4 Footnotes:

a. The following evaluations will be performed in patients who discontinue the study prematurely (after Study Day 182). If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.
b. Vital signs include heart rate, blood pressure, respiratory rate and temperature.
c. Includes Na, K, Cl, bicarbonate, BUN, creatinine, AST, ALT, bilirubin, alkaline phosphatase, and random glucose.
d. Includes urine dipstick tests and microscopy for red blood cells and white blood cells.
e. Oropharyngeal swabs (performed by investigator or qualified designee) for HSV-1 and HSV-2; vaginal swabs (self-collected, female patients only, or collected by an MD/OBGYN or qualified medical personnel such as an appropriately trained nurse practitioner, if approved by the sponsor) for HSV-1 and HSV-2, and HPV; and blood samples for EBV and cytomegalovirus tests.
f. Photographs of up to two target skin lesions (if present) are requested but not required for study participation. Photographs will only be performed at North American sites only.
g. Includes spot morning urine for protein/creatinine ratio and estimated glomerular filtration rate calculated based on the Cockcroft-Gault equation (Cockcroft, 1976).
h. Includes ANA, anti-Ro, anti-La, anti-RNP, anti-Sm, IgG and IgM anti-cardiolipin antibodies, total hemolytic complement, anti-dsDNA, C3, and C4 measurements.

Screening

Note: All screening laboratory assessments must be performed within 28 days before Study Day 0. The screening evaluations may be carried out over more than one visit.

1. Written informed consent
2. Verify eligibility criteria
3. Screening medical history
4. Screening physical examination
5. AE/SAE assessment
6. BILAG/SELENA-SLEDAI assessments
7. Physician global assessment
8. Screening ECG
9. Chest x-ray
10. TB skin test (unless known to be positive)
11. Urine Collection
    - Urinalysis
    - Renal function tests
12. Blood collection for screening
    - Screening chemistry panel (Na, K, Cl, bicarbonate, AST, ALT, alkaline phosphatase, total bilirubin, BUN, creatinine, and random glucose)
    - CBC with differential and platelet count
    - Autoantibody and complement levels
    - Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody, and HIV-1 and HIV-2 antibodies
    - Serum βHCG
    - RNA analysis and storage
    - MEDI-545 serum concentration (patients who had previous administration of MEDI-545 only)
    - Anti-MEDI-545 antibodies (patients who had previous administration of MEDI-545 only)

Study Day 0: Randomization and Study Drug Administration

1. Verify eligibility criteria
2. Update screening medical history and physical examination (any new findings since screening)
3. Body weight
4. Baseline urine collection
    - Urine βHCG
    - Urinalysis
    - Renal function tests
5. Baseline blood collection
    - Chemistry panel
    - CBC with differential and platelet count

- Autoantibody and complement levels
- IFN-α assays and storage
- RNA analysis and storage
- Flow cytometry analysis
- Disease biomarker analysis
- Safety biomarker analysis
- Pre-dose MEDI-545 serum concentration
- Anti-MEDI-545 antibodies

6. Viral cultures and titers
7. Evaluation of lupus
   - BILAG/SELENA-SLEDAI assessments
   - Active joint count
   - Physician global assessment
   - Skin photographs (optional; if present)
   - ANAM tests (optional)
   - Beck Depression Index
   - Patient global assessment
   - MHAQ
   - Krupp Fatigue Severity questionnaire
   - Work productivity questionnaire
   - SF-36
8. Randomization and assignment of PID
9. Vital signs before administration of study drug (temperature, blood pressure, pulse rate, respiratory rate)
10. Administration of study drug
11. AE/SAE assessment
12. Monitor vital signs (approximately every 15 minutes during infusion, at the end of infusion [within 10 minutes after the infusion has stopped], and approximately every 30 minutes after the completion of the infusion until stable, as judged by the investigator). Measure blood pressure and heart rate prior to discharge from the site.
13. Post-dose blood collection
    - MEDI-545 serum concentration (immediately after [within 10 minutes after the infusion has stopped] and 2 hours after the completion of study drug administration)
14. Record concomitant medications

Study Days 14, 42, 70, 98, 126, 154 (±3 days): Study Drug Administration

1. Urine collection
   - Urine βHCG
   - Urinalysis
2. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Pre-dose MEDI-545 serum concentration
   - DNA analysis (optional; Study Day 14 only)

3. Vital signs before administration of study drug
4. Administration of study drug
5. AE/SAE assessment
6. Monitor vital signs (approximately every 15 minutes during infusion, at the end of infusion [within 10 minutes after the infusion has stopped], and approximately every 30 minutes after the completion of the infusion until stable, as judged by the investigator). Measure blood pressure and heart rate prior to discharge from the site
7. Record concomitant medications

Study Days 28, 56, 112 (±3 days): Study Drug Administration

1. Urine collection
   - Urine βHCG
   - Urinalysis
   - Renal function tests
2. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Autoantibody and complement levels
   - IFN-α assays and storage
   - RNA analysis and storage
   - Flow cytometry analysis
   - Disease biomarker analysis
   - Pre-dose MEDI-545 serum concentration
   - Anti-MEDI-545 antibodies
3. Viral cultures and titers
4. Evaluation of lupus
   - BILAG/SELENA-SLEDAI assessments Active joint count
   - Physician global assessment
   - Skin photographs (optional; if present)
   - ANAM tests (optional)
   - Beck Depression Index
   - Patient global assessment
   - MHAQ
   - Krupp Fatigue Severity questionnaire
   - Work productivity questionnaire
   - SF-36 (Study Days 56 and 112 only)
5. Vital signs before administration of study drug
6. Administration of study drug
7. AE/SAE assessment
8. Monitor vital signs (approximately every 15 minutes during infusion, at the end of infusion [within 10 minutes after the infusion has stopped], and approximately every 30 minutes after the completion of the infusion until stable, as judged by the investigator). Measure blood pressure and heart rate prior to discharge from the site
9. Record concomitant medications

Study Days 84 and 140 (± 3 days), 182 (± 2 days): Study Drug Administration

1. Physical examination (Study Day 84 only)
2. Body weight (Study Day 182 only)
3. ECG (Study Day 84 only)
4. Urine collection
   - Urine βHCG
   - Urinalysis
   - Renal function tests
5. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Autoantibody and complement levels
   - Pre-dose MEDI-545 serum concentration
6. Viral cultures and titers (Study Days 84, 140 only)
7. Evaluation of lupus
   - BILAG/SELENA-SLEDAI assessments
   - Physician global assessment
8. Vital signs before administration of study drug
9. Administration of study drug
10. AE/SAE assessment
11. Monitor vital signs (approximately every 15 minutes during infusion, at the end of infusion, and approximately every 30 minutes after the completion of the infusion until stable). Measure blood pressure and heart rate prior to discharge from the site
12. Post-dose blood collection (Study Day 182 only)
    - MEDI-545 serum concentration (immediately and 2 hours after the completion of study drug administration)
13. Record concomitant medications

Study Days 168 (±3 days): Study Drug Administration

1. Urine collection
   - Urine βHCG
   - Urinalysis
   - Renal function tests
2. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Autoantibody and complement levels
   - IFN-α assays and storage
   - Pre-dose MEDI-545 serum concentration
3. Viral cultures and titers
4. Evaluation of lupus
   - BILAG/SELENA-SLEDAI assessments Active joint count
   - Physician global assessment

- Skin photographs (optional; if present)
- ANAM tests (optional)
- Beck Depression Index
- Patient global assessment
- MHAQ
- Krupp Fatigue Severity questionnaire
- Work productivity questionnaire

5. Vital signs before administration of study drug
6. Administration of study drug
7. AE/SAE assessment
8. Monitor vital signs (approximately every 15 minutes during infusion, at the end of infusion [within 10 minutes after the infusion has stopped], and approximately every 30 minutes after the completion of the infusion until stable, as judged by the investigator). Measure blood pressure and heart rate prior to discharge from the site.
9. Record concomitant medications

Unscheduled Visit

Evaluations may be performed during unscheduled visits as deemed warranted by the investigator.

Study Discontinuation Visit

If a patient discontinues the study prematurely prior to Study Day 182, he or she should return to the study site and complete the following evaluations. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

1. Physical examination
2. Body weight
3. ECG
4. Urine collection
   - Urine βHCG
   - Urinalysis
   - Renal function tests
5. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Autoantibody and complement levels
   - IFN-α assays and storage
   - RNA analysis and storage
   - Flow cytometry analysis
   - Disease biomarker analysis
   - Pre-dose MEDI-545 serum concentration
   - Anti-MEDI-545 antibodies
6. Viral cultures and titers

7. Evaluation of lupus
   - BILAG/SELENA-SLEDAI assessments Active joint count
   - Physician global assessment
   - Skin photographs (optional; if present)
   - ANAM tests (optional)
   - Beck Depression Index
   - Patient global assessment
   - MHAQ
   - Krupp Fatigue Severity questionnaire
   - Work productivity questionnaire
   - SF-36
8. Vital signs before administration of study drug
9. Administration of study drug
10. AE/SAE assessment
11. Monitor vital signs
12. Record concomitant medications

Study Days 185 (+ 1 day) and 189 (±1 day): Follow-up

1. Vital signs
2. AE/SAE assessment
3. Blood collection
   - MEDI-545 serum concentration

Study Day 196 (±3 days): Follow-up

1. Physical examination
2. ECG
3. Vital signs
4. AE/SAE assessment
5. Record concomitant medications
6. Urine collection
   - Urinalysis
   - Renal function tests
7. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Autoantibody and complement levels
   - IFN-α assays and storage
   - RNA analysis and storage
   - Flow cytometry analysis
   - Disease biomarker analysis
   - MEDI-545 serum concentration
   - Anti-MEDI-545 antibodies

8. Viral cultures and titers
9. Evaluation of lupus
    - BILAG/SELENA-SLEDAI assessments Active joint count
    - Physician global assessment
    - Skin photographs (optional; if present)
    - ANAM tests (optional)
    - Beck Depression Index
    - Patient global assessment
    - MHAQ
    - Krupp Fatigue Severity questionnaire
    - Work productivity questionnaire
    - SF-36

Study Days 210 (±3 days), 266 (±7 days), 322 (±7 days): Follow-up

1. Vital signs
2. AE/SAE assessment
3. Record concomitant medications
4. Urine collection
    - Urinalysis
    - Renal function tests
5. Blood collection
    - Chemistry panel
    - CBC with differential and platelet count
    - Autoantibody and complement levels
    - IFN-α assays and storage (Study Day 210 only)
    - RNA analysis and storage (Study Day 210 only)
    - MEDI-545 serum concentration
6. Evaluation of lupus
    - BILAG/SELENA-SLEDAI assessments Physician global assessment

Study Days 238, 294, 350 (±7 days): Follow-up

For Study Day 350 only, if a patient discontinues the study prematurely after Study Day 182, he or she should return to the study site and complete the following evaluations. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

1. Physical examination (Study Day 350 only)
2. Body weight (Study Day 350 only)
3. Vital signs
4. AE/SAE assessment
5. Record concomitant medications
6. Viral cultures and titers
7. Urine collection
    - Urinalysis

- Renal function tests
- Urine βHCG (Study Day 238 only)

8. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Autoantibody and complement levels
   - IFN-α assays and storage
   - RNA analysis and storage
   - Flow cytometry analysis
   - Disease biomarker analysis
   - MEDI-545 serum concentration
   - Anti-MEDI-545 antibodies
9. Evaluation of lupus
   - BILAG/SELENA-SLEDAI assessments Active joint count
   - Physician global assessment
   - Skin photographs (optional; if present)
   - Beck Depression Index
   - Patient global assessment
   - MHAQ
   - Krupp Fatigue Severity questionnaire
   - Work productivity questionnaire
   - SF-36 (Study Day 350 only)

3.5 Patient Evaluation Methods

3.5.1 Routine Laboratory Evaluations

Routine laboratory tests during screening and during the study will be performed in a licensed central clinical laboratory. A laboratory manual will be provided specifying specific procedures for collection, processing, storage, and shipping of samples. Medically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24-48 hours). Routine laboratory assessments include the following:

1. CBC with differential, platelets
2. Serum chemistry to include Na, K, Cl, bicarbonate, BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, and random glucose
3. Urinalysis to include urine dipstick tests and microscopy for red blood cells and white blood cells

3.5.1.1 Pregnancy Tests

The following tests will be used to monitor pregnancy in women of child-bearing potential:

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

3.5.1.2 Other Laboratory Tests

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

1. Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody and HIV-1 antibody (screening only)
2. Renal function includes spot morning urine for protein/creatinine ration and estimated glomerular filtration rate calculated based on the Cockcroft-Gault equation (Cockcroft, 1976)
3. Autoantibody levels include ANA, anti-Ro, anti-RNP, anti-LA, anti-Sm, IgG, and IgM anti-cardiolipin antibodies
4. Complement levels include total hemolytic complement, anti-dsDNA, C3, and C4 measurements

3.5.2 Viral Cultures and Titers

Viral infections will be monitored through viral cultures and titers as indicated in Table 3 and Table 4. The investigator or qualified designee will collect oropharyngeal swabs for HSV-1 and HSV-2 testing. Vaginal swabs will be self collected for HSV-1, HSV-2, and HPV testing; these swabs may also be collected by an MD/OBGYN or qualified medical personnel such as an appropriately trained nurse practitioner, if approved by the sponsor. In addition, peripheral blood samples will be collected and tested for EBV and cytomegalovirus using polymerase chain reaction tests.

3.5.3 Pharmacokinetic and Immunologic Evaluations

Details for collection, aliquoting, storage, and shipment of serum samples for PK and IM evaluations are presented in a separate laboratory manual. All PK and IM laboratory evaluations will be performed by MedImmune. MEDI-545 serum concentrations and MEDI-545 antibody detection will be measured by ELISA. Sera that are collected may be used for additional PK analyses (MEDI-545 characterization) and MEDI-545 antibody analyses.

3.5.4 Safety Biomarkers

Whole blood will be collected for baseline assessment of safety biomarkers on Study Day 0 as described in Table 3. In addition, if a Grade 1 or higher infusion reaction occurs during or after study drug administration, whole blood for assessment of safety biomarkers will be collected as soon as possible after the event, at 60 minutes after the event, and at discharge (see Section 3.3.4 for details). Safety biomarkers include serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies.

3.5.5 Effects on Type I IFN-Inducible Gene Expression

Type I IFN-inducible genes will be used to measure the pharmacodynamics of MEDI-545. Whole blood samples will be used to analyze the effects of MEDI-545 on levels of mRNA for type I IFN-inducible genes. This analysis is performed using Affymetrix whole genome expression array and taqMan-based assay on selected panel of genes.

3.5.6 Effects on Other Markers of Disease Mechanisms

Whole blood and serum samples will be taken to investigate the effects of MEDI-545 on various mechanisms and pathogenesis in SLE, including B cell subset counts and potential SLE biomarkers. Blood samples will also be stored for future exploratory analyses. Flow cytometry of blood samples will be performed at selected sites in North America.

3.5.7 Effects on Disease Activity

The following disease evaluations will be performed: BILAG score, SELENA-SLEDAI score and flares (using SELENA-SLEDAI and/or BILAG criteria). The BILAG/SELENA-SLEDAI assessments will only be performed by rheumatologists who were trained by a MedImmune-approved trainer. Exceptions to this must be approved in writing by the MedImmune Medical Monitor. Non-exempt rheumatologists must attend a MedImmune-sponsored BILAG/SELENA-SLEDAI training prior to conducting assessments. The SELENA-SLEDAI score should reflect the last 28 days. The BILAG/SELENA-SLEDAI assessments must be completed by the same rheumatologist for the same patient throughout the study. The occurrence and total dose of burst oral corticosteroids, intra-articular or intramuscular corticosteroid injections to treat SLE during the treatment period will be assessed along with the changes from baseline in immunosuppressive treatment for SLE during the follow-up period. Other evaluations include the physician global assessment, renal function measured by spot protein/creatinine ratio, estimated glomerular filtration rate, BUN, and serum creatinine. Autoantibodies and complement levels in blood will also be measured.

The period to be considered for disease activity assessments, will cover the previous 28 days or, if less, through the period to the previous evaluation.

3.5.7.1 Photography of Skin Lesions

Photographs of skin lesions will be requested at screening but are not required for study participation (North American sites only). For patients who have skin lesions at screening, up to 2 representative lesions will be chosen by the investigator and serial photographs will be taken at visits as indicated in Section 3.4. For patients who do not have skin lesions at screening but subsequently develop lesions during the study, up to 2 lesions will be selected by the investigators and serial photographs will be taken during the rest of the study period. See Appendix B for instructions.

3.5.8 Patient-Reported Outcomes

The following patient-reported indicators by patients will be evaluated: ANAM tests (optional) for cognitive function (Holliday, 2003; Roebuck-Spencer, 2006), MHAQ, patient global assessment, Beck Depression Index, the Krupp Fatigue Severity score, work productivity questionnaire, and SF-36.

3.5.8.1 DNA Analysis

To investigate characteristics associated with patients' clinical response and safety, one blood sample (8.5 mL) will be collected on Study Day 14 and frozen at –80°C for DNA sample

preparation. The sample will be frozen and stored until used in exploratory analyses. The specific tests include analyses for DNA single nucleotide polymorphisms (SNPs) and microsatellite or short tandem repeats to further evaluate particular genes involved in the signaling pathway relevant to type I interferons.

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

All specimen and patient identifiers must be removed from the DNA blood samples such that under no circumstances can the DNA blood samples be linked back to a specific patient. In most cases, this will require that DNA blood samples have current labeling removed and the tubes relabeled. Special labeling capable of adhering to frozen tubes must be used. If it is not possible to remove the original labeling, then it must be determined whether the DNA blood samples can go through a freeze thaw and be re-aliquoted in order to maintain confidentiality. All re-labeled DNA blood samples must be cross referenced to the original demographics in a secure database to ensure that only appropriate laboratory personnel have access to these data. A special release must be obtained prior to use of specified DNA blood samples.

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

Patients will be considered to have completed the study if they were followed up through the Study Day 350 visit.

If a patient discontinues his or her participation prior to Study Day 182, the patient will return to the study site and complete the Study Discontinuation Visit evaluations. If the patient discontinues after Study Day 182, the patient will return to the study site and complete the Study Day 350 evaluations. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

Patients will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the patient's status at Study Day 350. Investigators or qualified designees should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, follow-up should resume according to the protocol.

Patients who participate in this study may have the option of terminating early to enter the MI-CP212 study. This includes both MEDI-545 and placebo patients, but excludes patients who discontinued from previous MEDI-545 clinical studies for safety reasons. Patients must complete the treatment period and follow up through study Day 266 of this study to participate in MI-CP212. Patients will be considered terminated from this study upon signing the MI-CP212 informed consent form between study Day 266 and Day 350. If possible, patients should complete the Study Day 350 evaluations on their last study visit. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

4 SAFETY ASSESSMENT

4.1 Adverse Events

4.1.1 Definition of Adverse Events

As defined by the ICH Guideline for Good Clinical Practice (CPMP/ICH/135/95), an Adverse Event (AE) is:

> Any untoward medical occurrence in a patient or clinical investigations subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (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.

Any adverse change from the study subject's baseline condition that occurs from the time the informed consent is signed through Study Day 350 is an AE. This includes the occurrence of a new AE or the worsening of a baseline condition, whether or not considered related to the study product. AEs include but are not limited to: adverse changes from baseline that are listed on the toxicity table in Attachment 1, adverse changes in the general condition of the study subject; signs and symptoms noted by the study subject or his/her care giver; concomitant disease with onset or increased severity after the start of study product administration and clinically meaningful adverse changes in laboratory safety parameters occurring after the start of study product administration. Day-to-day fluctuations in pre-existing conditions that represent a clinically significant change in the subject's status should be reported as AEs.

An AE occurring during a clinical trial that is not related to the study drug, but is considered by the investigator or medical monitor to be related to the research conditions. An example of this protocol related AE may be an event related to a medical procedure required by protocol prior to dosing of the study medication.

4.1.2 Study Reporting Period for Adverse Events

The reporting period for AEs is the period from the time the informed consent is signed through Study Day 350. AEs will not be recorded for patients deemed screening failures.

4.1.3 Recording of Adverse Events

Adverse events will be reported using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the study product, possible etiologies and whether the event meets criteria as a serious adverse event and therefore requires immediate notification of the sponsor. See Sections 4.3 and 4.4 regarding guidelines for assessment of severity and relationship, respectively, and Section 4.2.1 for the definition of serious adverse events. If the event has not resolved at the end of the study reporting period, it will be documented as ongoing. If an AE evolves into a condition which becomes "serious" the investigator will additionally report to the Sponsor on the ***SERIOUS ADVERSE EVENT (SAE) REPORT FORM.***

4.1.4 Recording of SLE Flares as Adverse Events

An SLE flare should not be recorded as an AE, if it is consistent with waxing and waning of the disease in the year before participation in the study.

An SLE flare should be recorded as an AE if it involves an organ system which was inactive for a year prior to study entry or the condition is significantly worse than the disease activity in a given organ system during the year prior to entering the study. The event term on the AE form should be "SLE Flare", and therefore, components of the flare, such as swelling or pain, should not be recorded separately as additional AEs. The elements of a flare recorded as an AE should be reported on the disease activity case report forms. If not, a note to file should be recorded to explain the rationale for considering the event a lupus flare. Sites will be queried if components of a flare are entered on the AE page in addition to the SLE Flare entry. Any AE seen in addition to the flare should have separate entries (e.g., if a lupus patient developed a flare of arthritis in the context of an upper respiratory infection, the upper respiratory infection should be recorded as an AE and the arthritis flare would be recorded as an AE only if it was inconsistent with the waxing and waning disease activity in the year before entering the study).

4.2 Serious Adverse Events

4.2.1 Definition of Serious Adverse Events

A Serious Adverse Event (SAE) is any AE that results in any of the following outcomes:

- Death
- Life-threatening*
- Inpatient hospitalization or prolongation of existing hospitalization‡
- Persistent or significant disability or incapacity†
- Congenital anomaly/birth defect (in the offspring of a subject)
- An important medical event that may not result in death, threaten life or require hospitalization may be considered an SAE when, **based upon appropriate medical judgment**, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

*Life threatening: An adverse event is life threatening if the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

‡Hospitalization: An inpatient hospitalization will be defined as an admission (or emergency room visit) for a period greater than 24 hours. Hospitalization for either elective surgery related to a pre-existing condition which did not increase in severity or frequency following initiation of the study or for routine clinical procedures¶ (including hospitalization for "social" reasons) that are not the result of an adverse

event need not be considered as adverse events and are therefore not serious adverse events.

¶Routine Clinical Procedure: A procedure which may take place during the study period and should not interfere with the study product administration or any of the ongoing protocol specific procedures. If anything untoward is reported during an elective procedure, that occurrence must be reported as an adverse event or serious adverse event, according to the usual criteria.

†Disabling/incapacitating: An adverse event is incapacitating or disabling if the event results in a substantial disruption of the subject's ability to carry out normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle).

4.2.2 Study Reporting Period for Serious Adverse Events

The reporting period for SAEs is the period from the time the informed consent is signed through Study Day 350. SAEs will also be recorded for patients deemed screening failures. SAEs must be followed until resolution by the investigator, even if this extends beyond the study reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

At any time after completion of the study, if an investigator becomes aware of an SAE that is suspected by the investigator to be related to study product, the event should be reported to MedImmune Product Safety.

4.2.3 Notification of Sponsor of Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the study product, the investigator must complete the *SERIOUS ADVERSE EVENT (SAE) REPORT FORM* and Safety Fax Notification Cover Page, and fax to MedImmune Product Safety.

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

MedImmune contact information:

Product Safety
MedImmune
[redacted]
Fax: [redacted]

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

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

The investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB or IEC must be informed in a timely manner by the principal investigator of SAEs occurring at their site during the study. Investigators must also submit safety information provided by MedImmune to the IRB or IEC as detailed in Section 7.2.

4.2.5 Recording of Serious Adverse Events

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

4.3 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by a health care professional who is qualified to review AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment and the severity categories of *Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5.* Severity of toxicity will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE V3.0), as described in detail in Attachment 1.

4.4 Assessment of Relationship

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

regulatory reporting only if the Investigator, Medical Monitor, and Product Safety Physician, if applicable, agree that the AE is not product-related.

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

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

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

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

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

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

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

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

4.5 Other Events Requiring Immediate Reporting

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

1. Any withdrawal of consent during the study
2. Pregnancy or intent to become pregnant*
3. Hypersensitivity (anaphylactic) reaction to the study drug, Grade 1 or higher
4. Infusion reaction, Grade 1 or higher
5. Severe viral infection, Grade 3 or higher
6. Any other event that, in the opinion of the investigator, contraindicated further dosing of study subject.

*Subjects who become pregnant or intend to become pregnant during the study period must not receive additional doses of study product and should proceed to the follow-up phase within 2 weeks of a positive pregnancy test or making the decision to become pregnant. The follow-up phase will start with the procedures scheduled for Study Day 185 and will end on Study Day 350. Patients who become pregnant during the follow-up period should continue the follow-up phase through Study Day 350. A pregnancy should be followed for outcome, any premature terminations reported, and the health status of the mother and child including date of delivery and the child's gender and weight should be reported to MedImmune Product Safety after delivery.

4.6 Safety Management during the Study

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

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

4.7 Interruption or Discontinuation of Study Dosing in Individual Patients

An individual patient will not receive any further study drug dosing if any of the following occur in the patient in question:

1. Withdrawal of consent;
2. Pregnancy;
3. Any life-threatening clinical event related to the study drug;
4. Severe hypersensitivity reaction (anaphylaxis) to the study drug, Grade 3 or higher;
5. Infusion reactions, Grade 3 or higher as defined in Table 2;
6. Serious clinical infections with a virus of the herpes family (including disseminated herpes infection, herpes encephalitis, or ophthalmic herpes infection) or with CMV or EBV;
7. If 3 consecutive doses of study drug are missed due to abnormal LFTs (ALT, AST).
8. Two consecutive total bilirubin values taken at least 1 week apart > 2 x ULN not due to Gilbert's syndrome or hemolysis; or
9. Any event that, in the opinion of the investigator or the Medical Monitor, contraindicates further dosing such as illnesses or complications.

Patients who are permanently discontinued from study drug for any of these reasons, with the exception of withdrawal of consent, will be followed for the full follow-up period (through Study Day 350), including the collection of any mandated blood and urine specimens.

4.8 Interruption or Discontinuation of Study Dosing and Randomization/Entry

If any of the following occurs, no further administration of study drug will take place in that dose cohort and no further patients will be randomized/entered into the dose cohort or a higher dose cohort until the event is reviewed by the Medical Monitor and the SMC:

1. Death of any patient in which the cause is determined by the investigator or the sponsor to be related to study drug; or death of any patient which, in the opinion of the sponsor, contraindicates further dosing;
2. Any life-threatening clinical event related to the study drug including anaphylaxis to study drug, Grade 4;
3. Serious infections with a virus of the herpes family (including disseminated herpes infection, herpes encephalitis, or ophthalmic herpes infection) or with CMV or EBV in any patient; or
4. Any event that, in the opinion of the Medical Monitor, contraindicates further dosing of study subjects.

If one of the above-listed events occurs, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted by the Medical Monitor and the SMC to determine whether dosing and study entry should be resumed, the protocol be modified, or the study be discontinued permanently. SMC review and approval are required for resumption of the study if study dosing and entry are stopped due to one of the above-listed events.

4.9 Dose Escalation

The study drug will be administered as an infusion over at least 60 minutes using an infusion pump.

Dose Cohort 1 (0.3 mg/kg) will be started first. Dosing at each next higher dose cohort (Cohort 2 [1.0 mg/kg], Cohort 3 [3.0 mg/kg], and Cohort 4 [10.0 mg/kg] will commence after the Medical Monitor has reviewed all cumulative, blinded safety information, including the safety data through Study Day 42 from the first 12 randomized patients in each preceding lower dose cohort and all cumulative safety data available in all cohorts, and has determined that the safety profile is acceptable.

The SMC will independently review cumulative safety surveillance data and the Medical Monitor's decisions on dose escalation, throughout the study and make recommendations regarding the study progression. The SMC can stop study entry and dosing as they deem necessary.

4.10 Monitoring of Dose Administration

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

However, patients should not be premedicated routinely, unless they have previously experienced an infusion reaction, since the primary objective of this study is to evaluate the

safety and tolerability of the study drug, including infusion reactions. If such reactions occur during or after study drug administration, they should be treated appropriately.

5 STATISTICAL CONSIDERATIONS

5.1 General Considerations

All data will be provided in data listings sorted by treatment group and patient number. All tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized by descriptive statistics including mean, standard deviation, median, minimum, and maximum. Baseline values will be defined as the last valid assessment prior to the first administration of study drug. All data will be collected from Study Day 0 through Study Day 350.

5.2 Sample Size

Approximately 148 patients (32 patients for Dose Cohorts 1 through 3 and 52 patients for Dose Cohort 4) will be randomized into the study. This excludes the 22 patients who were treated prior to 10/Oct/2007. Within each cohort, the number of patients receiving MEDI-545 versus the number of patients receiving placebo is 3 to 1. In addition, a dose cohort may be expanded by up to 4 additional patients if eligible patients are already in screening at the time 32 patients in Dose Cohorts 1 through 3 or 52 patients in Dose Cohort 4 have been randomized into the dose cohort. An unspecified number of patients may be enrolled in the study for replacement of nonevaluable patients as described in Section 2.4.1. No formal calculation was performed to determine sample size because safety is the primary outcome and this will be assessed with descriptive analyses.

5.3 Patient Populations

There will be 2 patient populations analyzed in this study. The primary patient population will include up to 164 new patients who receive study drug (excluding patients who received study drug prior to 10/Oct/2007). The secondary patient population will include the 22 patients who received study drug prior to 10/Oct/2007.

Efficacy data will be analyzed primarily based on the modified Intent-to-Treat Population including all randomized patients who received any study drug. Safety and IM will be analyzed in all patients who receive any study drug. Evaluability for analyses of MEDI-545 serum concentrations will be determined based upon the frequency and timing of the serum samples obtained.

5.4 Primary Endpoint

The safety and tolerability of MEDI-545 will be assessed primarily by summarizing treatment-emergent AEs/SAEs and by assessing changes in viral cultures and titers, including oropharyngeal swabs for herpes simplex virus HSV-1 and HSV-2; vaginal swabs for HSV-1, HSV-2, and HPV; and peripheral blood test (using polymerase chain reaction tests) for EBV and cytomegalovirus. The occurrence of treatment-emergent AEs and SAEs will be summarized from the first administration of study drug through Study Day 350. Treatment-emergent AEs

and SAEs that occur after the first administration of study drug will be summarized by system organ class and preferred terms, by severity, and by relationship to study drug. For the primary population, treatment-emergent AEs and SAEs will be summarized for placebo, each of the MEDI-545 dose cohorts, and for all MEDI-545 doses combined.

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

For the secondary patient population, safety data will be summarized for the placebo and MEDI-545 1.0 mg/kg group.

5.5 Secondary Endpoints

The secondary endpoints of this study are the PK and IM of multiple IV doses of MEDI-545. PK parameters such as peak concentration (C_{max}), time to peak concentration (T_{max}), area under the concentration curve within a dosing interval (AUC_{τ}) after the first dose will be estimated. PK parameters at steady state such as peak concentration ($C_{ss,\,max}$) and trough concentration ($C_{ss,\,min}$) at steady state, time to peak concentration at steady state ($T_{ss,\,max}$), area under the concentration curve within a dosing interval at steady state ($AUC_{ss,\tau}$), total body clearance at steady state (CL_{ss}), steady state volume of distribution (Vd_{ss}), terminal phase volume of distribution (Vd_z) and terminal phase half-life ($T_{1/2}$) will also be estimated. All PK parameters will be estimated by noncompartamental analysis.

The highest observed concentration will be recorded as C_{max} and the time to C_{max} will be recorded as T_{max}. Terminal phase elimination rate constant (λ_z) will be estimated by regression of the linear portion of the post-absorption serum concentration-time profile after the last dose and $T_{1/2}$ will be estimated as the ratio of natural log and λ_z. The area under the curve within a dosing interval will be estimated using the linear trapezoidal rule. Total body clearance at steady state (CL_{ss}) will be estimated as the ratio of dose and $AUC_{ss,\tau}$. Steady state volume of distribution will be estimated as the product of mean residence time (MRT) and CL_{ss}. Terminal phase volume of distribution will be estimated as the ratio of CL_{ss} and λ_z. Accumulation to steady state will be assessed as the ratio of $C_{ss,max}$:C_{max} and $AUC_{ss,\tau}$:AUC_{τ}.

IM results will be analyzed by summarizing the number and percentage of SLE patients who develop detectable anti-MEDI-545 antibodies by treatment and dose cohort.

PK and IM results will be analyzed separately for the primary and secondary patient populations.

5.6 Exploratory Endpoints

Results will be analyzed for the primary patient population. The potential effects of study drug on type I IFN, SLE disease mechanisms, disease activity, and patient-reported outcomes will be evaluated.

The major clinical measures of disease activity will include BILAG score, SELENA-SLEDAI score, flares, and physician global assessment. The SELENA-SLEDAI and BILAG scores are valid, reliable, and sensitive clinical assessments of lupus disease activity. The SELENA-SLEDAI assessment consists of 24 lupus-related items while the BILAG index consists of 86 items with respect to 8 organ systems (general, mucocutaneous, neurological, musculoskeletal, cardiorespiratory, vasculitis, renal, and hematologic). The global scores for SLEDAI and BILAG will be computed. These scores, as well as their changes from baseline, will be summarized descriptively at each visit by treatment group. Disease activities will also be measured by the proportion of patients achieving a SLEDAI or BILAG global score of 0 during the study period. The physician global assessment (PGA) represents physician's overall assessment on disease severity on a 3-inch visual scale with a 0 indicating none, a 1 indicating mild, a 2 indicating moderate, or 3 indicating severe. The proportion of patients with a PGA score >0.5 at baseline and reaching PGA $\leq$ 0.5 subsequently will be computed. Mild to moderate lupus flares and severe flares are defined as increases in the SLEDAI score of $\geq$ 3 to $\leq$12 points or $\geq$ 12 points, respectively, from the previous visit. Another measurement of flare by the SELENA-SLEDAI SLE criteria is worsening of SELENA-SLEDAI score of more than 3 points from baseline. According to the BILAG index, a lupus flare can also be defined as a new A or B score in at least one system following a C, D, or E score. The incidence of lupus flares and time to the first flare will be summarized by treatment group descriptively. In order to summarize disease activity over time, the adjusted mean SLEDAI will be developed by computing the area under the curve of SLEDAI global score over time divided by time interval. The adjusted mean SLEDAI will be summarized at each visit by treatment group. A responder index, which is a composite of elements in the SLEDAI, BILAG, and physician global assessment, will be defined to evaluate subject's response during the study. Specifically, subjects who show at least 4 point reduction from baseline in SLEDAI global score without worsening in BILAG (no new A organ system score and no new B organ system score) or physician global assessment (<0.3 points increase from baseline) will be classified as responders. The response rate will be compared between treatment groups and over time. In addition, the frequency and total dose of burst corticosteroids, changes from baseline in immunosuppressive treatment, clinical response, renal function, autoantibodies and complements in blood will be descriptively analyzed.

The following patient-reported outcomes will be evaluated: MHAQ, patient global assessment, Beck Depression Index, the Krupp Fatigue Severity score, work productivity questionnaire, and the SF-36. These outcomes will be summarized descriptively for placebo, each of the MEDI-545 dose cohorts, and for all MEDI-545 doses combined from patients.

5.7 Interim Analyses

Interim analyses of the type I IFN-inducible genes expression data will be performed after all patients in each dose cohort complete Study Day 28 evaluations.

Interim analyses on the safety and efficacy endpoints can be performed at the following time points:

- When at a minimum the 25th patient in Dose Cohort 3 completes Study Day 84;
- When at a minimum the 20th patient in Dose Cohort 4 completes Study Day 56;
- When at minimum 39 patients in Dose Cohort 4 complete Study Day 84
- When all patients in Dose Cohort 4 complete Study Day 196.

6 DATA COLLECTION AND MONITORING

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

Data recorded on source documents will be transcribed onto a validated data collection method provided by MedImmune or designee. Collected data will be reviewed by the sponsor or designee, with a copy retained by the investigator.

The study will be monitored by MedImmune or its designee on a regular basis throughout the study period. All study documents (patient files, signed informed consent forms, copies of case report forms, Study File Notebook, etc.) must be kept secured for a period of 2 years following marketing of MEDI-545 or for 2 years after centers have been notified that the IND has been discontinued. There may be other circumstances for which MedImmune is required to maintain study records and, therefore, MedImmune should be contacted prior to removing study records for any reason.

7 HUMAN SUBJECTS

7.1 Ethics and Regulatory Considerations

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

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

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

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the FDA, Health Canada, the State Food and Drug Administration of China, the Central Drugs Standard Control Organisation of India, local health authorities, or the sponsor of the clinical trial. The principal investigator must also comply with all applicable privacy regulations (e.g. Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

7.2 Institutional Review Board or Independent Ethics Committee

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

Any documents that the IRB/IEC may need to fulfill its responsibilities, such as protocol amendments, and information concerning patient 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 and the informed consent form 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 study drug supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

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

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

7.3 Informed Consent

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

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

Patients must be informed about the aims, expected benefits, possible risks (including a statement that the particular treatment or procedure may involve risks to the patient or the fetus, if the patient should become pregnant) which are currently unforeseeable. They must also be informed of alternative procedures. Patients must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. They must be informed whom to contact for answers to any questions relating to the research project. The patients must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time, without penalty or loss of benefits to which they are otherwise entitled. The extent of the confidentiality of patient records must be defined, and patients must be informed that applicable data protection legislation will be complied with. Patients must be informed that the monitor(s), auditor(s), IRB/IEC members, and the regulatory authorities will be granted direct access to the patient's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the patient or the patient's legally acceptable representative is authorizing such access.

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

8 STUDY COMPLETION

All materials or supplies provided by the sponsor will be returned to the sponsor upon study completion. The investigator will notify the IRB/IEC when the study has been completed.

9 PUBLICATIONS

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

10 CHANGES IN THE PROTOCOL

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

Summary of Changes from Version 1.0 to Version 2.0 of the Study Protocol

Version 1.0 of the protocol (dated [redacted]) was amended to Version 2.0 (dated [redacted]). The major changes include reducing the starting dose of MEDI-545 from 1.0 to 0.3 mg/kg, reducing the highest dose of MEDI-545 from 30 to 20 mg/kg, and setting the infusion volume to 100 mL, and the infusion time to 60 minutes. Other changes include revising the dose-escalation criteria; updating the safety information on MEDI-545; changing the Medical Monitor; clarifying several inclusion and exclusion criteria; addition of international sites; addition of urine pregnancy testing prior to each dose of study drug; and clarification of text. The changes made to Version 1.0 of the protocol to create Version 2.0 are summarized in Appendix D.

Summary of Changes from Version 2.0 to Version 3.0 of the Study Protocol

Version 2.0 of the protocol (dated [redacted]) was amended to Version 3.0 (dated [redacted]). The major changes include updating preclinical and clinical information; identification of specific safety biomarkers to analyze infusion reactions; addition of infusion reactions as an immediately reported event; update of statistical methodology for exploratory endpoints; and clarification of text. The changes made to Version 2.0 of the protocol to create Version 3.0 are summarized in Appendix D.

Summary of Changes from Version 3.0 to Version 4.0 of the Study Protocol

Version 3.0 of the protocol (dated [redacted]) was amended to Version 4.0 (dated [redacted]). The major changes include changing the medical monitor's name from [redacted] to [redacted], updating preclinical and clinical information; reducing the highest dose of MEDI-545 from 20.0 to 10.0 mg/kg; reducing the number of evaluable patients from 192 to 160; reducing the number of dose cohorts from six to five; indicating that CRPS will no longer be blinded to the studies, although they will continue to be part of the project team; changing the timing of the interim analysis; including a classification of infusion reactions table; and clarification of routine laboratory procedures. Other revisions were made to the inclusion and exclusion criteria; the statistical considerations section; and clarification of text. The changes made to Version 3.0 of the protocol to create Version 4.0 are summarized in Appendix D.

Summary of Changes from Version 4.0 to Version 5.0 of the Study Protocol

Version 4.0 of the protocol (dated [redacted]) was amended to Version 5.0 (dated [redacted]). The major changes include removing the open-label extension phase of the study, changing the medical monitor's name, updating preclinical and clinical information; updating the countries in which the study is being conducted; changing the number of dose cohorts from 5 to 4, decreasing the number of evaluable patients from 160 to 148; providing clarification that a physician must be present at the site during all administrations of study drug; providing clarification that the BILAG/SELENA-SLEDAI assessments must be completed by the same rheumatologist for the same patient throughout the study; providing clarification that any study drug remaining in the tubing must be flushed with 10mL to 20ML normal saline to complete study drug administration; clarification that the patient self-collected vaginal swabs may also may also be collected by qualified medical personnel, if approved by the sponsor; moving the optional DNA analysis from Study Day 0 to Study Day 14; changing the requirements that need to be met to initiate an interim analysis; providing instructions for the recording of SLE flares as

adverse events; and providing clarification of general study procedures. The changes made to Version 4.0 of the protocol to create Version 5.0 are summarized in Appendix D.

Summary of Changes from Version 5.0 to Version 6.0 of the Study Protocol

Version 5.0 of the protocol (dated [redacted]) was amended to Version 6.0 (dated [redacted] The major changes include: changing the medical monitor; updating the clinical experience with MEDI-545; including the option for patients to enter the long-term study MI-CP212; adding toxicity management guidelines for blood chemistry abnormalities; clarifying medical monitor and Safety Monitoring Committee responsibilities; including 2 additional conditions in which dosing should be discontinued; clarifying the circumstance of patient death as it applies to interruption of study dosing and randomization (ie, death of any subject which, in the opinion of the sponsor, contraindicates further dosing); changing the number of study sites from 40 to 50 to 30 to 40; changing the third interim analysis (which was to occur after all patients in Dose Cohort 4 completed Day 84) to when a minimum of 39 patients in Dose Cohort 4 complete Study Day 84; and providing guidance in Appendix C for the management of abnormal LFTs. Some of these changes occur in multiple places in the protocol including the Study Abstract, when applicable. Changes to the protocol are described in Appendix D.

references

American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Guidelines for Referral and Management of systemic lupus erythematosus in adults. Arthritis Rheum. 1999; 42:1785-96.

Baechler EC, Batliwalla FM, Karypis G, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci. 2003; 100(5):2610-5.

Baechler EC, Gregersen PK, Behrens TW. The emerging role of interferon in human systemic lupus erythematosus. Curr Opin Immunol. 2004; 16(6):801-7.

Bengtsson AA, Sturfelt G, Truedsson L, et al. Activation of type I interferon system in systemic lupus erythematosus correlates with disease activity but not with antiretroviral antibodies. Lupus. 2000; 9(9):664-71.

Bennett L, Palucka AK, Arce E, et al. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. J Exp Med. 2003; 197(6):711-23.

Blomberg S, Eloranta ML, Cederblad B, Nordlin K, Alm GV, Ronnblom L. Presence of cutaneous interferon-alpha producing cells in patients with systemic lupus erythematosus. Lupus. 2001; 10(7):484-90.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.

Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Parks CG, Gilkeson GS. Hormonal, environmental, and infectious risk factors for developing systemic lupus erythematosus. Arthritis Rheum. 1998 Oct;41(10):1714-24.

Crow M. Interferon-α: a new target for therapy in systemic lupus erythematosus? Arthritis Rheum. 2003; 48:2396-401.

Dall'era MC, Cardarelli PM, Preston BT, Witte A, Davis JC. Type I interferon correlates with clinical and serologic manifestations of systemic lupus erythematosus. Ann Rheum Dis. 2005; 64(12):1692-7.

Dobkin PL, Da Costa D, Dritsa M, et al. Quality of life in systemic lupus erythematosus patients during more and less active disease states: differential contributors to mental and physical health. Arthritis Care Res. 1999; 12(6):401-10.

Farkas L, Beiske K, Lund-Johansen F, Brandtzaeg P, Jahnsen FL. Plasmacytoid dendritic cells (natural interferon- alpha/beta-producing cells) accumulate in cutaneous lupus erythematosus lesions. Am J Pathol. 2001; 159(1):237-43.

Feng X, Wu H, Grossman JM, et al. Association of increased interferon-inducible gene expression with disease activity and lupus nephritis in patients with systemic lupus erythematosus. Arthritis Rheum. 2006; 54(9):2951-62.

Ho A, Magder LS, Barr SG, Petri M. Decreases in anti-double stranded DNA levels are associated with concurrent flares in patients with systemic lupus erythematosus. Arthritis Rheum. 2001; 44(10):2342-49.

Hochberg MC. The incidence of systemic lupus erythematosus in Baltimore, Maryland, 1970–1977. Arthritis Rheum. 1985; 28(1):80-6.

Holliday SL, Navarrete MG, Hermosillo-Romo D, et al. Validating a computerized neuropsychological test battery for mixed ethnic lupus patients. Lupus. 2003; 12: 697-703.

Hua J, Kirou K, Lee C, Crow MK. Functional assay of type I interferon in systemic lupus erythematosus plasma and association with anti-RNA binding protein autoantibodies. Arthritis Rheum. 2006; 54(6):1906-16.

Ioannou Y, Isenberg DA. Current evidence for the induction of autoimmune rheumatic manifestations by cytokine therapy. Arthritis Rheum. 2000; 43(7):1431-1442.

Kirou KA, Lee C, George S, et al. Coordinate overexpression of interferon-alpha-induced genes in systemic lupus erythematosus. Arthritis Rheum. 2004; 50(12):3958-67.

Kirou KA, Lee C, George S, Louca K, Peterson MG, Crow MK. Activation of the interferon-alpha pathway identifies a subgroup of systemic lupus erythematosus patients with distinct serologic features and active disease. Arthritis Rheum. 2005; 52(5):1491-503.

Kono DH, Baccala R, Theofilopoulos AN. Inhibition of lupus by genetic alteration of the interferon-alpha/beta receptor. Autoimmunity. 2003; 36(8):503-10.

Lahita RG. The role of sex hormones in systemic lupus erythematosus. Curr Opin Rheumatol. 1999; 11(5):352-6.

Lameire N, Adam A, Becker CR, et al; CIN Consensus Working Panel. Baseline renal function screening. Am J Cardiol. 2006; 98(6A):21K-26K.

Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum. 1998; 41(5):778-99.
Lupus Foundation of America. http://www.lupus.org. Accessed 9 February, 2007.

Niewold TB, Swedler WI. Systemic lupus erythematosus arising during interferon-alpha therapy for cryoglobulinemic vasculitis associated with hepatitis C. Clin Rheumatol. 2005; 24(2):178-81.

Okamoto H, Katsumata Y, Nishimura K, Kamatani N. Interferon-inducible protein 10/CXCL10 is increased in the cerebrospinal fluid of patients with central nervous system lupus. Arthritis Rheum. 2004; 50(11):3731-2.

Petri M. Long-term outcomes in lupus. Am J Managed Care. 2001; S480-S485.

Roebuck-Spencer TM, Yarboro C, Nowak M, et al. Use of computerized assessment to predict neuropsychological functioning and emotional distress in patients with systemic lupus erythematosus. Arthritis Rheum. 2006; 55(3): 434-41.

Santiago-Raber ML, Baccala R, Haraldsson KM, et al. Type-I interferon receptor deficiency reduces lupus-like disease in NZB mice. J Exp Med. 2003; 197(6):777-88.

Theofilopoulos AN, Baccala R, Beutler B, Kono DH. Type I Interferons (α/β) in immunity and autoimmunity. Immunol Rev. 2005; 204:9-26.

Uramoto KM, Michet CJ Jr, Thumboo J, Sunku J, O'Fallon WM, Gabriel SE. Trends in the incidence and mortality of systemic lupus erythematosus, 1950-1992. Arthritis Rheum. 1999; 42(1):46-50.

Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med. 1976; 60(2):221-5.

Von Feldt JM. Systemic lupus erythematosus: recognizing its various presentations. Postgrad Med. 1995; 97(4):79–94.

Wallace D. Advances in the management of systemic lupus erythematosus. Bull Rheum Dis. 2003; Vol 52, Number 11.

Ytterberg SR, Schnitzer TJ. Serum interferon levels in patients with systemic lupus erythematosus. Arthritis Rheum. 1982; 25(4):401-6.

APPENDIX A ACR Criteria for SLE Classification

Item	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds
Discoid rash	Erythematous, raised patches with adherent keratotic scaling and follicular plugging: atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Pleuritis or pericarditis	a. Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *OR* b. Pericarditis – documented by electrocardiogram or rub or evidence of pericardial effusion
Renal disorder	a. Persistent proteinuria >0.5 gm per day or >3+ if quantitation not performed *OR* b. Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	a. Seizures—in the absence of offending drugs or known metabolic derangement, e.g., uremia, ketoacidosis, or electrolyte imbalance *OR* b. Psychosis—in the absence of offending drugs or known metabolic derangement, e.g., uremia, ketoacidosis, or electrolyte imbalance
Hematologic disorder	a. Hemolytic anemia with reticulocytosis *OR* b. Leukopenia--<4,000/mm^3 on ≥2 occasions *OR* c. Lymphopenia--<1,500/mm^3 on ≥2 occasions *OR* d. Thrombocytopenia--<100,000/ mm^3 in the absence of offending drugs
Immunologic disorder	a. Anti-DNA: antibody to native DNA in abnormal titer *OR* b. Anti-Sm: presence of antibody to Sm nuclear antigen *OR* c. Positive finding of antiphospholipid antibodies based on: 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies; 2) a positive test result for lupus anticoagulant using a standard method; or 3) a false-positive test result for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test.
Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time in the absence of drug.

APPENDIX B Serial Photographic Documentation of SLE

Locations:

- ID card and color card w/mm scale (2 each)
- Global view of the entire target area w/mm scale to measure the size of the entire lesion (2 each)

Equipment:

- Camera: Canon PowerShot S3 IS Digital 6 Mega Pixel Camera
- MM Scale Attachment Arm
- 512MB SD Cards
- SD card reader
- Color Card/Patient ID Holder
- Target Area Identification Labels
- Standardized Photographic Background

Procedures:
In these clinical photographs, for the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (furniture, etc.) is to be eliminated from the photographic field from the entry visit through the final visit. The necessity of good end-of-study photos should be stressed to the patients to ensure their cooperation. Lighting, framing, exposure and reproduction ratios must be held constant. In the end, the pictures should read like a time-lapse movie.

1. The supplied equipment is to be used exclusively for this study. No modification, adjustments or repairs of the camera equipment is to be undertaken without the expressed instruction of [redacted]
2. The supplied standardized background is to be used. Do not use folded or wrinkled material.
3. Close-Up Magnification: A standardized reproduction ratio of 1:3 (35MM equivalent) for the close-up view of the target area (s) is utilized. The focusing of the camera lens at 1:3 is accomplished by placing the camera in "C" (Custom) mode and confirming that the mm scale is at the bottom of the rear LCD window. The attached mm scale at the base of the camera ensures accurate focal distance.
4. Global Magnification: A standardized reproduction ratio of 1:9 (35MM equivalent) for the global view of the target area (s) is utilized. The focusing of the lens at 1:9 is accomplished by disabling the macro mode and holding the camera so that the front of the lens is approximately 37" from the surface of the target area (s).
5. If there is any doubt in your mind as to the correctness of your photographic technique, please re-shoot immediately.

6. Each photographic session includes an exposure series of:
   a. Patient ID, which will include the following legible information in black indelible ink. (2 exposures)
      Protocol No.
      Date
      Center Number
      Visit Number
      Patient's Initials
      Patient's ID Number
      Photographer's Initials
      Color Card
   b. Close-up of each patient's target area (s) identified with a numbered label (2 exposures)
   c. Global view of each patient's target area (s) identified with a numbered label (2 exposures)

7. A secure, validated, compliant web server set up at [redacted] is used for secure transfer of study images by study sites. Images are transferred the day recorded. Remote access to all images by the Sponsor is also provided. Only approved individuals by Sponsor have access to the web site.

8. [redacted] is to provide each study site with the necessary hardware (card reader) and instructions, as well as technical support as needed.

9. All supplied photographic equipment and photographic originals remain the property of the sponsor. Any questions or issues regarding the photographic portion of this protocol are to be forwarded to the Project Manager at [redacted].

[redacted]

APPENDIX C Guidance for Abnormal Liver Function Tests Management

This guidance is based on the October 2007 Draft Guidance of Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation.

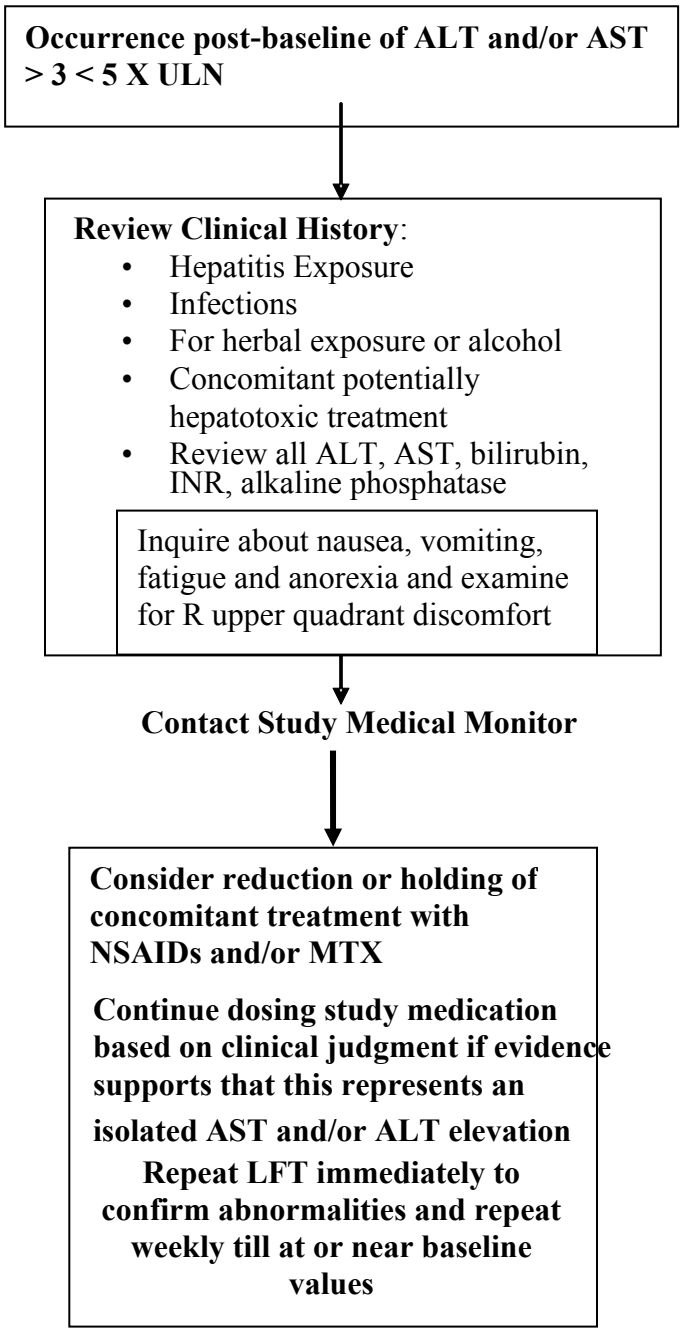
Section IV of the FDA document deals with the clinical evaluation of and monitoring of drug-induced liver injury, and this protocol-specific guidance has adopted the draft recommendations on detection of drug-induced liver disease, confirmation of abnormal ALT/AST with regard to retesting, follow-up observation, advice on appropriate history gathering and advice on the need for obtaining additional laboratory tests and consultations as needed. We have adopted a conservative approach to holding administration of study drug based on abnormal 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 study drug permanently. The 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-545 as well as input from the principle 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 study drug 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.

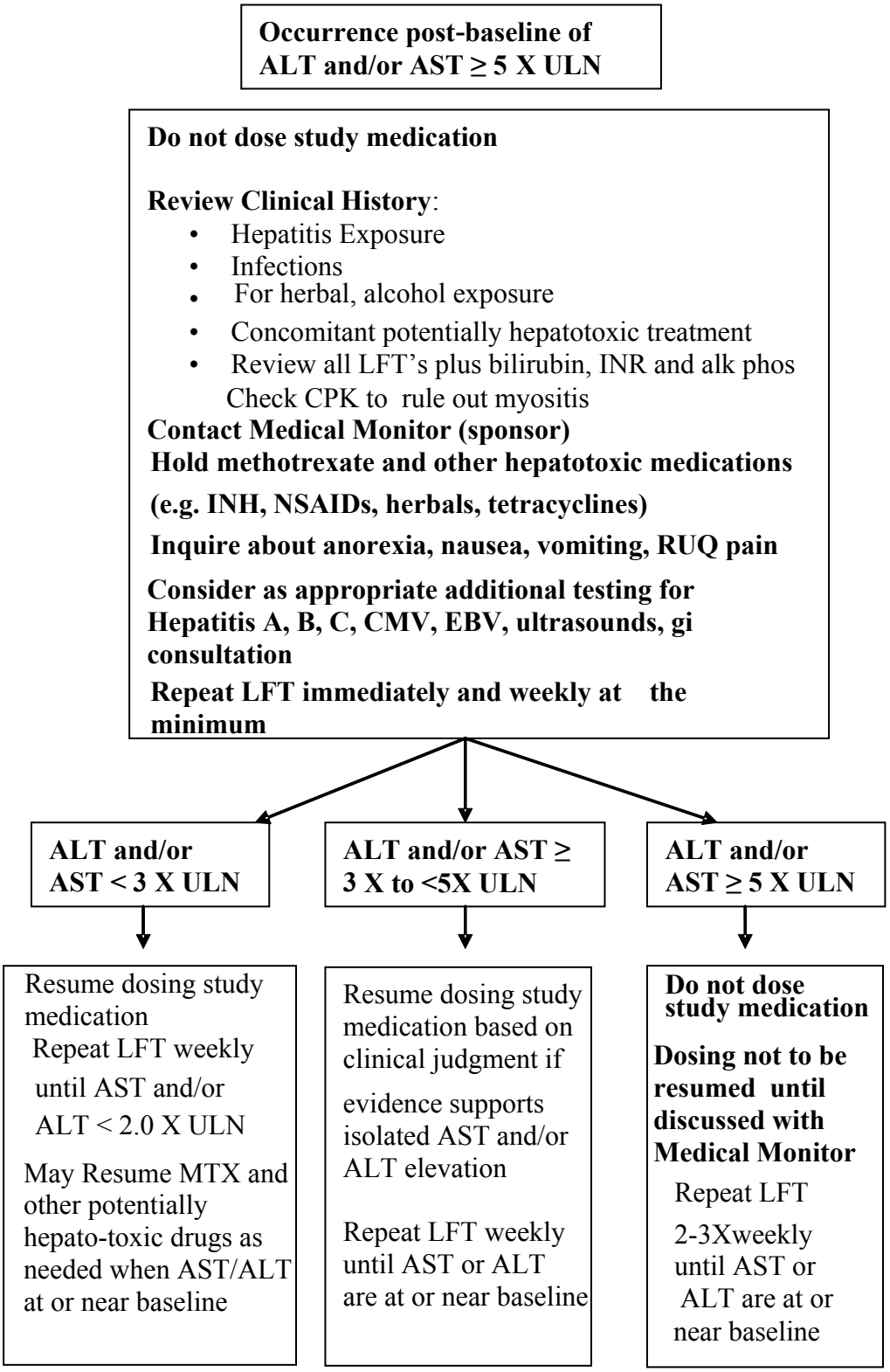
For the purpose of this document, LFTs will be AST, ALT, total bilirubin, and alkaline phosphatase.

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

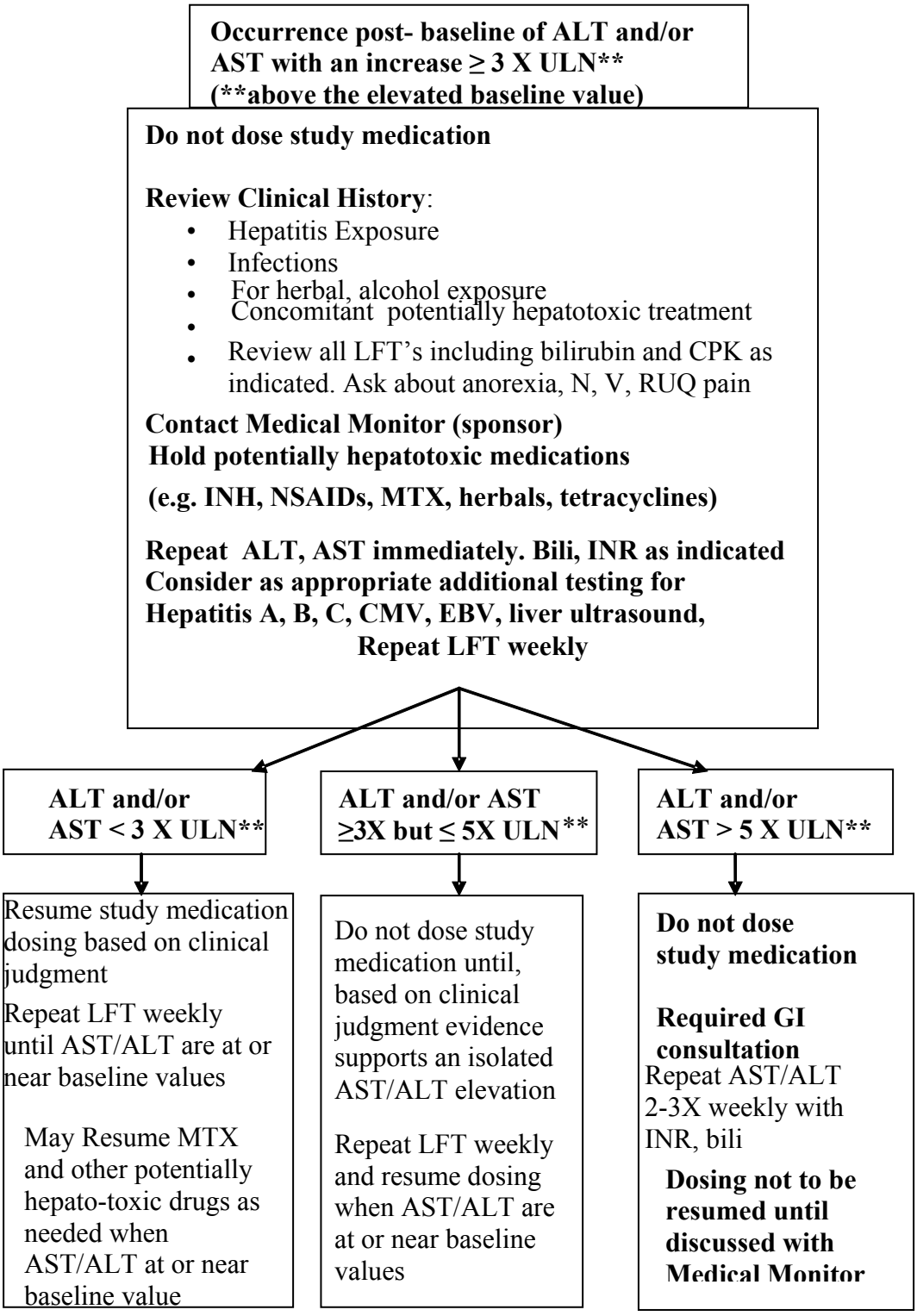
Copies of the document “Draft Guidance of Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation” can be located at http://www.fda.gov/cder/guidance/index/index.htm.

Guidance for abnormal Liver Function Tests during Study 152 or 179 that develop post-baseline in individuals with ALT or AST ≤2X ULN at baseline due to liver involvement by SLE in the opinion of the investigator.




Occurrence post-baseline of ALT and/or AST ≥ 5 X ULN
Do not dose study medication
Review Clinical History:
• Hepatitis Exposure
• Infections
• For herbal, alcohol exposure
• Concomitant potentially hepatotoxic treatment
• Review all LFT's plus bilirubin, INR and alk phos
Check CPK to rule out myositis
Contact Medical Monitor (sponsor)
Hold methotrexate and other hepatotoxic medications
(e.g. INH, NSAIDs, herbals, tetracyclines)
Inquire about anorexia, nausea, vomiting, RUQ pain
Consider as appropriate additional testing for Hepatitis A, B, C, CMV, EBV, ultrasounds, gi consultation
Repeat LFT immediately and weekly at the minimum
ALT and/or AST < 3 X ULN
ALT and/or AST ≥ 3 X to <5X ULN
ALT and/or AST ≥ 5 X ULN
Resume dosing study medication
Repeat LFT weekly until AST and/or ALT < 2.0 X ULN
May Resume MTX and other potentially hepato-toxic drugs as needed when AST/ALT at or near baseline
Resume dosing study medication based on clinical judgment if
evidence supports isolated AST and/or ALT elevation
Repeat LFT weekly until AST or ALT are at or near baseline
Do not dose study medication
Dosing not to be resumed until discussed with Medical Monitor
Repeat LFT
2-3Xweekly until AST or ALT are at or near baseline

Guidance for abnormal Liver Function Tests during Study 152 or 179 that develop post-baseline in individuals with ALT or AST > 2X ULN at baseline due to liver involvement by SLE in the opinion of the investigator



APPENDIX D Changes to the Protocol

Summary of Changes from Version 1.0 to Version 2.0 of the Study Protocol

Version 1.0 of the protocol (dated [redacted]) was amended to Version 2.0 (dated [redacted]). The major changes include reducing the starting dose of MEDI-545 from 1.0 to 0.3 mg/kg, reducing the highest dose of MEDI-545 from 30 to 20 mg/kg, and setting the infusion volume to 100 mL, and the infusion time to 60 minutes. Other changes include revising the dose-escalation criteria; updating the safety information on MEDI-545; changing the Medical Monitor; clarifying several inclusion and exclusion criteria; addition of international sites; addition of urine pregnancy testing prior to each dose of study drug; and clarification of text. The changes made to Version 1.0 of the protocol to create Version 2.0 are summarized below.

Some of these changes occur in multiple places in the protocol but are presented in the most relevant sections. These changes, if applicable, also apply to the Study Abstract. Text that has been added is shown bolded and underlined; text that has been deleted is shown bolded and strike-through.

1. Overall Changes
   - Study drug doses were changed and an additional cohort was added. The original doses were 1.0, 3.0, 10.0, or 30.0 mg/kg. The doses are now 0.3, 1.0, 3.0, 10.0, or 20.0 mg/kg
   - Infusion volume is 100 mL
   - Infusion time is over 60 minutes
   - Sample size increased to 192 for blinded phase of the study and 238 for open-label extension.
   - The HAQ was changed to the MHAQ
   - Tender and swollen joint count was changed to active joint count
   - BILAG and SELENA-SLEDAI assessments were added to screening
   - Chest x-ray was added to screening (if not performed within the previous 6 months)
   - Whole blood for safety biomarkers and autoantibody and complement levels was added to screening
   - A negative urine βHCG for women (unless surgically sterile or 2 years after menopause) is required on all study drug administration days
   - Serum for safety biomarkers was separated from the CBC with differential, platelets
   - Screening period was changed from 21 to 28 days

2. Title Page
   The Medical Monitor for the study has been changed as follows:

   [redacted]
   ~~**Senior**~~ Director, Clinical Development
   MedImmune, Inc.
   Phone: [redacted]
   Fax: [redacted]

3. Section 1.1

Corrected the following reference citation, (**Lupus Foundation of America** ~~**LFA**~~, 2007).

4. Section 1.4
The clinical experience with MEDI-545 was updated to reflect the status of current clinical trials.

Reason for Change: This was updated to provide current information on clinical experience with MEDI-545.

5. Section 1.5 (also referenced in Study Abstract under Rationale)
The study rationale was updated to include current data from clinical trials with MEDI-545**.**

Reason for Change: To provide the rationale for reducing the starting dose and the highest dose, increasing the infusion volume and time, and changing the dose-escalation criteria in the study.

6. Section 2.4.1 (Also referenced in Study Abstract under Design)

Changed to read:

Approximately 20 to 25 international sites ~~**(United States of America, Canada, India, and China)**~~ **(USA, Canada, India, China, Brazil, Argentina, and Chile~~**~~**, UK, Germany, France, Italy, Spain, and the Czech Republic)** will participate in this study.

Reason for Change: Additional international sites were added.

7. Section 2.4.1.1 (Also referenced in Study Abstract under Design)
Changed to read:
A total of ~~**128**~~ **192** evaluable patients are planned for the blinded phase of the study~~**, in which 4 escalating doses of MEDI-545 will be tested (1.0, 3.0, 10.0, or 30.0 mg/kg)**~~. **Five escalating doses of MEDI-545 (0.3, 1.0, 3.0, 10.0, or 20.0 mg/kg) or placebo will be tested using an infusion time of 60 minutes; a sixth dose cohort (10.0 mg/kg MEDI-545 or placebo) will be tested using an infusion time of 30 minutes, if a review of data from prior cohorts indicates that this shorter infusion time is safe. This excludes the 22 patients who were treated prior to 10/Oct/2007.**

Reason for change: The protocol is being amended reduce the starting dose, reduce the highest dose, and lengthen the infusion time and volume. An additional cohort was added to look at a shorter infusion time of 30 minutes.

Changed to read:

MEDI-545 or placebo will be administered once every 2 weeks as an IV infusion **(60 minutes for Cohorts 1-5 and 30 minutes for Cohort 6 if a review of data from prior cohorts indicates that this shorter infusion time is safe)** for 26 weeks, for a total of 14

doses. Study drug administration will start on Study Day 0 and continue through Study Day 182.

Reason for change: Data from Cohorts 1-5 will be examined and if possible, Cohort 6 will be enrolled with a shorter infusion time of 30 minutes.

Added: Patients who were treated with study drug prior to 10/Oct/2007 will continue to be followed for safety reasons according to the schedule of patient evaluations from Study Day 238 through Study Day 350 as described in Table 2.

Reason for Change: To gather additional safety information.

8. Section 2.4.1.2

Changed to read:
Patients randomized and treated with ~~**placebo**~~ **study drug** in the blinded phase of the study will have the option of entering the open-label extension after their treatment unblinding. **In addition, patients treated with study drug prior to 10/Oct/2007 will have the option of entering the open-label extension after completing the safety follow-up period (Study Days 238-350).** The dose of MEDI-545 chosen for the open-label extension will be determined based on findings in the blinded phase of the study; it will not exceed the highest dose determined to be safe and tolerable in the blinded phase of the study or ~~**30.0**~~ **20.0** mg/kg.

Reason for Change: Change the highest dose in the study, and increase the amount of safety date to be collected.

9. Section 3.1.1 (Also referenced in Study Abstract under Patient Population, Inclusion Criteria)

Changed to read:

5. Have at least one system with a score of A or two systems with a score of B on the BILAG index at screening, or have a SELENA- SLEDAI score ≥~~**8**~~ **6**;

Reason for Change: Broaden patient population by allowing greater numbers of appropriate patients with moderate disease.

10. Section 3.1.1 (Also referenced in Study Abstract under Patient Population, Inclusion Criteria)

Change to read:

6. Sexually active women, unless surgically sterile or at least ~~**1 year**~~ **2 years** post-menopausal, must use an effective method of avoiding pregnancy (including oral, **injectable,** transdermal, or implanted contraceptives, intrauterine device, ~~**female condom with spermicide,**~~ diaphragm with spermicide, cervical cap, abstinence, ~~**use of a condom with spermicide by the sexual partner or**~~ **and** sterile sexual partner) **in addition to the use of condoms (male or female condoms with spermicide) from screening through**

the end of the study. ~~**for 21 days prior to study drug administration, and must agree to continue using such precautions through Study Day 350.**~~ Cessation of birth control after this point should be discussed with a responsible physician. Sexually active men, unless surgically sterile, must likewise **practice two effective methods** ~~**use an effective method**~~ of birth control (condom with spermicide **or abstinence**) and must **use such precautions from Study Day 0 through the end of the study.** ~~**agree to continue using such precautions through Study Day 350**~~;

Reason for Change: Added more stringent criteria for preventing pregnancies in the study.

11. Section 3.1.2 (Also referenced in Study Abstract under Patient Population, Exclusion Criteria)

Changed the time requirement from 21 days to 28 days for Exclusion Criteria 8, 12, 13, and 21 to accommodate the change in the screening period from 21 to 28 days.

12. Section 3.1.2 (Also referenced in Study Abstract under Patient Population, Exclusion Criteria)

Changed to read:

Exclusion criterion #3: Weight ≥ 120 kg **for patients randomized to Dose Cohorts 1 through 5 or weight ≥ 100 kg for patients randomized to Dose Cohort 6)**;

Reason for Change:

Changed to read:

Exclusion criterion #5. Have received the following dosages of medications within 28 days before randomization/entry: hydroxychloroquine > 600 mg/day, mycophenolate mofetil > 3 g/day, methotrexate > 25 mg/week, leflunomide > 20 mg/day, azathioprine > 3 mg/kg/day, ~~**or any dose of dapsone,**~~ cyclophosphamide, cyclosporine, or thalidomide;

Reason for Change: There is no clinical reason why patients on dapsone would be at greater risk when taking study drug.

13. Section 3.1.2 (Also referenced in Study Abstract under Patient Population, Exclusion Criteria)

Changed to read:

13. Pregnancy (women, unless surgically sterile or at least 2 years post-menopausal, must have a negative serum pregnancy test within ~~**21**~~ **28** days before receiving the study drug and a negative urine pregnancy test on ~~**Study Day 0**~~ **days of study drug administration** before receiving the study drug);

Reason for Change: Clarification of text.

14. Section 3.1.2 (Also referenced in Study Abstract under Patient Population, Exclusion Criteria)

Changed to read:

18. History of active tuberculosis (TB) **infection** or positive TB skin test (defined as a reaction ≥ 10 mm in diameter) ~~**without a completed course of appropriate medical treatment**~~;
19. **history of latent tuberculous infection without completion of an appropriate course of treatment**;

Reason for Change: Clarification of text.

15. Section 3.2.1.1

Changed to read:

The randomization procedures are the following:

- Investigator or qualified designee confirms the patient meets all eligibility criteria and has signed an informed consent form;
- ~~**Investigator or qualified designee calls the IVRS on Study Day 0 and provides at a minimum the initials, date of birth, and body weight of the patient;**~~
- MedImmune calls the IVRS before Study Day 0 to ~~**and**~~ provide~~**s**~~ **the results of the** ~~**strength (low/undetectable or high) of the expression of mRNA for**~~ type I IFN~~-~~**mRNA gene expression for** ~~**inducible genes in**~~ the patient;
- **The IVRS notifies the investigator or qualified designee that the patient may be randomized into the study;**
- **The Investigator or qualified designee calls the IVRS on Study Day 0 and provides at a minimum the initials, date of birth, and body weight of the patient;**
- **The IVRS** randomly assigns a treatment (MEDI-545 or placebo) to the patient along with a PID and blinded study drug kit to be used for that patient; and
- A confirmatory fax or e-mail with this information is sent to the investigator or qualified designee.

Reason for Change: Clarification of text.

16. Section 3.2.3

Changed to: Patients who have received ~~**placebo**~~ **study drug** during the blinded phase of the study will be offered the option to receive MEDI-545 in an open-label extension after the unblinding of treatment in the blinded phase. **In addition, patients treated with study drug prior to 10/Oct/2007 will have the option of entering the open-label extension after completing the safety follow-up period (Study Days 238-350).** Their participation in the open-label extension is not a requirement for participation in the blinded phase of the study.

Reason for Change: Clarification of text.

17. Section 3.2.3

Rewritten to reflect blinding procedures.

Reason for Change: Clarification of text.

18. Section 3.3.2.1

Changed to: A total of ~~**128**~~ **192** evaluable patients are planned for the blinded phase of the study~~**, which consists of 4 escalating dose cohorts (1.0, 3.0, 10.0, or 30.0 mg/kg)**~~. **Up to 24 additional patients may be enrolled (4 patients in each of 6 cohorts), if those patients are in screening at the time 32 patients have been randomized in each cohort. Five escalating doses of MEDI-545 (0.3, 1.0, 3.0, 10.0, or 20.0 mg/kg) or placebo will be tested using an infusion time of 60 minutes; a sixth dose cohort (10.0 mg/kg MEDI-545 or placebo) will be tested using an infusion time of 30 minutes, if a review of data from prior cohorts indicates that this shorter infusion time is safe. This excludes the 22 patients who were treated prior to 10/Oct/2007.**
Reason for Change: Include patients who may be in screening when a cohort has filled. Other changes to clarify text and include protocol revisions to dose and infusion time.

19. Section 3.3.3

Changed to add:

- **Initially dilute study drug to 20 mL;**
- **Remove 20 mL from a 100 mL bag of 0.9% Sodium Chloride for Injection, USP and inject the 20 mL study drug solution into the bag;**
- **Infuse the study drug solution using an infusion pump over 60 minutes for Dose Cohorts 1-5 and over 30 minutes for Dose Cohort 6, if a review of data from prior cohorts indicates that this shorter infusion time is safe (Table 1).**

Table 1 Summary of Infusion Volume, Duration, and Rate

Dose Cohort	Dose (mg/kg)	Infusion Volume (mL)	Infusion Duration	Infusion Rate (mL/hr)	Maximum Infusion Rate (mg/min)[a]
1	0.3	100	60 minutes	100	0.6
2	1.0	100	60 minutes	100	2.0
3	3.0	100	60 minutes	100	6.0
4	10.0	100	60 minutes	100	20.0
5	20.0	100	60 minutes	100	40.0
6	10.0	100	30 minutes	200	16.6

a. Maximum infusion rate is based on the maximum allowable weight per cohort.

Reason for Change: Clarify drug dilution, volume, and infusion time.

20. Section 3.3.4 (Administration of Study Drug)

Changed to add:

The study drug should be dispensed by the pharmacist or qualified designee and administered **~~preferably as a slow IV push in a syringe~~** **as either a 60-minute (Dose Cohorts 1-5) or 30-minute (Dose Cohort 6) IV infusion using an infusion pump according to the instructions provided in the Clinical Trial Material Manual**. **Do not administer by intravenous push (IVP) or bolus injection.** **~~The drug can also be administered as an IV infusion as determined by the investigator, which should be prepared in 0.9% sodium chloride in a 50 mL or 100 mL infusion bag according to the instructions provided in the Clinical Trial Material Manual.~~**

~~Patients should not be premedicated, since the primary objective of this study is to evaluate the safety and tolerability of the study drug. However, if reactions to the IV push/infusion occur during or after study drug administration, they should be treated appropriately.~~

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) **~~should~~** will be monitored before**, every 15 minutes during infusion, at the end of the infusion, and every 30 minutes after completion of the infusion until stable.** **~~and after the study drug administration and every 30 minutes after study drug administration until stable for at least 2 hours or until the patient is stable, whichever is longer. If the drug is given through IV infusion, vital signs should be monitored every 15 minutes during infusion, at the end of infusion, and every 30 minutes after study drug administration for at least 2 hours after the end of infusion or until the patient is stable.~~**

If a mild infusion reaction occurs during or after study drug administration, the patient will remain at the study site for a minimum of 2 hours for observation and undergo the following procedures unless transfer to an emergency or hospital facility is deemed warranted:

- **Clinical evaluation and stabilization of patient according to standard medical practice;**
- **Repeat vital signs every 15 minutes until stable and then every 30 minutes thereafter until discharge;**
- **Collect whole blood for assessment of safety biomarkers as soon as possible after the event, at 60 minutes after the event, and at discharge; and**
- **Consider adding prophylactic treatment (ie, acetaminophen and diphenhydramine) prior to the next infusion of study drug.**

Reason for Change: Clarification of post-drug administration safety assessments.

21. Section 3.4 (Tables 1a/1b and Description of Visits), Section 2.4.2 (also referenced in Study Abstract under Patient Evaluations and Follow-Up)

The schedules of patient evaluations (Table 1a and Table 1b) and associated footnotes were revised as follows:

- Addition of chest x-ray at Screening
- Addition of ECG on Study Days 84 and 196
- Addition of urine βHCGs on all study drug infusion days
- Addition of BILAG/SLEDAI at Screening
- Addition of blood collection for assessment of anti-MEDI-545 antibodies on Study Days 28 and 56.
- Addition of physician global assessment at Screening and on Study Days 84, 140, 182, 210, 266, and 322
- Addition of renal function testing at Screening and on Study Days 84, 140, 182, 210, 266, and 322
- Addition of autoantibody/complement levels at Screening, and Days 84, 140, 182, 210, 266, and 322
- Blood samples for flow cytometry and biomarkers were separated on different lines of the table
- HAQ was changed to MHAQ
- Editorial clarification in table footnote "h" that vaginal swabs will be self-collected for HSV-1 and HSV-2, and HPV

Changed the time window for Study Day 182 to (± 2 days) and for Study Day 185 to (+1 Day) to avoid overlapping of evaluations.

Reason for Change: Clarification of text.

Added:

Unscheduled Visit
Evaluations may be performed during unscheduled visits as deemed warranted by the investigator.

Reason for Change: Investigators can bring patients in for unscheduled visits for evaluations as warranted.

22. Section 3.4 (Table 1a and Table 1b Footnotes and Description of Visits)
Made the following changes to the Table 1a and Table 1b footnotes:

a. Within ~~**21**~~ **28** days prior to Study Day 0.
d. Women, unless surgically sterile or at least 2 years post-menopausal, must have a negative serum pregnancy test within 21 days before randomization/entry, and a negative

urine pregnancy test on Study Day 0 **and all subsequent study drug infusion days** before receiving the study drug.

e. Vital signs include heart rate, blood pressure, respiratory rate and temperature. Blood pressure should be obtained with the patient in the position to be used for drug administration. Vital signs are obtained before, **every 15 minutes during infusion, at the end of the infusion, and every 30 minutes after completion of the infusion until stable.** ~~**and after study drug administration through IV push. If study drug is administered as an IV infusion, vital signs should be measured before the infusion, every 15 minutes during the infusion, and at the end of the infusion. After study drug administration, vital signs should be monitored every 30 minutes for at least 2 hours or until stable and before discharge.**~~

.h. Oropharyngeal swabs (performed by investigator or qualified designee) for HSV-1 and HSV-2; vaginal swabs (**self-collected,** female patients only) for HSV-1 and HSV-2, and HPV; and blood samples for EBV and cytomegalovirus tests.

J. Includes spot morning urine for protein/creatinine ratio and estimated glomerular filtration rate calculated based on the ~~**Modification of Diet in Renal Disease equation (Lameire, 2006)**~~ **Cockcroft-Gault equation (Cockcroft, 1976)**.

k. Includes ANA, anti-Ro, anti-La, anti-RNP, anti-Sm, IgG and IgM anti-cardiolipin antibodies, total hemolytic complement, **dsDNA,** C3, and C4 measurements.

p. **Chest x-ray taken within 6 months of screening is considered suitable for screening and need not be repeated.**

q. The following evaluations will be performed in patients who discontinue the study prematurely.

r. A blood sample will be collected immediately after completion of study drug administration.

s. ANAM will be performed only on English-speaking subjects at sites in North America.

Reason for Change: Clarification of text.

23. Section 3.5.1

Changed to read:

A urine pregnancy test will be performed on ~~**Study Day 0**~~ **all days of study drug administration** at the site using a licensed test.
Reason for Change: To ensure negative pregnancy tests prior to all study drug infusions.

24. Section 3.5.2
Changed to read:
Vaginal swabs ~~**(in women)**~~ **will be self collected** for HSV-1, HSV-2, and HPV testing.

Reason for Change: Clarified that vaginal swabs for HSV-1, HSV-2, and HPV testing will be self-collected.

25. Section 3.5.6

Added:

The period to be considered for disease activity assessments will cover the previous 28 days or, if less, through the period to the previous evaluation.

Reason for Change: Clarification of text.

26. Section 4.1.1

Added:

Protocol-related adverse events are adverse events occurring during a clinical trial that are not related to the study drug but are considered by the investigator or Medical Monitor to be related to the research conditions. For example, a protocol-related event may be an event occurring during a washout period or during a protocol required procedure.

Reason for Change: Added language to account for adverse events that occur prior to study drug administration.

27. Section 4.1.2 and 4.2.2

Changed to read:

The reporting period for AEs is the period from **the first administration of study drug randomization/entry** through Study Day 350 **for both the blinded and open-label phases of the study**. ~~**For patients who participate in the open-label extension, AEs will be reported during the blinded phase of the study as well as the open-label extension.**~~

Reason for change: Clarification of text.

28. Section 4.1.3

Changed to read:

Adverse events will be reported ~~**on the Adverse Event Case Report Form**~~ 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 study product, possible etiologies and whether the event meets criteria as a serious adverse event and therefore requires immediate notification of the sponsor. See Sections 4.3 and 4.4 regarding guidelines for assessment of severity and relationship, respectively, and Section 4.2.1 for the definition of serious adverse events. If the event has not resolved at the end of the study reporting period, it will be documented as ~~**still present on the case report form**~~. ~~**Information**~~

~~**recorded on the Adverse Event Case Report form must be substantiated in the source documents. If an adverse event evolves into a condition which becomes "serious," it will be reported on the Serious Adverse Event (SAE) Report form.**~~ **If the event has not resolved at the end of the study reporting period it will be documented as ongoing. If an AE evolves into a condition which becomes "serious" the investigator will additionally report to the Sponsor on the *SERIOUS ADVERSE EVENT (SAE) REPORT FORM*.**

Reason for Change: Clarification of text.

29. Section 4.2.3

Changed to read:
Within 24 hours of identifying an SAE, regardless of the presumed relationship to the study product, the investigator must complete the *SERIOUS ADVERSE EVENT (SAE) REPORT FORM* and Safety Fax Notification Cover Page, and fax to MedImmune Product Safety.

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

~~**1) Notify MedImmune Product Safety by telephone with the following information:**~~
- ~~**Protocol number, name and contact number of the Principal Investigator**~~
- ~~**Subject identification number, initials, and date of birth**~~
- ~~**SAE, event onset date, date of last study product administration and current status of subject**~~

~~**Note: Investigators should not wait to collect additional information to fully document the event before notifying MedImmune of an SAE.**~~

~~**AND**~~

~~**2) Fax the following documents to MedImmune Product Safety:**~~
- ~~**Safety Fax Notification Cover Page**~~
- ~~**Serious Adverse Event Report Form**~~
- ~~**Supplemental Serious Adverse Event Report Form**~~
- ~~**Medical History Case Report Form**~~
- ~~**SLE History Case Report Form**~~
- ~~**Concomitant Medication Case Report Form or a list of concomitant medications**~~
- ~~**Immunomodulatory Medications Case Report Form**~~
- ~~**Relevant laboratory/diagnostic test results and medical record progress notes**~~

Reason for Change: Clarification of text.

30. Section 4.2.5

Changed to read:

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

Reason for Change: Clarification of text.

31. Section 4.4

Added:

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

Reason for Change: Clarification of text.

32. Section 4.7

Added:

Patients who were treated with study drug prior to 10/Oct/2007 will continue to be followed for safety reasons according to the schedule of patient evaluations from Study Day 238 through Study Day 350 as described in Table 2. After completion of the Study Day 350 visit, patients treated prior to 10/Oct/2007 may enter the open-label phase of the study. After study unblinding, all patients randomized and treated in the blinded phase of the study will have the opportunity to participate in the open-label phase of the study.

Reason for change: Clarification of procedures.

33. Section 4.9

Changed to read:

Dose Cohort 1 (~~**1.0**~~ **0.3** mg/kg) will be started first. Dosing at each next higher dose cohort (Cohort 2 [~~**3.0**~~ **1.0** mg/kg], Cohort 3 [~~**10.0**~~ **3.0** mg/kg], Cohort 4 [~~**30.0**~~ **10.0** mg/kg], **Cohort 5 [20.0 mg/kg], and Cohort 6 (10.0 mg/kg]**) will commence after the Medical Monitor has reviewed all cumulative, blinded safety information, including the safety data through Study Day **42** ~~**84**~~ from the first **12** ~~**16**~~ patients in each preceding lower dose cohort and all cumulative safety data available in all cohorts, and has determined that the safety profile is acceptable.

~~**Available PK data from the study MI-CP126 indicated that MEDI-545 has a serum half-life of 15 to 18 days and a linear increase in serum concentrations with dose. As such, the serum MEDI-545 concentration at Study Day 42 is anticipated to be near steady state.**~~

Reason for Change: The protocol is being amended to modify the dose-escalation criteria in the study due to the occurrence of an SAE of Grade 3 allergic reaction in the first dose cohort (MEDI-545 [1.0 mg/kg] or placebo). The revised criteria require 16 patients to provide safety data for dose escalation through Study Day 84.

34. Section 4.10

Changed to read:

However, patients should **not** be premedicated **routinely, unless they have previously experienced an infusion reaction,** since the primary objective of this study is to evaluate the safety and tolerability of the study drug, including infusion reactions. If such reactions occur during or after study drug administration, they should be treated appropriately.

Reason for change: Clarification of text.

35. Section 5.3

Changed to read:

There will be ~~**two**~~ **three** patient populations analyzed in this study. The primary patient population will include **up to 216 new** ~~**all**~~ patients who receive study drug in the blinded phase of the study. The secondary patient population will include the patients who receive ~~**placebo**~~ **study drug (including patients who received study drug prior to 10/Oct/2007 and completed the safety follow-up period (Study Days 238-350)** in the blinded phase and later receive MEDI-545 in the open-label extension. **The tertiary patient population will include the 22 patients who received study drug prior to 10/Oct/2007 and completed the safety follow-up period (Study Days 238-350).**

Reason for change: Clarification of text.

36. Section 5.4

Changed to read:

A separate analysis will be performed **~~by combining data from~~** **for** the **~~primary~~** **secondary** patient population **~~during the blinded phase and data from the secondary patient population during the open-label extension. Additional analyses may be performed for the secondary patient population by comparing their data in the blinded phase of the study with that in the open-label extension.~~** **by summarizing their data from the open-label extension**. **For the tertiary patient population, safety data will be compared between the placebo and MEDI-545 1.0mg/kg group during the blinded-phase.**
Reason for Change: Clarification of text.

37. Section 5.5

Deleted:
~~A separate analysis will be performed by combining data from the primary patient population during the blinded phase and data from the secondary patient population during the open-label extension. Additional analyses may be performed for the secondary patient population by comparing their data in the blinded phase of the study with that in the open-label extension.~~

Reason for Change: Clarification of text.

38. Section 5.6

Deleted:
~~Longitudinal models may be used to analyze the data over time with comparisons among the dose cohorts and treatment groups. A separate analysis will be performed by combining data from the primary patient during the blinded phase and data from the secondary patient population during the open-label extension. Additional analyses may be performed for the secondary patient population by comparing their data in the blinded phase of the study with that in the open-label extension.~~

Reason for Change: Clarification of text.

39. Section 5.7

Changed to read:

Interim analyses of the type I IFN-inducible genes expression data will be performed after all patients in each dose cohort complete Study Day 28 evaluations.

Interim analyses **on the safety and efficacy endpoints** will be performed at the following time points:

- ~~**After all patients randomized and treated in the 3.0 mg/kg MEDI-545/Placebo dose cohort complete Study Day 84 evaluations;**~~
- After all patients randomized and treated in the **second** dose cohort complete Study Day 84 **of the blinded phase**;

Reason for Change: Clarification of text.

40. Section 10 (new section)

Added:

10.0 CHANGES IN THE PROTOCOL

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

Reason for Change: Required protocol text.

41. Section 11

Deleted the following non-referred to references:

~~**Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [Letter]. Arthritis Rheum. 1997; 40:1725.**~~

~~**Mirzayan MJ. Schmidt RE, Witte T. Prognostic parameters for flare in systemic lupus erythematosus. Rheumatology. 2000; 39:1316-19.**~~

~~**Tan E, Cohen A, Fries J, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982; 25(11):1271-7.**~~

Summary of Changes from Version 2.0 to Version 3.0 of the Study Protocol

Version 2.0 of the protocol (dated [redacted]) was amended to Version 3.0 (dated [redacted]). The major changes include updating preclinical and clinical information; identification of specific safety biomarkers to analyze infusion reactions; addition of infusion reactions as an immediately reported event; update of statistical methodology for exploratory endpoints; and clarification of text. The changes made to Version 2.0 of the protocol to create Version 3.0 are summarized below.

Some of these changes occur in multiple places in the protocol but are presented in the most relevant sections. These changes, if applicable, also apply to the Study Abstract. Text that has

been added is shown bolded and underlined; text that has been deleted is shown bolded and strike-through.

1. Title Page

Change in Medical Monitor as follows:

[redacted]
~~**Director**~~Vice President, Clinical Development
MedImmune, Inc.
Phone: [redacted]
Fax: [redacted]

2. Section 1.2

Changed to read:

MEDI-545 is a fully human monoclonal immunoglobulin (Ig) G1κ antibody that binds to and neutralizes a ~~**number**~~ majority of **the subtypes of human IFN-α subtype** ~~**molecules**~~. MEDI-545 may, therefore, have potential as a treatment for SLE.

~~**Fully human, IFN-α̃ specific monoclonal antibodies (Mab) were generated in mouse hybridoma using lymphoblastoid IFN. An $IgG_{4κ}$ antibody, 13H5, was selected based on functional assays as having the most desirable properties for a potential therapeutic agent. Subsequently, the lead antibody, 13H5, was cloned into Chinese Hamster Ovary cells as an IgG1 isotype and selected for further characterization and preclinical development. Subsequent antibody characterization, including mechanism of action studies and neutralization of SLE plasma bioactivity, was performed.**~~

MEDI-545 was generated by immunizing the Medarex transgenic HuMab-Mouse® with natural human IFN-α. The human anti-IFN-α monoclonal antibody-expressing hybridoma, 13H5, was derived by fusing murine Sp2/0-Ag14 myeloma cells with splenocytes from an immunized Medarex transgenic male mouse. The 13H5 hybridoma was subsequently cloned into Chinese Hamster Ovary cells as an IgG1 isotype selected for further characterization and preclinical development with an initial designation of MDX-1103, now referred to as MEDI-545.

Reason for Change: Clarification of text regarding derivation of MEDI-545.

3. Section 1.4

Changed to read:

MEDI-545 is currently being investigated in four clinical trials, including the current study. The first clinical trial is a Phase 1 study (MI-CP126) in patients with SLE. MI-CP126 is a randomized, double-blind, placebo-controlled, single-dose, dose-escalation study with an

open-label extension evaluating the safety and tolerability of single IV doses of MEDI-545 ranging from 0.3 to 30.0 mg/kg. A total of 67 patients were treated in the study, including 50 patients (17 in the placebo group and 33 in the MEDI-545 group) in the blinded phase and 17 patients in the open-label extension. Adverse event (AE) data are available on ~~all~~ **the** patients in the **blinded phase of the** study.

MEDI-545 was well tolerated in this study. In the blinded phase of the study, the majority of AEs in both the placebo and MEDI-545 dose groups were mild (Grade 1) in severity. **The most common AEs reported by >15% of patients in the MEDI-545 group were blood bicarbonate decreased, blood glucose decreased, and systemic lupus erythematous (9 patients each, 27.3%); hemoglobin decreased and protein urine present (6 patients each, 18.2%); and diarrhea and headache (5 patients each, 15.2%). The most common AEs reported by >15% of patients in the placebo group were systemic lupus erythematous (8 patients, 47.1%); hemoglobin decreased and protein urine present (6 patients each, 35.3%); blood glucose decreased (5 patients, 29.4%); and headache and pain in extremity (3 patients each, 17.6%). Severe (Grade 3) AEs occurred in 4 (23.5%) patients in the placebo group (diverticulitis, post-traumatic pain, systemic lupus erythematous, and sciatica in 1 patient each) and 2 (6.1%) patients in the MEDI-545 group (anemia and hemoglobin decreased); none of these events was judged by the investigator as being related to treatment. Life-threatening (Grade 4) events did not occur in the placebo group and occurred in 1 patient (blood potassium increased) in the MEDI-545 group. Three patients reported serious adverse events (SAEs), which included 1 patient (anemia) in the MEDI-545 group and 2 patients (diverticulitis and post-traumatic pain) in the placebo group; none of these SAEs were judged by the investigator as being related to treatment. MEDI-545 mean serum concentrations following IV administration exhibited a bi-phasic decline with a shallow initial distribution phase followed by a prolonged terminal elimination phase. MEDI-545 PK were linear and dose proportional, and mean half-life was about 15 to 24 days. No anti-MEDI-545 antibodies were detected following treatment. Results of exploratory analyses showed a dose-dependent neutralization of type I IFN gene signature by MEDI-545. In addition, results of clinical outcome measures suggested possible clinical activity by MEDI-545 in this patient population.** ~~**The most common AEs reported by >15% of patients in the MEDI-545 group were blood glucose decreased, hemoglobin decreased, and protein urine present (10 patients each, 30.3%), systemic lupus erythematosus (9 patients, 27.3%), blood bicarbonate increased (6 patients, 18.2%), and alanine aminotransferase increased, nasopharyngitis, and vessel puncture site hematoma (5 patients each, 15.2%). The most common AEs reported by >15% of patients in the placebo group were systemic lupus erythematosus (8 patients, 47.1%), headache (6 patients, 35.3%), blood glucose decreased, blood bicarbonate decreased, upper respiratory tract infection, and proteinuria (4 patients each, 23.5%), and lymphopenia, anemia, and nausea (3 patients each, 17.6%). Severe (Grade 3) AEs occurred in 2 (11.8%) patients in the placebo group (systemic lupus erythematosus and sciatica) and 4 (12.1%) in the MEDI-545 group (anemia, diverticulitis, post-traumatic pain, and hemoglobin decreased); none of these events was judged by the investigator as being related to MEDI-545. A life-threatening (Grade 4) event (blood potassium increased) occurred in the placebo group. Serious adverse events (SAEs) occurred in 3**~~

~~**patients in the MEDI-545 group and included anemia, diverticulitis, and post-traumatic pain; none of these events was judged by the investigator as being related to MEDI-545. In the open-label phase, the safety profile was similar to the MEDI-545 group in the blinded phase of the study. One (5.9%) patient had a severe (Grade 3) AE (lymphopenia), and no patient had an SAE. MEDI-545 mean serum concentrations following IV administration exhibited a bi-phasic decline with a shallow initial distribution phase followed by a prolonged terminal elimination phase. MEDI-545 PK were linear and dose proportional, and mean half-life was about 18 to 22 days. No anti-MEDI-545 antibodies were detected following treatment. Results of exploratory analyses showed a dose-dependent neutralization of type I IFN gene signature by MEDI-545. In addition, results of clinical outcome measures suggested possible clinical activity by MEDI-545 in this patient population.**~~

MI-CP145 is a Phase 1, multicenter, randomized, double-blind, placebo-controlled, dose-escalation study of single-dose IV MEDI-545 (0.3, 1.0, 3.0, 10.0, or 30.0 mg/kg) in 40 adult patients with chronic plaque psoriasis. As of 10/Oct/2007, 36 patients have been treated in this study with blinded AE data available on all patients. The majority of AEs were mild (Grade 1) in severity. The most common AE was nasopharyngitis. On 09/Oct/2007, the first patient in the 30.0 mg/kg dose cohort had an SAE of **anaphylactic reaction associated with Grade 4 hypotension**~~**Grade 4 hypotensive event**~~ during administration of study drug and was hospitalized for three days. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug. As a result of this event, the study was stopped pending further notice. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies, that tryptase levels 10 hours after the event were normal, that the drug product met quality standards, and that when this ~~**hypotensive**~~ event occurred, the patient was receiving drug at a relatively high rate of infusion, 0.96 mg/kg/minute. After thorough review, the Medical Monitor judged this event to be an infusion reaction.

The current study, MI-CP152, is a Phase 1b, multicenter, multinational, randomized, double-blind, placebo-controlled, dose-escalation study with an open-label extension to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (~~**1.0 to 30.0**~~ 0.3 to 20.0 mg/kg) in adult patients with SLE. In this study, MEDI-545 will be administered every 2 weeks for a total of 14 doses over 26 weeks. The planned starting dose of MEDI-545 (~~**1.0**~~ 0.3 mg/kg) in MI-CP152 is less than one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated IV administrations every 2 weeks for 27 weeks). The first 12 ~~**enrolled**~~ **randomized** patients in each dose cohort will provide safety data for dose escalation; the additional 20 patients planned for each dose cohort are intended to increase safety data and provide adequate numbers of patients for exploratory analyses of effect of MEDI-545 on the inhibition of type I IFN gene signature. A total of 22 patients had been treated in this study, with safety follow-up ongoing. On 28/Sep/2007, one patient experienced an SAE of **Grade 3 hypersensitivity reaction characterized by chills, rigors, swollen hands, hives, moderate hypotension and several bouts of diarrhea** ~~**Grade 3 reaction characterized by rash, pruritus, and mild hypotension,**~~ following the fifth dose of MEDI-545 (1.0 mg/kg), which resolved the same day. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug. The patient was discharged home several hours after the infusion. Further evaluation of the event indicated this patient had no anti-

MEDI-545 antibodies and that when this ~~**hypotensive**~~ event occurred, the patient was receiving drug at a relatively high rate of infusion, 1.~~)~~.0 mg/kg/minute. After thorough review, the Medical Monitor judged this event to be an infusion reaction. Study MI-CP152 was stopped on 10/Oct/2007 due to an SAE of **anaphylactic reaction associated with Grade 4 hypotension**~~**Grade 4 hypotensive event**~~ in MI-CP145.

Reason for Change: Update of clinical information.

4. Section 1.5 (also referenced in Study Abstract under Rationale)

Changed to read:

MEDI-545 is a fully human monoclonal IgG1κ antibody that binds to and neutralizes a number of type I IFN-α subtypes and therefore may be potentially effective as a treatment for SLE. In preclinical studies of MEDI-545 in cynomolgus monkeys, no treatment-related toxicological findings except transient, localized reactions at the injection sites were observed. This included a repeated-dose toxicity study in which MEDI-545 was administered **intravenously** every 2 weeks for 27 weeks (a total of 14 injections). No antibodies against MEDI-545 were detected in immunogenicity (IM) studies in cynomolgus monkeys.

MEDI-545 is currently being investigated in patients with SLE (MI-CP126), psoriasis (MI-CP145), and myositis (MI-CP151). The first clinical trial of MEDI-545, MI-CP126, is a randomized, double-blind, placebo-controlled, single-dose, dose-escalation study with an open-label extension evaluating the safety and tolerability of single IV administrations of MEDI-545 at doses ranging from 0.3 to 30 mg/kg. A total of 67 patients were treated in the study, including 50 patients (17 in the placebo group and 33 in the MEDI-545 group) in the blinded phase and 17 patients in the open-label extension. Adverse event data are available on patients in the blinded phase of the study. MEDI-545 was well tolerated in this study. The majority of AEs were mild (Grade 1) in severity. The most common AEs in the MEDI-545 group were blood bicarbonate decreased, blood glucose decreased, systemic lupus erythematosus, hemoglobin decreased, protein urine present, diarrhea, and headache. Severe (Grade 3) AEs occurred in 2 patients in the MEDI-545 group (anemia and hemoglobin decreased); none of these events was judged by the investigator as being related to MEDI-545. One patient in the MEDI-545 group had an SAE of anemia, which was judged by the investigator as not being related to MEDI-545. There were no reports of MEDI-545-related SAEs, deaths, interruptions of study drug administration, medically important events, anaphylaxis, or immune complex disease in this study. MEDI-545 PK were linear and dose proportional, and mean half-life was about 15 to 24 days. No anti-MEDI-545 antibodies were detected following treatment. Results of exploratory analyses showed a dose-dependent neutralization of type I IFN gene signature by MEDI-545. In addition, results of clinical outcome measures suggested possible clinical activity by MEDI-545 in this patient population.

MI-CP145 is a Phase 1, multicenter, randomized, double-blind, placebo-controlled, dose-escalation study of single-dose IV MEDI-545 (0.3, 1.0, 3.0, 10.0, or 30.0 mg/kg) in 40 adult patients with chronic plaque psoriasis. As of 10/Oct/2007, 36 patients have been treated in this study with blinded AE data available on all patients. The majority of AEs were mild (Grade 1) in severity. The most common AE was nasopharyngitis. On 09/Oct/2007, the first patient in the 30.0 mg/kg dose cohort had an SAE of **anaphylactic reaction associated with Grade 4 hypotension**~~Grade 4 hypotensive event~~ during administration of study drug and was hospitalized for three days. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug. As a result of this event, the study was stopped pending further notice. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies, that tryptase levels 10 hours after the event were normal, that the drug product met quality standards, and that when this ~~hypotensive~~ event occurred, the patient was receiving drug at a relatively high rate of infusion, 0.96 mg/kg/minute. After thorough review, the Medical Monitor judged this event to be an infusion reaction.

The current study, MI-CP152, is a Phase 1b, multicenter, multinational, randomized, double-blind, placebo-controlled, dose-escalation study with an open-label extension to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (~~1.0 to 30.0~~ 0.3 to 20.0 mg/kg) in adult patients with SLE. In this study, MEDI-545 will be administered every 2 weeks for a total of 14 doses over 26 weeks. The planned starting dose of MEDI-545 (~~1.0~~ **0.3** mg/kg) in MI-CP152 is less than one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated administrations every 2 weeks for 27 weeks). The first 12 ~~enrolled~~ **randomized** patients in each dose cohort will provide safety data for dose escalation; the additional 20 patients planned for each dose cohort are intended to increase safety data and provide adequate numbers of patients for exploratory analyses of effect of MEDI-545 on the inhibition of type I IFN gene signature. A total of 22 patients had been treated in this study, with safety follow-up ongoing. On 28/Sep/2007, one patient experienced an SAE of **Grade 3 hypersensitivity reaction characterized by chills, rigors, swollen hands, hives, moderate hypotension and several bouts of diarrhea**~~Grade 3 reaction characterized by rash, pruritus, and mild hypotension,~~ following the fifth dose of MEDI-545 (1.0 mg/kg), which resolved the same day. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug. The patient was discharged home several hours after the infusion. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies and that when this ~~hypotensive~~ event occurred, the patient was receiving drug at a relatively high rate of infusion, 1.0~~)~~ mg/kg/minute. After thorough review, the Medical Monitor judged this event to be an infusion reaction. Study MI-CP152 was stopped on 10/Oct/2007 due to an SAE of **anaphylactic reaction with Grade 4 hypotension** ~~Grade 4 hypotensive event~~ in MI-CP145.

Reason for Change: Update of clinical information.

5. Section 2.4.1 (also referenced in Study Abstract under Design)

Changed to read:
Approximately ~~20 to 25~~**30 to 40** international sites (USA, Canada, South America, ~~Europe,~~ Asia, and Australia) will participate in this study.

Reason for Change: Clarification of text.

6. Section 2.4.1.2 (also referenced in Study Abstract under Design), Section 3.2.2, and Section 3.3.2.2

   Changed to read:

   Patients randomized and treated with study drug **(MEDI-545 or placebo)** in the blinded phase of the study will have the option of entering the open-label extension after their treatment unblinding.

   Reason for Change: Clarification of text.

7. Section 2.4.2 (also referenced in Study Abstract under Patient Evaluation and Follow-up)
   Added assessment of AEs/SAEs at screening.

   Deleted vital signs and collection of whole blood for safety biomarkers at screening.

   Changed to read:

   Safety assessments include AE and SAE evaluation, physical examination, vital signs, serum chemistry panel, CBC with differential and platelets, serum for safety biomarkers **in any patient with an infusion reaction (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies)**, urinalysis, and viral cultures and titers via oropharyngeal swabs for herpes simplex virus (HSV)-1 and HSV-2; vaginal swabs (women) for HSV-1, HSV-2, and human papillomavirus (HPV); and blood tests for Epstein Barr virus (EBV) and cytomegalovirus.

   Reason for Change: Identification of specific safety biomarkers to analyze infusion reactions in the study.

8. Section 3.1.1 (also referenced in Study Abstract under Patient Population)

   Changed to read:

   2. Written informed consent obtained from the patient **or the patient's legal representative**;
   4. Have positive ANA test at ≥ 1:80 serum dilution in the past or at screening **(prior positive ANA test must be documented via a lab report)**;
   6. Sexually active women, unless surgically sterile **(including tubal ligation)** or at least 2 years post-menopausal, must use an effective method of avoiding pregnancy (including oral, injectable, transdermal, or implanted contraceptives, intrauterine device, diaphragm with spermicide, cervical cap, abstinence, sterile sexual partner) in addition to the use of condoms (male or female condoms with spermicide) from screening through the end of the study. Cessation of birth control after this point should be discussed with a responsible physician. Sexually active men, unless surgically sterile, must likewise

practice two effective methods of birth control (condom with spermicide or abstinence) and must use such precautions from Study Day 0 through the end of the study.

Reason for Change: Clarification of text.

9. Section 3.1.2 (also referenced in Study Abstract under Patient Population)

Changed to read:

2. History of allergy or reaction to any component of the ~~**MEDI-545**~~**study drug** formulation;

Reason for Change: Clarification of text.

10. Section 3.3

Changed to read:

~~**Study drug will be prepared for IV infusion as follows:**~~

~~**1. Initially dilute study drug to 20 mL of 0.9% Sodium Chloride;**~~
~~**2. Remove 20 mL from a 100 mL bag of 0.9% Sodium Chloride for Injection, USP and inject the 20 mL study drug solution into the bag;**~~
~~**3. Infuse the study drug solution using an infusion pump over 60 minutes for Dose Cohorts 1-5 and over 30 minutes for Dose Cohort 6, if a review of data from prior cohorts indicates that this shorter infusion time is safe (Table 1).**~~

Study drug (MEDI-545 or placebo) for administration must be prepared using aseptic technique. Study drug will be diluted in 0.9% normal saline and the volume **of the dilution** will be standardized to 100 mL. The study drug will be administered using an infusion pump over 30 to 60 minutes as described in Table 1.

Reason for Change: Clarification of text.

11. Section 3.3.4

Changed to read:

The study drug should be dispensed by the pharmacist or qualified designee and administered as either a 60-minute (Dose Cohorts 1-5) or 30-minute (Dose Cohort 6) IV infusion using an infusion pump ~~**according to the instructions provided in the Clinical Trial Material Manual**~~. Do not administer by intravenous push (IVP) or bolus injection.

Infusion reactions have occurred with administration of MEDI-545. Infusion reactions are defined as AEs related to the infusion of the study drug itself that usually occur within first 24 hours after infusion and are characterized by a complex of symptoms that may include flu-like illness, fever, chills/rigors, nausea, urticaria, headache,

bronchospasm, angioedema, hypotension, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. If **an** ~~**mild**~~ infusion reaction occurs during or after study drug administration, the patient will remain at the study site for a minimum of 2 hours for observation and undergo the following procedures unless transfer to an emergency or hospital facility is deemed warranted:

- Clinical evaluation and stabilization of patient according to standard medical practice;
- Repeat vital signs every 15 minutes until stable and then every 30 minutes thereafter until discharge;
- Collect whole blood for assessment of safety biomarkers **(including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies)** as soon as possible after the event, at 60 minutes after the event, and at discharge; and
- Consider adding prophylactic treatment (ie, acetaminophen and diphenhydramine) prior to the next infusion of study drug.

Reason for Change: Provide definition of infusion reaction and clarify the type of biomarkers to analyze if an infusion reaction occurs.

12. Section 3.4

Added AE/SAE assessment at screening.

Clarified in Table 2 that skin photographs and DNA analysis are optional tests that require an additional signed informed consent.

Added SF-36 at Study Discontinuation Visit for clarification of text.

Corrected the sequence of footnotes to Table 2.

Clarified that skin lesion photography will only be performed at North American sites.

Clarified Table 2 footnote "r" as follows for clarification of text:

r. A blood sample **for assessment of safety biomarkers (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies)** will be collected **in all patients prior to study drug administration on Study Day 0 and in any patient with an infusion reaction** ~~**immediately after completion of study drug administration.**~~**as soon as possible after the event, 60 minutes after the event, and at discharge (see Section 3.3.4 for details)**.

Changed Table 2 footnote "q" to read as follows for clarification of text:

q. The following evaluations will be performed in patients who discontinue the study prematurely **(prior to Study Day 182). If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.**

Added Table 2 footnote "t" as follows for clarification of text:

t. The following evaluations will be performed in patients who discontinue the study prematurely (after Study Day 182). If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

Added collection of blood for assessment of safety biomarkers on Study Day 0 prior to administration of study drug.

Added detailed description of Study Discontinuation Visit for clarification of text.

13. Section 3.5.3

Added that PK and IM laboratory evaluations on samples from sites other than those in North America will be performed at other locations for clarification of text.

14. Section 3.5.4 (New Section)

Added:

3.5.4 Safety Biomarkers

Whole blood will be collected for assessment of safety biomarkers on Study Day 0 as described in Table 2. In addition, if an infusion reaction occurs during or after study drug administration, whole blood for assessment of safety biomarkers will be collected as soon as possible after the event, at 60 minutes after the event, and at discharge (see Section 3.3.4 for details). Safety biomarkers include serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies.

Reason for Change: To provide more information for the collection of blood samples for analysis of safety biomarkers.

15. Section 3.6

Changed to read:
If a patient discontinues his or her participation in the study**, the patient will return to the study site and complete the Study Discontinuation Visit evaluations if the patient discontinues prior to Study Day 182 or complete the Study Day 350 evaluations if the patient discontinues after Study Day 182.** ~~**, the assessments designated for Study Day 350 will be performed at the discontinuation visit.**~~ If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

Reason for Change: Clarification of text.

16. Sections 4.1.2 and 4.2.2

Expanded the reporting period for collection of adverse events and serious adverse events to the time when the informed consent is signed to capture protocol-related adverse events.

17. Section 4.5

Added infusion reaction to events that require immediate reporting due to the observance of infusion reactions in patients treated with MEDI-545.

18. Section 5.4 (also referenced in Study Abstract under Assessment of Endpoints)

Changed to read:

The safety and tolerability of MEDI-545 will be assessed primarily by summarizing **treatment-emergent** AEs**/SAEs** and by assessing changes in viral cultures and titers, including oropharyngeal swabs for herpes simplex virus HSV-1 and HSV-2; vaginal swabs for HSV-1, HSV-2, and HPV; and peripheral blood test (using polymerase chain reaction tests) for EBV and cytomegalovirus. The occurrence of **treatment-emergent** AEs and SAEs will be summarized from the first administration of study drug through Study Day 350 for both the blinded and open-label phases of the study. **Treatment-emergent** AEs and SAEs that occur after the first administration of study drug will be summarized by system organ class and preferred terms, by severity, and by relationship to study drug. For the primary population, **treatment-emergent** AEs and SAEs will be summarized for placebo, each of the MEDI-545 dose cohorts, and for all MEDI-545 doses combined from patients during the blinded phase.

Reason for Change: Clarification of text.

19. Section 5.6

Changed to read:

The major clinical measures of disease activity will include BILAG score, SELENA-SLEDAI score, flares, and physician global assessment. The SELENA-SLEDAI and BILAG scores are valid, reliable, and sensitive clinical assessments of lupus disease activity. The SELENA-SLEDAI assessment consists of 24 lupus-related items while the BILAG index consists of 86 items with respect to 8 organ systems (general, mucocutaneous, neurological, musculoskeletal, cardiorespiratory, vasculitis, renal, and hematologic). The global scores for SLEDAI and BILAG will be computed. These scores, as well as their changes from baseline, will be summarized descriptively at each visit by treatment group. **Disease activities will also be measured by the proportion of patients achieving a SLEDAI or BILAG global score of 0 during the study period. The physician global assessment (PGA) represents physician's overall assessment on disease severity of 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The proportion of patients with a PGA score >0.5 at baseline and reaching PGA<=0.5 subsequently will be computed. Mild to moderate lupus flares and severe flares are defined as increases in the SLEDAI score of ≥ 3 to <12 points or ≥ 12 points, respectively, from the previous visit. Another measurement of flare by the SELENA-SLEDAI SLE criteria is worsening of SELENA-SLEDAI score of more than 3 points from baseline. According to the BILAG index, a lupus flare can also be defined as a new A or B score in at least one system following a C, D, or E score. The**

incidence of lupus flares and time to the first flare will be summarized by treatment group descriptively. In order to summarize disease activity over time, the adjusted mean SLEDAI will be developed by computing the area under the curve of SLEDAI global score over time divided by time interval. The adjusted mean SLEDAI will be summarized at each visit by treatment group. A responder index, which is a composite of elements in the SLEDAI, BILAG, and physician global assessment, will be defined to evaluate subject's response during the study. Specifically, subjects who show at least 4 points reduction from baseline in SLEDAI global score without worsening in BILAG (no new A organ system score and no new B organ system score) or physician global assessment (<0.3 points increase from baseline) will be classified as responders. The response rate will be compared between treatment groups and over time. ~~**The maximum disease activity indicated by either maximum SLEDAI or BILAG score during the entire study period will be compared between the placebo and the MEDI-545 dose cohorts. Changes in organ system scores as measured by BILAG at post-baseline visits will also be analyzed. As part of the SLEDAI scale, the physician global assessment represents physician's overall assessment on disease severity of 0 (none), 1 (mild), 2 (moderate), or 3 (severe). Lupus flares and severe flares are defined as increases in the SLEDAI score of ≥ 3 or ≥ 12 points, respectively, from the previous visit. A flare of active lupus can also be defined as a new A or B score in at least one system while a moderate disease flare be defined as a new B score following a C, D, or E score according to the BILAG index. The incidence of lupus flares and time to the first flare will be summarized by treatment group descriptively. A responder index, which composes of elements in SLEDAI, BILAG, and physician global assessment, will be defined to evaluate subject's response during the study. Specifically, subjects who show at least 4 points reduction from baseline in SLEDAI global score without worsening in BILAG (no new A organ system score and no more than 1 new B organ system score) or physician global assessment (<0.3 points increase from baseline) will be classified as responders. The response rate will be compared between treatment groups and over time.**~~ In addition, the frequency and total dose of burst corticosteroids, changes from baseline in immunosuppressive treatment, complete clinical response, renal function, autoantibodies and complements in blood will be descriptively analyzed.

Reason for Change: Update of statistical methodology for exploratory endpoints.

Added SF-36 to list of patient-reported indicators for clarification of text.

20. Section 6

Changed to read:

Data recorded on source documents will be transcribed onto a validated data collection method provided by MedImmune or designee. Collected data will be reviewed by the sponsor or designee, with a copy retained by the investigator. ~~**Data recorded on source documents will be transcribed onto case report forms provided by MedImmune or designee. Completed original case report forms will be retrieved by the sponsor or**~~

~~**designee. A copy of each completed case report form will be retained by the investigator.**~~

Reason for Change: Clarification of text.

21. Section 10
Moved description of specific changes made to the protocol to Appendix D.

22. Appendix D

Added Appendix D to capture specific changes made to the protocol.

Summary of Changes from Version 3.0 to Version 4.0 of the Study Protocol

Version 3.0 of the protocol (dated [redacted]) was amended to Version 4.0 (dated [redacted]). The major changes include changing the medical monitor's name from [redacted] to [redacted], updating preclinical and clinical information; reducing the highest dose of MEDI-545 from 20.0 to 10.0 mg/kg; reducing the number of evaluable patients from 192 to 160; reducing the number of dose cohorts from six to five; indicating that CRPS will no longer be blinded to the studies, although they will continue to be part of the project team; changing the timing of the interim analysis; including a classification of infusion reactions table; and clarification of routine laboratory procedures. Other revisions were made to the inclusion and exclusion criteria; the statistical considerations section; and clarification of text. The changes made to Version 3.0 of the protocol to create Version 4.0 are summarized below.

Some of these changes occur in multiple places in the protocol but are presented in the most relevant sections. These changes, if applicable, also apply to the Study Abstract. The text that has been added is shown bolded and underlined; text that has been deleted is shown bolded and strike-through. Changes that are similar in nature throughout the text may be listed only once.

1. Cover page

Changed to read:

Medical Monitor: [redacted]
~~Vice President~~ **Senior Director**, Clinical Development
MedImmune
Phone: [redacted]
Fax: [redacted]

Reason for change: Change in Medical Monitor.

2. Section 1.3

   The preclinical experience with MEDI-545 was updated to reflect the results of the SC studies.

   Reason for change: The results were not available prior to this version of the protocol.

3. Section 1.4

   The clinical experience with MEDI-545 was updated to reflect the status of current clinical trials.

   Reason for Change: This was updated to provide current information on clinical experience with MEDI-545.

4. Section 1.5

   Changed to read:

   MEDI-545 is a fully human ~~mab~~ i**mmunoglobulin IgG1κ antibody** that binds to and neutralizes a ~~number of type I IFN-α subtypes~~ **majority** of **the** subtypes **of human IFN-α**. MEDI-545 is currently being investigated in SLE and psoriasis. To date, compelling evidence exists to support a role for IFN-α in the pathogenesis of autoimmune diseases such as SLE, psoriasis, and IIM and the studies performed to date strongly suggest that the neutralization of IFN-α by MEDI-545 is safe and effective. Because patients with IIM have a similar magnitude of the expression of type I IFN inducible genes in whole blood as those with SLE, and an initial study of MEDI-545 in SLE shows evidence of clinical activity, MEDI-545 may be effective in other autoimmune diseases such as IIM.

   MEDI-545 is being investigated in patients with SLE (MI-CP126, MI-CP152 [this study], MI-CP179), psoriasis (MI-CP145), and myositis (MI-CP151). Studies MI-CP126 and MI-CP145 evaluated the safety and tolerability of single IV administration of MEDI-545, and studies MI-CP151 and MI-CP152 are evaluating the safety and tolerability of multiple IV administration of MEDI-545. Study MI-CP179 is evaluating the safety and tolerability of multiple SC dose schedules of MEDI-545 and/or placebo. Two SAEs have occurred with MEDI-545 that were judged to be related to IV infusion of MEDI-545 at relatively rapid rates. Otherwise, MEDI-545 has had an acceptable safety profile.

   Dose-dependent inhibition of type I IFN gene signature in whole blood and skin has been observed, and evidence suggesting clinical activity of MEDI-545 was observed in MI-CP126.

   The current study, MI-CP152, is a Phase 1b, multicenter, multinational, randomized, double-blind, placebo-controlled, dose-escalation study with an open-label extension to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3 to ~~2~~**1**0.0 mg/kg) in adult

patients with SLE. In this study, MEDI-545 will be administered every 2 weeks for a total of 14 doses over 26 weeks **in the blinded phase. (This regimen will be repeated should the subject decide to enter the open-label extension.).** The planned starting dose of MEDI-545 (0.3 mg/kg) in MI-CP152 is less than one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated administrations every 2 weeks for 2**6**~~7~~ weeks). The first 12 randomized patients in each dose cohort will provide safety data for dose escalation; the additional 20 patients planned for each dose cohort are intended to increase safety data and provide adequate numbers of patients for exploratory analyses of effect of MEDI-545 on the inhibition of type I IFN gene signature. **In 22 patients treated prior to 10/Oct/2007, the majority of AEs were mild (Grade 1) to moderate (Grade 2) in severity. The most common AEs were blood bicarbonate decreased (5 subjects, 22.7%), blood potassium decreased (4 subjects, 18.2%), urinary tract infection (3 subjects, 13.6%), and nausea (3 subjects, 13.6%).** ~~A total of 22 patients had been treated in this study, with safety follow-up ongoing.~~ On 28/Sep/2007, 1 patient experienced an SAE of Grade 3 hypersensitivity reaction characterized by chills, rigors, swollen hands, hives, moderate hypotension and several bouts of diarrhea following the fifth dose of MEDI-545 (1.0 mg/kg), which resolved the same day. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies and that when this event occurred, the patient was receiving drug at a relatively high rate of infusion, **> 0 .75** mg/kg/minute. After thorough review, the Medical Monitor judged this event to be an infusion reaction. **This study** was stopped on 10/Oct/2007 due to an SAE of anaphylactic reaction associated with Grade 4 hypotension in MI-CP145 **and restarted in January 2008. In addition to the 22 patients dosed prior to 10/Oct/2007, a total of 32 new patients have been dosed in this study as of 13/Aug/2008 and dose escalation to 1.0 mg/kg has been approved**.

A review of the safety data from both MI-CP145 and MI-CP152 concluded the aforementioned SAEs were most likely due to MEDI-545 administered at a high rate of infusion (**> 0.75** mg/kg/min). As a result of this determination, the **MI-CP152** protocol **was** amended to reduce the starting dose of MEDI-545 from 1.0 to 0.3 mg/kg, reduce the highest dose of MEDI-545 from 30**.0** to **10.0** mg/kg, and set the infusion volume and time to 100 mL and **at least** 60 minutes **for Dose Cohorts 1 through 4 (0.3 to ~~2~~10 mg/kg MEDI-545 or placebo) and for at least 30 minutes for Dose Cohort 5 (10 mg/kg MEDI-545 or placebo), if a review of data from Dose Cohorts 1 through4 indicates that this shorter infusion time is likely to be safe. In addition, the MICP151 protocol was also amended to reduce the starting dose of MEDI-545 from 1.0 to 0.3 mg/kg, reduce the highest dose of MEDI-545 from 30 mg/kg to 10 mg/kg, and set the infusion volume and time to 100 mL and at least 60 minutes.**

A third study of MEDI-545 in patients with SLE (MI-CP179) is evaluating the safety and tolerability of multiple SC dose schedules of MEDI-545 and/or placebo. In this study, a total of 80 patients will be randomized in a 1:1:2:2:2 ratio to receive 1 of 5 treatment arms of MEDI-545 or placebo as follows: (1) SC MEDI-545 100 mg once; SC Placebo × 12 doses on other weeks; (2) SC MEDI-545 100 mg every 4 weeks × 4 doses; SC Placebo × 9 doses on other weeks; (3) SC MEDI-545 100 mg every 2 weeks × 7 doses; SC Placebo × 6 doses on other weeks; (4) SC MEDI-545 100 mg every week × 13

doses; and (5) SC Placebo every week × 13 doses. Two patients have been dosed in this study as of 13/Aug/2008.

Reason for Change: The description of MEDI-545 was clarified; the number of patients, the number of dose cohorts, and doses were updated. The description of a new study of Medi-545 (MI-CP179) needed to be included in this section.

5. Section 2.4.1.1

Changed to read:

A total of ~~192~~ **160** evaluable patients are planned for the blinded phase of the study. ~~Five~~ **Four** escalating doses of MEDI-545 (0.3, 1.0, 3.0, or ~~2~~**1**0.0 mg/kg) or placebo will be tested using an infusion time of **at least** 60 minutes; a ~~sixth~~ **fifth** dose cohort (10.0 mg/kg MEDI-545 or placebo) will be tested using an infusion time of 30 minutes, if a review of data from prior cohorts indicates that this shorter infusion time is likely to be safe. This excludes the 22 patients who were treated prior to 10/Oct/2007. Within each dose cohort, 32 patients will be randomized in a 3:1 ratio, using central randomization (without regard to site) and stratified by the level of type I IFN-inducible gene signature (low/undetectable versus high), to receive either MEDI-545 or placebo (ie, 24 patients will receive MEDI-545 and 8 patients will receive placebo).

Reason for Change: The number of patients and the number of dose cohorts were updated; the highest dose of MEDI-545 was changed from 20.0 mg/kg to 10.0 mg/kg.

6. Section 2.4.1.1

Revised the study schema.

Reason for Change: The study schema was updated to reflect the changes in the number of patients, the number of dose cohorts, and the new maximum dose allowed in this study.

7. Section 2.4.1.2

Changed to read:

Patients randomized and treated with study drug (MEDI-545 or placebo) in the blinded phase of the study will have the option of entering the open-label extension ~~after their treatment unblinding~~. **following the completion of the last follow-up visit and unblinding of each dose cohort.. However, their participation in the open-label extension is not a requirement for participation in the blinded phase of the study. Likewise, since the 22 patients treated with study drug prior to 10/Oct/2007 have already completed the safety follow-up period (Study Days 238-350), they will have the option to participate in the open-label extension after the unblinding of their treatment and approval of dose escalation to the 3.0 mg/kg cohort.**

If patients opt to re-consent their participation in the open-label extension, they will restart the study procedures from screening, followed by treatment and follow-up periods. Patients will receive MEDI-545 every 2 weeks as an IV infusion for 26 weeks, for a total of 14 doses. Patients will be treated at the dose that was specified for their cohort if they achieved a response (defined as having mild or inactive disease with a SLEDAI < 3 or no BILAG A and no more than 1 BILAG B score) at the end of treatment (Study Day 196). Patients will be treated at the next higher dose if they do not achieve a response at the end of treatment provided the dose does not exceed 10.0 mg/kg. Follow-up for the open-label extension will continue for an additional 12 weeks. Up to 202 patients are planned for the open-label extension, which includes 22 patients who were treated prior to 10/Oct/2007 ~~The dose of MEDI-545 chosen for the open-label extension will be determined based on findings in the blinded phase of the study; it will not exceed the highest dose determined to be safe and tolerable in the blinded phase of the study or 20.0 mg/kg.~~

Reason for Change: Enrollment into the open-label phase will be done per dose cohort as soon as their treatment is unblinded. The dose for each patient in the open-label phase will be based on their response to treatment during the blinded phase of the study.

8. Section 2.4.2

Changed to read:

Clinical disease activity is assessed using the following indicators: ~~occurrence and total dose~~ **requirement of rescue oral, IV or intramuscular corticosteroids or other potential disease modifying therapies** ~~of burst corticosteroids~~ to treat SLE during the treatment period, changes from baseline in SLE treatment during the follow-up period, BILAG scores, SELENA-SLEDAI score, flares, active joint count, physician global assessment, photographs of skin lesions (optional, if present), and renal function. In addition, autoantibodies and complement levels in blood will be measured.

Reason for Change: All potential disease modifying therapies, not just corticosteroids will be monitored during the study to determine if a patient is a responder to treatment alone or with the aid of other therapies.

9. Section 3.1.2

Changed to read:

~~3. Weight ≥ 120 kg for patients randomized to Dose Cohorts 1 through 5 or weight ≥ 100 kg for patients randomized to Dose Cohort 6);~~

6. Have received leflunomide > 20 mg/day in the 6 months prior to Study Day 0.

19. ~~18~~. History of latent TB infection **or newly positive TB skin test (reaction defined as ≥ 10 mm in diameter if not on systemic immunosuppressive medication or ≥ 5 mm if on systemic immunosuppressive medication)** without completion of an appropriate course of treatment **or ongoing prophylactic therapy**;

22. At screening blood tests (within 28 days before randomization/entry), any of the following:
    - AST > 2 × upper limit of the normal range (ULN)**, unless caused by SLE**,
    - ALT > 2 × ULN **unless caused by SLE**,

Reason for Change: Clarification of exclusion of patients with a history of active tuberculosis infection; removal of body weight limit; exclusion of patients receiving leflunomide >20 mg/day.

10. Section 3.2.3

Changed to read:

The study has a double-blind phase and an open-label extension. **All MedImmune and contract personnel associated with this study with the exception of MedImmune Clinical Research and Pharmacy Services (CRPS)**,~~During the blinded phase of the study, all protocol-associated MedImmune personnel or designees~~, **including the medical monitor, project management, statistician, site monitors, and data management, will be blinded to the treatment randomization until the study is completed and the database is closed.** ~~including the medical monitor, project manager, drug supply management, statistician and site monitors, will be blinded to treatment assignments.~~ In addition, the patient and the clinical site staff including the investigators, study nurses, coordinators, and the Clinical Trial Material Manager (CTMM) will also be blinded.

A limited number of MedImmune personnel independent of the project team, who will perform and interpret assays such as gene expression signature analyses or PK/PD analyses, ~~A limited number of MedImmune personnel, independent of the project team will perform and interpret assays such as gene expression signature analyses on blood samples,~~ will be unblinded during the conduct of the study. Unblinded MedImmune personnel involved in all interim assessments will not be associated with the clinical conduct of the study and will not reveal the treatment assignment of individual patients to any clinical personnel involved in the study. Only changes to the clinical development plan that affect individuals involved in the clinical conduct of the study will be communicated, ie, the actual results of the interim analyses will not be communicated. In addition, once the last patient of each dose cohort has completed Study Day 28 of the double-blind phase and the gene expression analyses are completed, an interim analysis of the gene expression data may be reviewed by senior management for the purpose of making clinical development decisions. Additional interim assessments of safety and clinical activity will be made when the ~~seond~~ third dose cohort completes Study Day 84 of the double-blind phase, when ~~last dose cohort~~ **Dose Cohort 4 completes** Study Day 84 of the double-blind phase, and when the last dose cohort completes Study Day 196 of the double-blind phase. These interim assessments are also for the purpose of making clinical development decisions.

Reason for Change: Clarification of who is blinded to the study.

11. Section 3.2.3

Changed to read:

The study has a double-blind phase and an open-label extension. All MedImmune and contract personnel associated with this study with the exception of MedImmune Clinical Research and Pharmacy Services (CRPS),~~During the blinded phase of the study, all protocol-associated MedImmune personnel or designees,~~ **including the medical monitor, project management, statistician, site monitors, and data management, will be blinded to the treatment randomization until the study is completed and the database is closed**.~~statistician and site monitors, will be blinded to treatment assignments.~~ In addition, the patient and the clinical site staff including the investigators, study nurses, coordinators, and the Clinical Trial Material Manager (CTMM) will also be blinded.

Reason for Change: CRPS became unblinded to the study for the better management of study drug supply.

12. Section 3.3.1

Changed to read:

PLACEBO:	**Placebo is supplied as a sterile liquid containing a 0.75 mL solution in a 3 mL single-use vial. The solution contains 25 mM histidine, 8% trehalose, and 0.02% polysorbate 80, and has a pH of 6.0.** ~~Placebo to match MEDI-545 is formulated in single-dose vials as a sterile liquid containing 20 mM citric acid, 100 mM sodium chloride, 1.5% Mannitol, 50 µM DTPA, 0.0 2% plant-derived polysorbate 80 (Tween™ 80), pH 6.0. It is supplied in 3 mL USP Type I borosilicate 20-mm clear glass vials containing 0.75 mL of liquid.~~

Reason for Change: Earlier versions of the protocol contained an incorrect description of the placebo. The placebo formulation has not changed and is accurately described here.

13. Section 3.3.2.2

Changed to read:

Patients randomized and treated with study drug (MEDI-545 or placebo) in the blinded phase of the study will have the option of entering the open-label extension **following the completion of the last follow-up visit and unblinding of each dose cohort. However, their participation in the open-label extension is not a requirement for participation in the blinded phase of the study. Likewise, since the 22 patients treated with study drug prior to 10/Oct/2007 have already completed the safety follow-up period (Study Days 238-350), they will have the option to participate in the open-label extension after the**

unblinding of their treatment **and approval of dose escalation to 3.0 mg/kg cohort.** ~~after their treatment unblinding. In addition, patients treated with study drug prior to 10/Oct/2007 will have the option of entering the open-label extension after completing the safety follow-up period (Study Days 238-350).~~

If patients opt to re-consent their participation in the open-label extension, they will restart the study procedures from screening, followed by treatment and follow-up periods. Patients will receive MEDI-545 every 2 weeks as an IV infusion for 26 weeks, for a total of 14 doses. Patients will be treated at the dose that was specified for their cohort if they achieved a response (defined as having mild or inactive disease with a SLEDAI < 3 or no BILAG A and no more than 1 BILAG B score) at the end of treatment (Study Day 196). Patients will be treated at the next higher dose if they do not achieve a response at the end of treatment provided the dose does not exceed 10.0 mg/kg. Follow-up for the open-label extension will continue for an additional 12 weeks. Up to 202 patients are planned for the open-label extension, which includes 22 patients who were treated prior to 10/Oct/2007 ~~as an IV infusion for 26 weeks, for a total of 14 doses.~~ Follow-up will continue for an additional **12** weeks. Up to **202** patients are planned for the open-label extension. ~~The dose of MEDI-545 given in the open-label extension will be determined from the blinded phase of the study; it will not exceed the highest dose determined to be safe and tolerable in the blinded phase of the study or 10.0 mg/kg.~~

Reason for Change: Clarification of study procedures during the open-label extension.

14. Section 3.3.3

Changed to read:

During the blinded phase, study drug in blinded kits will be sent to the study sites before randomization. The dose of study drug for IV administration will be prepared by the CTMM using aseptic techniques. **During the open-label extension, MEDI-545 will be sent out as open label to the study sites before treatment assignment.** Detailed instructions on study drug preparation can be found in the Clinical Trial Material Manual provided to the study sites.

Reason for Change: Clarification of study drug shipment procedures.

15. Section 3.3.4

Changed to read:

The study drug should be dispensed by the pharmacist or qualified designee and administered as **an infusion over at least**~~either a~~ 60~~-~~ minute**s** (Dose Cohorts 1 **through 4** ~~5~~) or **over at least** 30-minute**s** (Dose Cohort **5** ~~6~~) ~~IV infusion~~ using an infusion pump. Do not administer by intravenous push (IVP) or bolus injection.

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be monitored before **infusion**, **approximately** every 15 minutes during infusion, at the end of the infusion, and **approximately** every 30 minutes after completion of the infusion until stable. **If an anaphylactoid-like infusion reaction or anaphylactic reaction occurs, vital signs will be taken more frequently, as warranted by the severity of the reaction. Blood pressure and heart rate will also be taken prior to discharge from the site on visits in which study drug is administered.**

Infusion reactions have ~~occurred~~**been reported** with **the** administration of **intravenous gammaglobulin (IVIG) and nearly all approved monoclonal antibodies. Infusion reactions have occurred with the investigational drug** MEDI-545. **For purposes of this protocol, i**nfusion reactions are defined as **anaphylactoid-like** AEs related to the infusion of the study drug itself that usually occur within first 24 hours after infusion, **especially within minutes to a few hours, and will be distinguished from true anaphylactic reactions by absence of measurable antibodies against the study drug. Infusion reactions are characterized by a complex of signs and symptoms that include** ~~and are characterized by a complex of symptoms that may include~~ flu-like illness, fever, chills/rigors, nausea, urticaria, headache, bronchospasm, angioedema, hypotension, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. **For purposes of this protocol, a classification of infusion reactions is given in Table 2, with suggested treatment options. Final treatment is at the discretion of the investigator and should reflect local standard of care.**

Table 2 Classification and Suggested Treatments for Infusion Reactions

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

Table 2 Classification and Suggested Treatments for Infusion Reactions

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

Table 2 Classification and Suggested Treatments for Infusion Reactions		
Severity of Symptoms	Treatment	Study Drug
Severe (Grade 3) or Above plus fever with rigors, hypo- or hypertension with > 40 point change in systolic BP, wheezing, angioedema, or stridor Life threatening (Grade 4) Defined as a reaction that is life threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion	• Stop study drug infusion immediately • Evaluate patient, including close monitoring of vital signs • Maintain airway, oxygen if available • Treat patient immediately, for example with − Normal saline (~500-1000 mL/hour IV) − Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local standard of care, example, epinephrine 1:1000, 0.5-1.0 mL administered SC for mild cases and IM for more severe cases − IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20-40 mg − Diphenhydramine 50 mg IV − Acetaminophen 500-650 mg • Call emergency medical transport for transport to hospital if − Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine − Any Grade 3 reaction at the discretion of the investigator − Grade 4	• Do not resume infusion • Discontinue further study drug administration

If a ~~medically significant~~ **Grade 1 or higher** infusion reaction occurs during or after study drug administration, the patient will remain at the study site for a minimum of 2 hours for observation **after resolution of symptoms** and undergo the following procedures unless transferred to an emergency or hospital facility is deemed warranted for a more severe reaction:

- Clinical evaluation**, treatment,** and stabilization of patient according to standard medical practice**, with suggested approaches outlined above;**
- **Close monitoring of** ~~Repeat~~ vital signs **for example every 5 to 10 minutes for Grade 1 or Grade 2 infusion reactions and every 2 to 5 minutes for Grade 3 or Grade 4 infusion**

reactions until stable~~every 15 minutes until stable and then every 30 minutes thereafter until discharge~~;

- Collect whole blood for assessment of safety biomarkers (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies) **for Grade 1 or higher infusion reactions** as soon as possible after the event, at 60 minutes after the event, and at discharge;

Reason for Change: To provide detailed information regarding anaphylactic infusion reactions and to suggest treatment procedures to the investigators, if any occur.

Changed to read:

Study drug must be administered within 8 hours after preparation. If the dose is not administered within 8 hours, a new dose must be prepared using a new vial as the study drug product contains no bacteriostatic agents. ~~If study drug is not administered within 1 hour after preparation, it should be stored at 2° to 8° C and used within 24 hours of preparation. In the event that the prepared study drug remains at room temperature, it should be given within 8 hours. If these conditions are not met, contact the Sponsor for further instructions~~

Reason for Change: Clarification of use and storage of study drug.

16. Section 3.3.5

Changed to read:

All concomitant medications used by the patient from randomization/entry through Study Day 350 **for the blinded phase and Study Day 266 for the open-label phase** will be recorded on the case report form. Patients may not receive the following concomitant medications from randomization through Study Day 350 **during the blinded phase and from screening to Study Day 266 during the open-label phase**:

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

The dosage of concomitant analgesics for SLE symptoms may be adjusted as needed throughout the study. The dosages of concomitant **NSAIDs,** antimalarials, mycophenolate, methotrexate, leflunomide, ~~and~~ **or** azathioprine must remain constant from 28 days before Study Day 0 through Study Day 196, **unless disease activity is not controlled by burst and taper corticosteroids, as outlined below. If doses of concomitant NSAIDs, antimalarials, mycophenolate, methotrexate, leflunomide, or azathioprine must to be adjusted to control disease activity, this should be discussed with the Medical Monitor first**. Dosage of oral corticosteroids should remain unchanged from 14 days before Study Day 0 through Study Day 196, but may be adjusted after Study Day 196 through Study Day 350 **during the blinded phase** (follow-up period) **and Study Day 266 during the open-label phase**, except burst-and taper treatment as described below.

Reason for Change: Clarification of the recording and type time of concomitant medication.

17. Section 3.4

Changed to read:

~~A~~ Schedules of screening, ~~and on-study visit~~ **treatment period, and follow-up** procedures **for the blinded phase of the study is are** presented in Table 3 **(screening and treatment periods)** and in Table 4 **(follow-up period**), followed by a detailed description of each visit. Schedules of screening, treatment, and follow-up procedures for the open-label extension are presented in Table 5 (screening and treatment periods) and Table 6 (follow-up period), followed by a detailed description of each visit.

~~The open-label extension will restart the study procedures from screening, followed by the treatment and follow-up periods. Eligible patients will receive IV MEDI-545 in an open-labeled manner on Study Day 0 of the open-label extension and once every 2 weeks thereafter for 26 weeks, for a total of 14 doses. These patients will be followed through Study Day 350~~

Reason for Change: Clarification of study procedures.

18. Table 5 and Table 6

Created Table 5 and Table 6 to separate the open-label study procedures from those of the blinded phase. In addition, created a detailed list of the study procedures for the open-label extension.

Reason for Change: Clarification of study procedures during the open-label extension.

19. Section 3.5

Changed to read:

~~Routine laboratory tests during screening and during the study will be performed by a central licensed clinical laboratory. A urine pregnancy test will be performed on all days of study drug administration at the site using a licensed test. New clinically significant abnormal laboratory results, which in the opinion of the investigator are related to safety, should be repeated as soon as possible (preferably within 24 – 48 hours).~~**Routine laboratory tests during screening and during the study will be performed in a licensed central clinical laboratory. A laboratory manual will be provided specifying specific procedures for collection, processing, storage, and shipping of samples. Medically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24-48 hours). Routine laboratory assessments include the following:**

1. **CBC with differential, platelets**

2. **Serum chemistry to include Na, K, Cl, bicarbonate, BUN, creatinine, AST, ALT, total bilirubin, alkaline phosphatase, and random glucose**
3. **Urinalysis to include urine dipstick tests and microscopy for red blood cells and white blood cells**

3.5.1.1 Pregnancy Tests

The following tests will be used to monitor pregnancy in women of child-bearing potential:

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

3.5.1.2 Other Laboratory Tests

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

1. **Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody and HIV-1 antibody (screening only)**
2. **Renal function includes spot morning urine for protein/creatinine ration and estimated glomerular filtration rate calculated based on the Cockcroft-Gault equation (Cockcroft, 1976)**
3. **Autoantibody levels include ANA, anti-Ro, anti-RNP, anti-LA, anti-Sm, IgG, and IgM anti-cardiolipin antibodies**
4. **Complement levels include total hemolytic complement, dsDNA, C3, and C4 measurements**

Reason for Change: Clarification of laboratory procedures.

20. Section 3.5.8.1

Changed to read:

DNA Analysis

To investigate characteristics associated with patients' clinical response and safety, one blood sample (8.5 mL) will be collected on Study Day 0 (Blinded Phase) and frozen at –80°C for DNA sample preparation. The sample will be frozen and stored until used in exploratory analyses. The specific tests include analyses for DNA single nucleotide polymorphisms (SNPs) and microsatellite or short tandem repeats to further evaluate particular genes involved in the signaling pathway relevant to type I interferons.

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

All specimen and patient identifiers must be removed from the DNA blood samples such that under no circumstances can the DNA blood samples be linked back to a specific patient. In most cases, this will require that DNA blood samples have current labeling removed and the tubes relabeled. Special labeling capable of adhering to frozen tubes must be used. If it is not possible to remove the original labeling, then it must be determined whether the DNA blood samples can go through a freeze thaw and be re-aliquoted in order to maintain confidentiality. All re-labeled DNA blood samples must be cross referenced to the original demographics in a secure database to ensure that only appropriate laboratory personnel have access to these data. A special release must be obtained prior to use of specified DNA blood samples.

Reason for Change: Protocol was missing the DNA analysis section.

21. Section 3.6

Changed to read:

Patients will be considered to have completed the study if they were followed up through the Study Day 350 visit of the blinded phase.

If a patient discontinues his or her participation **during the blinded phase and prior to Study Day 182,** ~~in the study~~, the patient will return to the study site and complete the Study Discontinuation Visit evaluations. If the patient discontinues **after** Study Day 182, the **patient will return to the study site and complete** ~~or complete~~ the Study Day 350 evaluations. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

If a patient discontinues his or her participation during the open-label extension and prior to Study Day 182, the patient will return to the study site and complete the Study Discontinuation Visit evaluations. If the patient discontinues after Study Day 182, the patient will return to the study site and complete the Study Day 266 evaluations. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

Patients will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the patient's status at Study Day 350 **of the blinded phase or Study Day 266 of the open-label phase.** Investigators or qualified designees should document attempts to re-establish contact

with missing patients throughout the study period. If contact with a missing patient is re-established, follow-up should resume according to the protocol.

Reason for Change: Clarification of study procedures.

22. Section 4.5

Changed to read:

1. Any withdrawal of consent during the study
2. Pregnancy or intent to become pregnant*
3. **Hypersensitivity (anaphylactic) reaction to the study drug, Grade 1 or higher**~~All severe (Grade 3 or higher, according to the NCI CTCAE, V3.0) AEs that occur during or after administration of the study drug through Study Day 350~~
4. **Infusion reaction, Grade 1 or higher**
5. **Severe viral infection, Grade 3 or higher**
6. ~~AEs that are considered to be infusion reactions (defined as AEs related to the infusion of the study drug itself that usually occur within first 24 hours after infusion and are characterized by a complex of symptoms that may include flu-like illness, fever, chills/rigors, nausea, urticaria, headache, bronchospasm, angioedema, hypotension, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock)~~
7. Any other event that, in the opinion of the investigator, contraindicated further dosing of study subject.

Reason for Change: Clarification of immediate reporting events.

23. Section 4.7

Changed to read:

An individual patient will not receive any further study drug dosing if any of the following occur in the patient in question:

1. Withdrawal of consent;
2. Pregnancy;
3. Any life-threatening clinical event related to the study drug;
4. ~~Pregnancy;~~
5. **Severe hypersensitivity** (anaphylaxis) **reaction to the study drug, Grade 3 or higher;**
6. **Infusion reactions, Grade 3 or higher as defined in Table 2;**
7. ~~Any life-threatening clinical event related to the study drug;~~
8. **Serious clinical infections with a virus of the herpes family (including disseminated herpes infection, herpes encephalitis, or ophthalmic herpes infection) or with CMV or EBV; or**
9. **Any event which, in the opinion of the investigator or the Medical Monitor, contraindicates further dosing such as illnesses or complications.** Anaphylactic reaction to study drug in any patient;

~~10. Disseminated herpes infection, herpes encephalitis, or ophthalmic herpes infection in any patient; or~~
~~11. Event which, in the opinion of the investigator or the Medical Monitor, contraindicates further dosing such as illnesses or complications.~~

Reason for Change: Clarification of the interruption or discontinuation of study dosing in individual patients

24. Section 5.2

Changed to read:

For the blinded phase of the study, 1~~92~~**60** patients (~~6~~5 cohorts of 32 patients each) will be randomized into the study. This excludes the 22 patients who were treated prior to 10/Oct/2007. Within each cohort, 24 patients will receive MEDI-545 and 8 patients will receive placebo. In addition, a dose cohort may be expanded by up to 4 additional patients if eligible patients are already in screening at the time 32 patients have been randomized into the dose cohort. An unspecified number of patients may be enrolled in the study for replacement of nonevaluable patients as described in Section 2.4.1.1. No formal calculation was performed to determine sample size because safety is the primary outcome and this will be assessed with descriptive analyses.

For the open-label extension, up to 2~~38~~**02** patients from the blinded phase of the study will be entered into the study **(including the 22 patients who received study drug prior to 10/Oct/2007 and have completed the safety follow-up period [Study Days 238-350]) will be given the option to enter into the study.**

There will be three patient populations analyzed in this study. The primary patient population will include up to ~~216~~**180** new patients who receive study drug in the blinded phase of the study. The secondary patient population will include the patients who receive study drug (including patients who received study drug prior to 10/Oct/2007 and completed the safety follow-up period (Study Days 238-350) in the blinded phase and later receive MEDI-545 in the open-label extension. The tertiary patient population will include the 22 patients who received study drug prior to 10/Oct/2007 and completed the safety follow-up period (Study Days 238-350).

Reason for Change: Change in number of patients and cohorts

25. Section 5.7

Changed to read:

Interim analyses of the type I IFN-inducible genes expression data will be performed after all patients in each dose cohort complete Study Day 28 evaluations.

Interim analyses on the safety and efficacy endpoints will be performed at the following time points:

- After all patients randomized and treated in the ~~second~~ third dose cohort complete Study Day 84 of the blinded phase;
- After all patients randomized and treated in the ~~blinded phase~~ **fourth dose cohort** complete Study Day 84 **of the blinded phase**; and
- After all patients randomized and treated in the blinded phase complete Study Day 196 evaluations.

Reason for Change: Clarification of the timing for each interim analysis.

Summary of Changes from Version 4.0 to Version 5.0 of the Study Protocol

Version 4.0 of the protocol (dated [redacted]) was amended to Version 5.0 (dated [redacted]). The major changes include removing the open-label extension phase of the study, changing the medical monitor's name, updating preclinical and clinical information; updating the countries in which the study is being conducted; changing the number of dose cohorts from 5 to 4, decreasing the number of evaluable patients from 160 to 148; providing clarification that a physician must be present at the site during all administrations of study drug; providing clarification that the BILAG/SELENA-SLEDAI assessments must be completed by the same rheumatologist for the same patient throughout the study; providing clarification that any study drug remaining in the tubing must be flushed with 10 mL to 20 mL normal saline to complete study drug administration; clarification that the patient self-collected vaginal swabs may also may also be collected by qualified medical personnel, if approved by the sponsor; moving the optional DNA analysis from Study Day 0 to Study Day 14; changing the requirements that need to be met to initiate an interim analysis; providing instructions for the recording of SLE flares as adverse events; and providing clarification of general study procedures. The changes made to Version 4.0 of the protocol to create Version 5.0 are summarized below.

Some of these changes occur in multiple places in the protocol but are presented in the most relevant sections and sometimes only once. These changes, if applicable, also apply to the Study Abstract. The text that has been added is shown bolded and underlined; text that has been deleted is shown bolded and strike-through. Changes that are similar in nature throughout the text may be listed only once.

1. General Change
   Since the study is being amended to remove the open-label extension, references to the blinded phase of the study were deleted. These changes occur throughout the document.

2. Cover page

   Changed to read:

   A PHASE IB, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-ESCALATION STUDY ~~WITH AN OPEN-LABEL~~

~~EXTENSION~~ TO EVALUATE THE SAFETY AND TOLERABILITY OF MULTIPLE INTRAVENOUS DOSES OF MEDI-545, A FULLY HUMAN ANTI-INTERFERON-ALPHA MONOCLONAL ANTIBODY, IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Reason for change: Study no longer includes an open-label extension.

Changed to read:

Medical Monitor: [redacted]
~~Senior~~ Director, Clinical Development
MedImmune
Phone: [redacted]
Fax: [redacted]

Reason for change: Change in Medical Monitor.

3. List of Abbreviations
   Updated list of abbreviations.

4. Section 1.3

   The preclinical experience with MEDI-545 was revised for purposes of clarification and updated to reflect the addition of toxicokinetics results

   Reason for change: The toxicokinetic results were not available prior to this version of the protocol.

5. Section 1.4

   The clinical experience with MEDI-545 was updated to reflect the status of current clinical trials (MI-CP151, MI-CP152, and MI-CP179) and to include the results of the MI-CP126 and MI-CP145 trials.

   Reason for Change: This section was updated to provide current information on the clinical experience with MEDI-545.

6. Section 1.5

   The clinical experience with MEDI-545 was updated to reflect the status of current clinical trials (MI-CP151, MI-CP152, and MI-CP179).

   Reason for Change: This section was updated to provide current information on the clinical experience with MEDI-545.

7. Section 2.4.1

Changed to read:

This is a multicenter, randomized, double-blind, placebo-controlled, dose-escalation study ~~with an open-label extension~~ to evaluate the safety and tolerability of multiple IV doses of MEDI-545 in adult patients with SLE. Approximately **50 to 55** ~~30 to 40~~ international sites (USA, Canada, ~~South America~~**, Brazil, Argentina and Chile**~~, and Asia~~) will participate in this study.

~~**2.4.1.1 Blinded Phase**~~

A total of ~~160~~ **148** evaluable patients are planned for the ~~blinded phase of the~~ study**; this excludes the 22 patients who were treated prior to 10/Oct/2007**. Four escalating doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo will be tested using an infusion time of at least 60 minutes. **Dose Cohorts 1 through 3 will include 32 patients each; while Dose Cohort 4 will include 52 patients.** ~~; a fifth dose cohort (10.0 mg/kg MEDI-545 or placebo) will be tested using an infusion time of 30 minutes, if a review of data from prior cohorts indicates that this shorter infusion time is likely to be safe. This excludes the 22 patients who were treated prior to 10/Oct/2007~~. ~~Within each dose cohort, 32~~ **All** patients will be randomized in a 3:1 ratio, using central randomization (without regard to site) and stratified by the level of type I IFN-inducible gene signature (low/undetectable versus high), to receive either MEDI-545 or placebo (ie, 24 patients **each in Dose Cohorts 1 through 3** will receive MEDI-545 and 8 patients will receive placebo **and 39 patients in Dose Cohort 4 will receive MEDI-545 and 13 patients will receive placebo**).

Patients are considered evaluable ~~for the blinded phase of the study~~ if they receive the first 4 doses of study drug (MEDI-545 or placebo) and complete the required evaluations, or if they discontinue study drug administration before the fourth dose for safety reasons. Nonevaluable patients will be replaced to maintain a size of at least 32 patients **each in Dose Cohorts 1 through 3 and 52 patients in Dose Cohort 4**. ~~per dose cohort.~~ Data from all patients will be included in the safety analyses. A dose cohort may be expanded by up to 4 additional patients ~~(for a maximum of 36 patinets per dose cohort)~~ if eligible patients are already in screening at the time 32 patients **in Dose Cohorts 1 through 3 or 52 patients in Dose cohort 4** have been randomized into the dose cohort.

MEDI-545 or placebo will be administered once every 2 weeks as an IV infusion (for at least 60 minutes ~~for Dose Cohorts 1 through 4 and for at least 30 minutes for Dose Cohort 5 if a review of data from prior cohorts indicates that this shorter infusion time is likely to be safe)~~for 26 weeks, for a total of 14 doses. Study drug administration will start on Study Day 0 and continue through Study Day 182. Patients will be generally maintained on the same stable dose of SLE treatment as baseline through Study Day 196. SLE treatment may be adjusted as clinically indicated after Study Day 196 through Study Day 350. See Section 3.3.5 for details on concomitant medications. The follow-up period ends on Study Day 350.

Decisions regarding dose escalation will be made by the Medical Monitor based on the review of all cumulative, blinded safety information, which includes the safety data through Study Day 42 from the first 12 randomized patients ~~(9 MEDI-545-treated and 3 placebo-~~

~~treated)~~ in the preceding lower dose cohort. Detailed dose escalation criteria are described in Section 4.9.

Figure 1 was updated with the new study design information.

Patients who participate in this study may have the option of entering a long-term safety study (MI-CP212). In this long-term study, all patients will receive MEDI-545 in an open-label manner.

Reason for Change: This was updated to provide the new description of the current design of the trial.

8. Section 2.4.2

Changed to read:

Screening evaluations include medical history, physical examination, ~~BILAG and SELENA-SLEDAI~~BILAG/SELENA-SLEDAI assessments, ECG, chest x-ray (or chest x-ray **with two views [anterior-posterior and lateral] or computed tomography (CT) scan**), TB skin test, blood tests for hepatitis A, B, C, human immunodeficiency virus (HIV)-1 and HIV-2, serum and urine βHCG for women (unless surgically sterile or 2 years after menopause), AEs/SAEs, serum chemistry (including Na, K, Cl, bicarbonate, blood urea nitrogen [BUN], creatinine, AST, ALT, bilirubin, alkaline phosphatase, and random glucose), CBC with differential and platelets, autoantibody and complement levels, and urinalysis. In addition, whole blood samples are taken to analyze levels of messenger mRNA for type I IFN-inducible gene expression; the results are used for randomization stratification. In patients who have received MEDI-545 previously, serum levels of MEDI-545 and antibodies to MEDI-545 at screening will be measured. A negative urine βHCG for women (unless surgically sterile or 2 years after menopause) on all study days is required before study drug administration.

Clinical disease activity is assessed using the following indicators: requirement of rescue oral, IV, **intra-articular,** or intramuscular corticosteroids or other potential disease modifying therapies to treat SLE during the treatment period, changes from baseline in SLE treatment during the follow-up period, BILAG scores, SELENA-SLEDAI score, flares, active joint count, physician global assessment, photographs of skin lesions (optional, if present), and renal function. In addition, autoantibodies and complement levels in blood will be measured.

Patient-reported outcomes are measured using the following instruments: patient global assessment, Automated Neuropsychological Assessment Metrics (ANAM) tests (**this test is optional and is only being done** ~~performed only~~ at **selected** North American sites), modified Health Assessment Questionnaire (MHAQ), Beck Depression Index (performed only at North American sites), the Krupp Fatigue Severity score, work productivity questionnaire, and **the** SF-36.

Reason for Change: Clarification of study procedures and inclusion of intra-articular corticosteroids to the list of disease modifying therapies.

9. Section 3.1.1
Clarified inclusion criterion #6 to change "and sterile sexual partner" to "or sterile sexual partner.

10. Section 3.1.2
Provided international standard units for creatinine, neutrophils, and platelet count in exclusion criterion 21.

11. Section 3.2.1
Clarified that the IVRS assigns a study drug kit number for the patient.

Changed to read:

Patients will receive either MEDI-545 or placebo in a blinded manner on Study Day 0. Patients are considered evaluable ~~for the blinded phase of the study~~ if they receive the first 4 doses of study drug (MEDI-545 or placebo), or if their discontinuation of study drug administration before the fourth dose is due to safety reasons. In each of the ~~5~~ **4** dose cohorts, if one of the first ~~32~~ patients is randomized but not treated, or not evaluable (or needs to be replaced for other reasons), the treatment assignment for this replaced patient will be used for the next patient enrolled in this cohort as a replacement. If more patients are to be replaced, the replaced patient's treatment assignment will be used in order of enrollment. A dose cohort may be expanded by up to 4 additional patients ~~(for a maximum of 36 patients per dose cohort)~~ if eligible patients are already in screening at the time 32 patients **in Dose Cohorts 1 through 3 or 52 patients in Dose Cohort 4** have been randomized into the dose cohort.

Reason for Change: Clarification of text.

12. Section 3.2.2

Clarified that this study is a double-blind study only.

Changed to read:

A limited number of MedImmune personnel independent of the project team, who will perform and interpret assays such as gene **signature** expression ~~signature~~ analyses or PK/PD analyses, will be unblinded during the conduct of the study. Unblinded MedImmune personnel involved in all interim assessments will not be associated with the clinical conduct of the study and will not reveal the treatment assignment of individual patients to any clinical personnel involved in the study. Only changes to the clinical development plan that affect individuals involved in the clinical conduct of the study will be communicated, ie, the actual results of the interim analyses will not be communicated. In addition, once the last patient of each dose cohort has completed Study Day 28 ~~of the double-blind phase~~ and the gene

expression analyses are completed, an interim analysis of the gene expression data may be reviewed by senior management for the purpose of making clinical development decisions. Additional interim assessments of safety and clinical activity **can** ~~will~~ be made **as follows: when at a minimum the 25th patient in Dose Cohort 3 completes Study Day 84; when at a minimum the 20th patient in Dose Cohort 4 completes Study Day 56; and when all patients in Dose Cohort 4 complete Study Day 84 and Study Day 196**~~when the third dose cohort complete Study Day 84 of the double-blind phase, when the last dose cohort completes Study Day 84 of the double-blind phase, and when the fourth cohort completes Study Day 196 of the double-blind phase~~. These interim assessments are also for the purpose of making clinical development decisions.

Reason for Change: Clarification of the timing of the interim analyses.

13. Section 3.3.2

Changed to read:

A total of ~~160~~ **148** evaluable patients are planned for the ~~blinded phase of the~~ study**; this excludes the 22 patients who were treated prior to 10/Oct/2007. A dose cohort may be expanded by up to 4 additional patients (for a maximum of 16 additional patients) if eligible patients are already in screening at the time 32 patients in Dose Cohorts 1 through 3 or 52 patients in Dose Cohort 4 have been randomized into the dose cohort** ~~Up to 20 additional patients may be enrolled (4 patients in each of 5 cohorts), if those patients are in screening at the time 32 patients have been randomized in each cohort.~~ Four escalating doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo will be tested using an infusion time of at least 60 minutes~~; a fifth dose cohort (10.0 mg/kg MEDI-545 or placebo) will be tested using an infusion time of at least 30 minutes, if a review of data from prior cohorts indicates that this shorter infusion time is likely to be safe. This excludes the 22 patients who were treated prior to 10/Oct/2007. In each dose cohort, 32 patients will be randomized in a 3:1 ratio to receive either MEDI-545 or placebo (ie, 24 patients will receive MEDI-545 and 8 patients will receive placebo).~~ **Dose Cohorts 1 through 3 will include 32 patients each; while Dose Cohort 4 will include 52 patients. All patients will be randomized in a 3:1 ratio to receive either MEDI-545 or placebo (ie, 24 patients each in cohorts 1 through 3 will receive MEDI-545 and 8 patients will receive placebo and 39 patients in Dose Cohort 4 will receive MEDI-545 and 13 patients will receive placebo).** MEDI-545 or placebo will be administered every 2 weeks as an IV infusion for 26 weeks, for a total of 14 doses.

Dose Cohort	N[a]	Treatment	Infusion Time
1	32	MEDI-545 0.3 mg/kg (n=24): Placebo (n=8)	60 minutes
2	32	MEDI-545 1.0 mg/kg (n=24): Placebo (n=8)	60 minutes
3	32	MEDI-545 3.0 mg/kg (n=24): Placebo (n=8)	60 minutes
4	~~32~~**52**	MEDI-545 10.0 mg/kg (n=~~24~~ **39**): Placebo (n=~~8~~ **13**)	60 minutes
~~5~~	~~32~~	~~MEDI-545 10.0 mg/kg (n=24): Placebo (n=8)~~	~~30 minutes[b]~~

a. ~~During the blinded phase of the study, a~~ **A** dose cohort may be expanded by up to 4 additional patients (for a maximum of **16 patients** ~~per dose cohort~~**)**, if eligible patients are in screening at the time 32 patients **in Dose Cohorts 1 through 3 and 52 patients Dose Cohort 4** have been randomized into the dose cohort.

b. ~~This cohort will be started if a review of data from prior cohorts indicates that this shorter infusion time is safe.~~

Reason for Change: This was updated to provide the new description of the current design of the trial.

14. Section 3.3.3

Changed to read:

Table 2 Summary of Infusion Volume, Duration, and Rate

Dose Cohort	Dose (mg/kg)	Infusion Volume [a] (mL)	Infusion Duration	Infusion Rate (mL/hr)	Maximum Infusion Rate (mg/min)[b]
1	0.3	100	≥ 60 minutes	100	0.6
2	1.0	100	≥ 60 minutes	100	2.0
3	3.0	100	≥ 60 minutes	100	6.0
4	10.0	100	≥ 60 minutes	100	20.0
~~5~~	~~10.0~~	~~100~~	~~≥ 30 minutes~~	~~100~~	~~33.3~~

a. ~~It is expected that~~ Some study drug will remain in the tubing at the end of the infusion**; the remaining study drug should be flushed with 10 mL to 20 mL of normal saline to complete the administration of the entire dose of study medication.**

b. The maximum infusion rates (mg/kg/min) are based on 120 kg~~/~~ of body weight ~~for Dose Cohorts 1 through 4 and 100 kg of body weight for Dose Cohort 5~~.

~~During the open-label extension, the dose to be used for participating patients will be determined by the sponsor and communicated to the study sites. The study drug dose will be prepared by the CTMM and administered to patients without blinding.~~

Reason for Change: The number of dose cohorts was reduced from 5 to 4; the 30-minute infusion is no longer applicable to the study; and clarification that any study drug remaining the tubing at the end of the infusion should be flushed to complete the administration of study drug. In addition, deleted mention of the open-label extension as it is no longer part of the study.

15. Section 3.3.4

Changed to read:

The study drug should be dispensed by the pharmacist or qualified designee and administered as an infusion over at least 60 minutes ~~(Dose Cohorts 1 through 4) or over at least 30 minutes (Dose Cohort 5)~~ using an infusion pump. Do not **ever** administer **study drug** by intravenous push (IVP) or bolus injection. **A physician must be present at the infusion site during all administrations of study drug.**

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be monitored before infusion **(at anytime the day of dosing, prior to infusion)**, approximately every 15 minutes during infusion, at the end of the infusion (**within 10 minutes after the infusion has stopped)**, and approximately every 30 minutes after completion of the infusion until stable, **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. Blood pressure and heart rate will also be taken prior to discharge from the site on visits in which study drug is administered.

Patients should not be premedicated unless they have had a prior infusion reaction, since the primary objective of this study is to evaluate the expected frequency of safety events and tolerability of the study drug. However, after a reaction determined to be an infusion reaction has been documented, the investigator may elect to administer prophylactically an anti-histamine or Tylenol for the comfort and safety of the patient prior to subsequent infusions.

Reason for Change: Clarification of study procedures.

16. Section 3.3.5

Added intra-articular corticosteroid for purposes of clarification.

17. Section 3.4

Changed to read:

Table 3: Changed DNA analysis from Study Day 0 to Study Day 14; added that disease activity assessments should be done before dosing.

Table 3 Footnotes:

a. Within 28 days prior to Study Day 0.
b. The following evaluations will be performed in patients who discontinue the study prematurely (prior to Study Day 182). If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.
c. Assessments may be performed up to ~~72~~ **24** hours prior to dosing ~~on Study Day 0~~.
d. **A chest x-ray taken within 6 months of screening is considered suitable for screening and need not be repeated; also, a previously obtained chest CT scan, prior to the screening**

period, can substitute for a chest x-ray if the CT has already been done within the previous 6 months. If the chest x-ray is done, it must be with 2 views (anterior-posterior and lateral). ~~Chest x-ray taken within 6 months of screening is considered suitable for screening and need not be repeated~~.

e. Do not administer TB skin test if the patient is known to be positive.
f. Women, unless surgically sterile or at least 2 years post-menopausal, must have a negative serum pregnancy test within 28 days before randomization/entry, and a negative urine pregnancy test on Study Day 0 and all subsequent study drug infusion days before receiving the study drug.
g. Vital signs include heart rate, blood pressure, respiratory rate and temperature. Blood pressure should be obtained with the patient in the position to be used for drug administration. Vital signs are obtained before **dosing (at anytime the day of dosing, prior to infusion)**, approximately every 15 minutes during infusion, at the end of the infusion **(within 10 minutes after the infusion has stopped)**, and approximately every 30 minutes after completion of the infusion until stable, **as judged by the investigator**. Blood pressure and heart rate will also be taken prior to discharge from the site on visits in which study drug is administered.
h. Includes Na, K, Cl, bicarbonate, BUN, creatinine, AST, ALT, bilirubin, alkaline phosphatase, and random glucose.
i. A blood sample for assessment of safety biomarkers (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies) will be collected in all patients **at any time** prior to study drug administration on Study Day 0 and in any patient with an infusion reaction as soon as possible after the event, 60 minutes after the event, and at discharge (see Section 3.3.4 for details).
j. Includes urine dipstick tests and microscopy for red blood cells and white blood cells.
k. Oropharyngeal swabs (performed by investigator or qualified designee) for HSV-1 and HSV-2; vaginal swabs (self-collected, female patients only, **or collected by an MD/OBGYN or qualified medical personnel such as an appropriately trained nurse practitioner, if approved by the sponsor**) for HSV-1 and HSV-2, and HPV; and blood samples for EBV and cytomegalovirus tests.
l. Photographs of up to two target skin lesions (if present) are requested but not required for study participation. Photographs will be performed at North American sites only.
m. ANAM **tests are optional** and will be performed only on English-speaking patients at **selected** sites in North America
n. Includes spot morning urine for protein/creatinine ratio and estimated glomerular filtration rate calculated based on the Cockcroft-Gault equation (Cockcroft, 1976).
o. Includes ANA, anti-Ro, anti-La, anti-RNP, anti-Sm, IgG and IgM anti-cardiolipin antibodies, total hemolytic complement, **anti-**dsDNA, C3, and C4 measurements.
p. Flow cytometry will be performed at selected North American sites.
q. For patients who had previously received MEDI-545 only.
r. Serum samples for MEDI-545 concentrations are collected immediately before study drug administration, immediately after, and 2 hours after the completion of study drug administration.
s. Blood samples should be collected before study drug administration.

Table 4: Added urine βHCG at Study Day 238, and deleted footnote g (ANAM).

Reason for Change: Clarification of text and study procedures.

18. Section 3.5.2

Changed to read:

Viral infections will be monitored through viral cultures and titers as indicated in Table 3 **and** ~~through~~ Table ~~6~~ **4**. The investigator or qualified designee will collect oropharyngeal swabs for HSV-1 and HSV-2 testing. Vaginal swabs will be self collected for HSV-1, HSV-2, and HPV testing**; these swabs may also be collected by an MD/OBGYN or qualified medical personnel such as an appropriately trained nurse practitioner, if approved by the sponsor.** In addition, peripheral blood samples will be collected and tested for EBV and cytomegalovirus using polymerase chain reaction tests.

Reason for Change: Clarification of text and study procedures.

19. Section 3.5.7

Changed to read:

The following disease evaluations will be performed: BILAG score, SELENA-SLEDAI score and flares (using SELENA-SLEDAI and/or BILAG criteria). **The BILAG/SELENA-SLEDAI assessments will only be performed by rheumatologists who were trained by a MedImmune-approved trainer. Exceptions to this must be approved in writing by the MedImmune Medical Monitor. Non-exempt rheumatologists must attend a MedImmune-sponsored BILAG/SELENA-SLEDAI training prior to conducting assessments. The SELENA-SLEDAI score should reflect the last 28 days. The BILAG/SELENA-SLEDAI assessments must be completed by the same rheumatologist for the same patient throughout the study. The** occurrence and total dose of burst oral corticosteroids, **intra-articular** or intramuscular corticosteroid injections to treat SLE during the treatment period **will be assessed along with the** changes from baseline in immunosuppressive treatment for SLE during the follow-up period. **Other evaluations include the** physician global assessment, renal function measured by spot protein/creatinine ratio, estimated glomerular filtration rate, BUN, and serum creatinine. Autoantibodies and complement levels in blood will **also** be measured.

Reason for Change: Clarification of text and study procedures.

20. Section 3.5.8.1

Changed to read:

To investigate characteristics associated with patients' clinical response and safety, one blood sample (8.5 mL) will be collected on Study Day ~~0~~ **14** ~~(Blinded Phase)~~ and frozen at –80°C for DNA sample preparation. The sample will be frozen and stored until used in exploratory analyses. The specific tests include analyses for DNA single nucleotide polymorphisms (SNPs) and microsatellite or short tandem repeats to further evaluate particular genes involved in the signaling pathway relevant to type I interferons.

Reason for Change: Blood draw for DNA analysis was moved from Study Day 0 to Study Day 14.

21. Section 4.1.2

Changed to read:

The reporting period for AEs is the period from the time the informed consent is signed through Study Day 350. **AEs will not be recorded for patients deemed screening failures.** ~~for the blinded phase of the study and through Study Day 266 for the open-label extension.~~

Reason for Change: Clarification of study procedures.

22. Section 4.1.4

Added:

An SLE flare should not be recorded as an AE, if it is consistent with waxing and waning of the disease in the year before participation in the study.

An SLE flare should be recorded as an AE if it involves an organ system which was inactive for a year prior to study entry or the condition is significantly worse than the disease activity in a given organ system during the year prior to entering the study. The event term on the AE form should be "SLE Flare", and therefore, components of the flare, such as swelling or pain, should not be recorded separately as additional AEs. The elements of a flare recorded as an AE should be reported on the disease activity case report forms. If not, a note to file should be recorded to explain the rationale for considering the event a lupus flare. Sites will be queried if components of a flare are entered on the AE page in addition to the SLE Flare entry. Any AE seen in addition to the flare should have separate entries (e.g., if a lupus patient developed a flare of arthritis in the context of an upper respiratory infection, the upper respiratory infection should be recorded as an AE and the arthritis flare would be recorded as an AE only if it was inconsistent with the waxing and waning disease activity in the year before entering the study).

Reason for Change: Clarification of study procedures when recording SLE flares as AEs.

23. Section 4.2.2

Changed to read:

The reporting period for SAEs is the period from the time the informed consent is signed through Study Day 350 f~~or the blinded phase and through Study Day 266 for the open-label extension~~. **SAEs will also be recorded for patients deemed screening failures.** SAEs must be followed until resolution by the investigator, even if this extends beyond the study

reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

Reason for Change: Clarification of study procedures.

24. Section 4.5

Changed to read:

*Subjects who become pregnant **or intend to become pregnant** during the study period must not receive additional doses of study product **and should proceed to the follow-up phase within 2 weeks of a positive pregnancy test or making the decision to become pregnant. The follow-up phase will start with the procedures scheduled for Study Day 185 and will end on Study Day 350. Patients who become pregnant during the follow-up period should continue the follow-up phase through Study Day 350** ~~but will be followed on study~~**.** A pregnancy should be followed for outcome, any premature terminations reported, and the health status of the mother and child including date of delivery and the child's gender and weight should be reported to MedImmune Product Safety after delivery.

Reason for Change: Clarification of study procedures for patients who become or want to become pregnant during the study and the follow-up period.

25. Section 5.2

Changed to read:

~~For the blinded phase of the study, 160~~ **Approximately 148** ~~160~~ patients ~~(5 cohorts of 32 patients each)~~ **(32 patients for Dose Cohorts 1 through 3 and 52 patients for Dose Cohort 4)** will be randomized into the study. This excludes the 22 patients who were treated prior to 10/Oct/2007. Within each cohort**, the number of patients receiving MEDI-545 versus the number of patients receiving placebo is 3 to 1**.~~24 patients will receive MEDI-545 and 8 patients will receive placebo.~~ In addition, a dose cohort may be expanded by up to 4 additional patients if eligible patients are already in screening at the time 32 patients **in Dose Cohorts 1 through 3 or 52 patients in Dose Cohort 4** have been randomized into the dose cohort. An unspecified number of patients may be enrolled in the study for replacement of nonevaluable patients as described in Section 2.4.1. No formal calculation was performed to determine sample size because safety is the primary outcome and this will be assessed with descriptive analyses.

~~For the open-label extension, up to 202 patients from the blinded phase of the study (including the 22 patients who received study drug prior to 10/Oct/2007 and have completed the safety follow-up period [Study Days 238-350]) will be given the option to enter into the study.~~

Reason for Change: The number of patients and dose cohorts were changed to reflect the current plans for the trial.

26. Section 5.3

Changed to read:

There will be ~~three~~ **2** patient populations analyzed in this study. The primary patient population will include up to ~~180~~ **164** new patients who receive study drug ~~in the blinded phase of the study~~ (~~in~~excluding patients who received study drug prior to 10/Oct/2007) ~~and completed the safety follow-up period (Study Days 238-350) in the blinded phase and later receive MEDI-545 in the open-label extension~~. The ~~tertiary~~ **secondary** patient population will include the 22 patients who received study drug prior to 10/Oct/2007. ~~and completed the safety follow-up period (Study Days 238-350).~~

Efficacy data will be analyzed primarily based on the Intent-to-Treat Population including all randomized patients. Safety and IM will be analyzed in all patients who receive any study drug. Evaluability for analyses of MEDI-545 serum concentrations will be determined based upon the frequency and timing of the serum samples obtained.

Reason for Change: Clarification of the analysis planned for the trial.

27. Section 5.7

Changed to read:

Interim analyses of the type I IFN-inducible genes expression data will be performed after all patients in each dose cohort complete Study Day 28 evaluations.

Interim analyses on the safety and efficacy endpoints **can** ~~will~~ be performed at the following time points:

- **When at a minimum the 25th patient in Dose Cohort 3 completes Study Day 84;**
- **When at a minimum the 20th patient in Dose Cohort 4 completes Study Day 56;**
- **When all patients in Dose Cohort 4 complete Study Day 84 and Study Day 196.**
- ~~After all patients randomized and treated in the third dose cohort complete Study Day 84 of the blinded phase; and~~
- ~~AFTER all patients randomized and treated in the fourth dose cohort complete Study Day 196 of the blinded phase.~~

Reason for Change: Clarification of the analysis planned.

Summary of Changes from Version 5.0 to Version 6.0 of the Study Protocol

Version 5.0 of the protocol (dated [redacted]) was amended to Version 6.0 (dated [redacted]) The major changes include: changing the medical monitor; updating the clinical experience with MEDI-545; including the option for patients to enter the long-term study MI-CP212; adding toxicity management guidelines for blood chemistry abnormalities; clarifying medical monitor and Safety Monitoring Committee responsibilities; including 2 additional conditions in which dosing should be discontinued; clarifying the circumstance of patient death

as it applies to interruption of study dosing and randomization (ie, death of any subject which, in the opinion of the sponsor, contraindicates further dosing); changing the number of study sites from 40 to 50 to 30 to 40; changing the third interim analysis (which was to occur after all patients in Dose Cohort 4 completed Day 84) to when a minimum of 39 patients in Dose Cohort 4 complete Study Day 84; and providing guidance in Appendix C for the management of abnormal LFTs. Some of these changes occur in multiple places in the protocol including the Study Abstract, when applicable.

.

1. Cover page

   Changed to read:

   Medical Monitor: [redacted]
   Associate Director, Clinical Development
   MedImmune
   Phone: [redacted]
   Fax: [redacted]

   Reason for change: Change in Medical Monitor.

2. List of Abbreviations
   Updated list of Abbreviations

3. Section 1.2

   Changed to read:

   MEDI-545 is a fully human $IgG_1\kappa$ MAb that binds to and neutralizes a majority of the subtypes of human IFN-α. MEDI-545 is composed of two identical heavy chains and two identical light chains, with an overall molecular weight of approximately 147 kD. The observed intact mass and peptide map are consistent with the expected protein, based on the DNA sequence. MEDI-545 has N-linked biantennary complex and high mannose type oligosaccharides attached to the heavy chain.

   The biological activity of MEDI-545 is quantified relative to reference standard using a luciferase reporter gene bioassay. This bioassay measures the inhibition of IFN-α-induced luciferase expression caused by the binding of MEDI-545 to IFN-α.

   ~~MEDI-545 is a fully human immunoglobulin (Ig) G1κ monoclonal antibody (Mab) that binds to and neutralizes a majority of the subtypes of human IFN-α. MEDI-545 may, therefore, have potential as a treatment for SLE.~~

   ~~MEDI-545 was generated by immunizing the Medarex transgenic HuMab-Mouse® with natural human IFN-α. The human anti-IFN-α monoclonal antibody-expressing hybridoma, 13H5, was derived by fusing murine Sp2/0-Ag14 myeloma cells with splenocytes from an~~

~~immunized Medarex transgenic male mouse. The 13H5 hybridoma was subsequently cloned into Chinese Hamster Ovary cells as an IgG1 isotype selected for further characterization and preclinical development with an initial designation of MDX-1103, now referred to as MEDI-545.~~

Reason for Change: MEDI-545 description updated.

4. Section 1.4

Changed to read:

Single-dose administration of IV MEDI-545 at doses ranging from 0.3 to 30.0 mg/kg to patients with mild to moderate SLE was well tolerated in this study. There were no deaths, no related SAEs, and no AEs that resulted in discontinuation of study drug reported in either the blinded phase or open-label extension. The pattern and type of AEs were generally consistent with the underlying conditions of this patient population. No dose effect was observed **for safety considerations**, and most AEs were associated with the system organ classes of Investigations and Musculoskeletal and Connective Tissue Disorders. **The most common adverse events in > 10% of patients in the sifalimumab group were blood bicarbonate decreased, blood glucose decreased, systemic lupus erythematosus flares, hemoglobin decreased, protein urine present, diarrhea, headache, nausea, and arthralgia**. ~~The most common AEs were blood bicarbonate decreased, blood glucose decreased, systemic lupus erythematosus (flares), hemoglobin decreased, protein urine present, diarrhea, headache, pain in extremity, arthralgia, fatigue, arthritis, hypoglycemia, and nausea.~~ The majority of AEs were Grade 1 (mild) in severity. Viral reactivation events occurred at a low frequency in both the placebo and MEDI-545 groups during the study. All but one event was Grade 1 in severity. MEDI-545 mean serum concentrations following IV administration exhibited a bi-phasic decline with a shallow initial distribution phase followed by a prolonged terminal elimination phase. In both the blinded phase and open-label extension, MEDI-545 PK was linear and dose proportional over the dose ranges tested. Mean C_{max} and AUC increased proportionally with dose. In the blinded phase, mean $T_{1/2}$ ranged between 15.4 and 23.5 days (excluding the 1.0 mg/kg dose group), and mean CL ranged between 143 and 197 mL/day. In the open-label extension, mean $T_{1/2}$ ranged between 19.8 and 28.0 days, and mean CL ranged between 147 and 184 mL/day. Both mean $T_{1/2}$ and CL values indicate that the target IFN-α does not seem to influence MEDI-545 PK. The low volumes of distribution, about 3 to 7 L, indicate limited distribution of MEDI-545 systemically. There was no detectable antibody response to MEDI-545 (defined as a titer with a dilution value of ≥1:10) seen for any patient at any time point for the blinded phase and open-label extension. A dose-dependent neutralization of type I IFN gene signature was noted following single IV administration of MEDI-545 at doses ranging from 0.3 to 30.0 mg/kg. Assessment of clinical outcome using standard SLE evaluation methods (ie, BILAG/SELENA-SLEDAI, and PGA) suggested improvement of disease by MEDI-545 in the blinded phase of the study. Clinical outcomes in the open-label extension were similar to those in the MEDI-545 group reported in the blinded phase. **After the study reporting period for serious adverse events had ended, a report of angiosarcoma of the left breast was reported for a patient that had participated in the MI-CP126 study. The patient**

had received a single 1.0 mg/kg dose of sifalimumab. Thirteen months after receipt of the single dose of sifalimumab, a left breast mass was detected and further investigated. The mass was determined to be an angiosarcoma.

MI-CP145 was a Phase 1, multicenter, randomized, double-blind, placebo-controlled, dose-escalation study of single-dose IV MEDI-545 (0.3, 1.0, 3.0, 10.0, or 30.0 mg/kg) in adult patients with chronic plaque psoriasis. A total of 36 patients received MEDI-545 or placebo in this study. This study was discontinued after the first patient in the 30.0 mg/kg dose cohort had an SAE of anaphylactic reaction (infusion reaction) during administration of study drug and was hospitalized for 3 days. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug in that patient. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies, that tryptase levels 10 hours after the event were normal, that the drug product met quality standards, and that when this anaphylactic event occurred, the patient was receiving drug at a relatively high rate of infusion. After thorough review, the Medical Monitor judged this event to be an infusion reaction and the Safety Monitoring Committee (SMC) concurred. Single-dose administration of IV MEDI-545 at doses ranging from 0.3 to 10.0 mg/kg to patients with chronic plaque psoriasis was well tolerated in this study. There were no deaths reported in the study. One patient randomized to the MEDI-545 30 mg/kg treatment group, discontinued investigational product due to a serious anaphylactic reaction. There were no other SAEs or AEs that resulted in discontinuation of investigational product. One other patient had an SAEs of myocardial infarction, which was judged by the investigator as not related to MEDI-545. No dose effect was observed, and most AEs were associated with the system organ class of Investigations. **The most common AEs in > 10% of patients in the sifalimumab group were nasopharyngitis, white blood cell count increase, back pain, pain in extremity, and headache.** ~~The most frequently reported AEs were nasopharyngitis, lymphocyte count decrease, white blood cell count increase, back pain, pain in extremity, and headache~~. MEDI-545 mean serum concentrations following IV administration exhibited a bi-phasic decline with a shallow initial distribution phase followed by a prolonged terminal elimination phase. MEDI-545 PK was linear and dose proportional over the dose range of 0.3 to 10.0 mg/kg. Mean C_{max} and AUC increased proportionally with dose from 14.9 µg/mL following 0.3 mg/kg to 338 µg/mL after 10.0 mg/kg, except for a high individual value of 1447 µg/mL in the 3.0 mg/kg dose cohort. Dose proportionality was also observed for $AUC_{(0-t)}$ and AUC over the dose range of 0.3 mg/kg to 10.0 mg/kg. Mean $T_{1/2}$ was about 21 days across the different doses; mean CL ranged between 115 and 194 mL/day across dose groups. Both mean $T_{1/2}$ and CL values indicate that the target IFN-α does not seem to influence MEDI-545 PK. The low volumes of distribution, about 3 to 6 L, and the similarity of mean Vd_{ss} and mean Vd_z values indicate limited distribution of MEDI-545. There was no detectable antibody response to MEDI-545 (defined as a titer with a dilution value of ≥1:10) seen for any patient at any time point, using a drug tolerant assay. There were no primary or secondary efficacy variables in this study; however, exploratory analyses were conducted to evaluate the potential effects of MEDI-545 on neutralization of type I interferon gene signature, clinical response, inflammatory histological features in skin biopsies, and patient-reported outcomes. The effects of MEDI-545 on neutralization of type I interferon gene signature showed no difference in inhibition of gene signature in involved skin at either Study Day 14 or Study Day 28. Changes in target lesions were similar between the placebo

and MEDI-545 group as were the changes in PASI score, PASI 50 responses, and PGA. In addition, the patient-reported outcomes showed little or no differences in the assessments of VAS, DLQI, SF36, and BDI.

MI-CP151 is a Phase 1b, multicenter, multinational, randomized, double-blind, placebo-controlled study to evaluate the safety of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) in 40 adult patients with dermatomyositis (DM) or polymyositis (PM). In this study, MEDI-545 or placebo is initially administered every 2 weeks for 12 weeks (7 doses) followed 2 weeks later by MEDI-545 every 2 weeks for another 12 weeks (7 doses) for a total of 26 weeks (14 doses). **The study is ongoing, and data remain blinded to treatment assignment. As of 02/Nov/2009, 51 patients have been dosed in MI-CP151. The majority of AEs are mild or moderate in severity. The most common AE (incidence > 10%) is headache. There is one viral reactivation AE (Grade 2 herpes zoster ophthalmic). There are no deaths reported in MI-CP151. Nine of the 51 patients (17.6%) have SAEs. For 1 patient, the SAE (hyponatremia) was judged by the investigator as related to study drug.** ~~10/Nov/2008, 9 patients have been dosed in MI-CP151. The most frequently reported AEs by 2 or more patients were aspartate aminotransferase and alanine aminotransferase increased (4 patients; 44.4%), followed by pain, blood bilirubin increased, blood bicarbonate decreased, leukopenia, hyponatraemia, and nausea (2 patients each; 22.2%). Any laboratory result outside the range of normal was reported as an AE, without regard to clinical significance. In terms of severity, the majority of AEs were Grade 2 (5 patients followed by Grade 3 (2 patients) and Grade 1 (2 patients). As of 11/Mar/2009, one patient reported an SAE of chest pain and was judged by the investigator as not related to the study drug (MEDI-545 or placebo). This patient had not received any study drug when the SAE occurred.~~

The current study, MI-CP152, is a dose-escalation study to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) in approximately 148 adult patients with SLE. In this study, MEDI-545 is being administered every 2 weeks for a total of 14 doses over 26 weeks. The planned starting dose of MEDI-545 (0.3 mg/kg) in MI-CP152 is less than one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated IV administrations every 2 weeks for 26 weeks). The first 12 randomized patients in each of the 4 dose cohorts will provide safety data for dose escalation; the additional patients planned (20 each in Dose Cohorts 1 through 3 and 40 in Dose Cohort 4) are intended to increase safety data and provide adequate numbers of patients for exploratory analyses of effect of MEDI-545 on the inhibition of type I IFN gene signature. ~~**In 22 patients treated prior to 10/Oct/2007, the majority of AEs were mild (Grade 1) to moderate (Grade 2) in severity. The most common AEs were blood bicarbonate decreased (5 subjects, 22.7%), blood potassium decreased (4 subjects, 18.2%), urinary tract infection (3 subjects, 13.6%), and nausea (3 subjects, 13.6%).**~~ On 28/Sep/2007, one patient in MI-CP152 experienced an SAE of Grade 3 hypersensitivity reaction characterized by chills, rigors, swollen hands, hives, moderate hypotension and several bouts of diarrhea following the fifth dose of MEDI-545 (1.0 mg/kg), which resolved the same day. This event was judged by the investigator as related to MEDI-545 and resulted in discontinuation of study drug. Further evaluation of the event indicated this patient had no anti-MEDI-545 antibodies and that when this event occurred, the patient was receiving drug at a relatively high rate of infusion. After thorough review, the Medical Monitor judged this event to be an infusion

reaction. This study was stopped on 10/Oct/2007 due to an SAE of anaphylactic reaction associated with Grade 4 hypotension in MI-CP145; it was restarted in January 2008.

A review of the safety data from both MI-CP145 and MI-CP152 concluded the aforementioned SAEs ~~were~~ **of an infusion reaction in each study were** most likely due to MEDI-545 administered at a high rate of infusion, approximately 92 and 75 mg per minute for these 2 patients weighing 92 and 122 kg respectively. As a result of this determination it was decided to decrease the likelihood of future events such as these by limiting the potential for administration of these high rates of MEDI-545 infusion by decreasing the maximum dose of MEDI-545 permitted and mandating a minimum period of administration. Consequently, the MI-CP152 and the MI-CP151 protocols were amended to reduce the starting dose of MEDI-545 from 1.0 to 0.3 mg/kg, reduce the highest dose of MEDI-545 from 30.0 to 10.0 mg/kg, and set the infusion volume and time to 100 mL over at least 60 minutes.

Reason for change: Update safety information.

Changed to read:

As of 02/Nov/2009, 183 patients have been dosed in the current study, MI-CP152. This study is ongoing, and data remain blinded to treatment assignment. The majority of AEs are mild or moderate in severity. The most common AEs (incidence >10%) are urinary tract infection, nasopharyngitis, lymphocyte count decreased, blood potassium decreased, nausea, diarrhoea, systemic lupus erythematosus flares, arthralgia, and headache. Viral reactivation AEs occurred in 10 patients. There have been 5 deaths in the study, four of which were judged by the investigator as unrelated to study drug. One death was due to multiple drug overdose, another due to congestive heart failure and another patient died in screening due to sepsis before receiving study drug. There was one death due to herpes encephalitis. The study drug was unblinded for this patient and the patient was receiving placebo. Finally one patient died due to liver failure, this event was judged by the investigator as being related to study drug, however the sponsor considers the event to be related to a blood infection and low blood pressure. This patient also took herbal medicines. The possibility exists that use of herbal medicines combined with sifalimumab may increase a risk of unexpected liver problems. SAEs occurred in 31 of the 183 patients (37.3%), with 8 patients having related SAEs. One patient had a diagnosis of lymphoma that occurred after the patient received 2 doses of study drug, although signs and symptoms of lymphoma were present before any study drug was given.

~~Since the re-initiation of the MI-CP152 study and as of 10/Nov/2008, the most frequently reported AEs (incidence > 10%) were decreased hemoglobin and systemic lupus erythematosus (flares) (13 patients each; 16.7%); decreased blood potassium (11 patients; 14.1%); decreased lymphocyte count and arthralgia (10 patients each; 12.8%); decreased blood bicarbonate (9 patients; 11.5%); increased blood alkaline phosphatase; and urinary tract infection (8 patients each; 10.3%). Any laboratory result outside the range of normal was reported as an AE, without regard to clinical significance. In terms of severity, the majority of adverse events reported were Grade 2 (30 patients) followed by Grade 1 (17~~

~~patients) and Grade 3 (10 patients). Since the re-initiation of the study and as of 11/Mar/2009, 3 patients reported SAEs judged by the investigator as possibly related to the study drug (MEDI-545 or placebo), which included 1 patient (herpes simplex), 1 patient (polyarthritis), and 1 patient (pneumonia). Three patients reported SAEs judged by the investigator as remotely related to the study drug, these included 1 patient (chest discomfort, PO2 increased, hyperventilation, gastroesophageal reflux disease, dizziness, and nausea); 1 patient (nausea and vomiting); and 1 patient (hip infection). A total of 10 patients reported SAEs judged by the investigator as not related to the study drug. Two of these patients had not received any study drug when the SAE occurred: 1 patient (chest pain) and 1 patient (sepsis). The other 8 patients with SAEs were: 1 patient (respiratory failure, renal failure, thrombocytopenia, diabetes mellitus, and cellulitis); 1 patient (dehydration); 1 patient (blindness transient); 1 patient (costochondritis); 1 patient (constipation); 1 patient (abdominal pain); 1 patient (psychotic disorder); and 1 patient (angioplasty).~~

A third study of MEDI-545 in patients with SLE (MI-CP179) is evaluating the safety and tolerability of multiple SC dose schedules of MEDI-545 and/or placebo. In this study, a total of 80 patients will be randomized in a 1:1:2:2:2 ratio to receive 1 of 5 treatment arms of MEDI-545 or placebo as follows: (1) SC MEDI-545 100 mg once; SC Placebo × 12 doses on other weeks; (2) SC MEDI-545 100 mg every 4 weeks × 4 doses; SC Placebo × 9 doses on other weeks; (3) SC MEDI-545 100 mg every 2 weeks × 7 doses; SC Placebo × 6 doses on other weeks; (4) SC MEDI-545 100 mg every week × 13 doses; and (5) SC Placebo every week × 13 doses. **As of 02/Nov/2009, ~~18~~ 74 patients have been dosed in MI-CP179. The majority of AEs are mild or moderate in severity. The most common AEs (incidence > 10%) are upper respiratory tract infection and nausea. There are no viral reactivation AEs. There was one case of breast cancer (angiosarcoma) that was judged by the investigator as being not related to study drug. There are no deaths reported in MI-CP179. Five of the 74 patients (6.8%) had SAEs. Two SAEs (cellulitis and pneumonia) were judged by the investigator as related to study drug.**~~10/Nov/2008, 18 patients have been dosed in MI-CP179. The most frequently reported AEs by 3 or more patients were blood potassium decreased and lymphocyte count decreased (3 patients each; 16.7%). Clinically significant laboratory results outside the range of normal were reported as an AE. In terms of severity, the majority of adverse events reported were Grade 1 (6 patients) followed by Grade 2 (2 patients) and Grade 3 (1 patient). As of 11/Mar/2009, 1 patient reported an SAE of abdominal pain and was judged by the investigator as possibly related to the study drug (MEDI-545 or placebo). One more patient reported two SAEs of intestinal obstruction and vomiting; both of which were judged by the investigator as not related to the study drug. As a fully human Mab, MEDI-545 is expected to have a safety profile similar to other agents in this class, including the potential for infusion reactions, injection-site reactions, fever, rashes, allergic reactions, bronchospasm, anaphylaxis, and serum sickness. In addition, potential reactions are expected to be related to the mechanism of action, the neutralization of most IFN-α subtypes, as well as the underlying patient population and treatments. IFN-α has a role in host defenses against viral infections. Patients at high risk for viral infections will be excluded from the current clinical study. Those enrolled in the study will be monitored clinically and through blood samples and cultures for viral infections.~~

Reason for change: Updated safety information.

5. Section 2.4.1

Changed to read:

This is a multicenter, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and tolerability of multiple IV doses of MEDI-545 in adult patients with SLE. Approximately ~~40 to 50~~ **30 to 40** international sites (USA, Canada, Brazil, Argentina, and Chile) will participate in this study.

Reason for change: Updated to reflect number of sites necessary to enroll trial.

Changed to read:

Patients who participate in this study may have the option of entering a long-term safety study (MI-CP212). **This includes both MEDI-545 and placebo patients, including the patients who were treated in MI-CP152 prior to 10Oct2007, but excludes patients who discontinued from previous MEDI-545 clinical studies for safety reasons.** ~~In this long-term study, all patients will receive MEDI-545 in an open-label manner~~. **Patients must complete the treatment period and follow up through Day 266 of this study to participate in MI-CP212. Patients must also qualify for the long term safety study (following written informed consent), as per the MI-CP212 protocol inclusion and exclusion criteria. If patients qualify, they will receive open-label MEDI-545. Patients may be treated for approximately 3 years and may be followed for an additional 3 months following the last dose of IV MEDI-545.**

Reason for change: Provide clarification on what patients may qualify to enter the CP212 open label extension study.

6. Section 3.3.1

Changed to read:

MEDI-545 (100 mg/mL): MEDI-545 is supplied as a sterile liquid containing 0.75 mL of MEDI-545 solution at a concentration of 100 mg/mL in a 3 mL single-use glass vial. The solution also contains 25 mM histidine**/histidine-HCl**, 8% **(w/v)** trehalose **dihydrate**, and 0.02% **(w/v)** polysorbate 80, and has a pH of 6.0.

Placebo: Placebo is supplied as a sterile liquid containing 0.75 mL solution in a 3 mL single use vial. The solution contains 25 mM histidine**/histidine-HCl**, 8% **(w/v)** trehalose, and 0.02% **(w/v)** polysorbate 80, and has a pH of 6.0.

Reason for change: Clarification of MEDI-545 and Placebo formulation description.

7. Section 3.3.4.2

Added:

3.3.4.2 Dose Modification for Toxicity Management: Blood Chemistry Abnormalities

If total bilirubin is > 2 × ULN at the central laboratory:

- **Do not administer study drug at next dosing visit.**
- **Repeat total bilirubin as well as direct and indirect values, liver function tests (LFTs; including AST, ALT, and alkaline phosphatase), evaluate reticulocyte count immediately to confirm abnormalities. Repeat all tests again in 1 week.**
  - **If bilirubin remains > 2 × ULN (not due to Gilbert's syndrome or hemolysis) do not administer study drug at next dosing visit**
  - **If bilirubin returns to within normal limits (< ULN), study drug may be administered at next scheduled dosing visit**
  - **If repeat bilirubin is < 2 × ULN but > ULN; hold dose and discuss with medical monitor.**

Study drug will be discontinued in subjects who miss 2 consecutive scheduled doses of study drug due to elevated bilirubin (see Section 4.7).

If ALT or AST is > 3 × ULN refer to Guidance for Abnormal Liver Function Tests in Appendix C.

Study drug will be discontinued in subjects who miss 3 consecutive scheduled doses of study drug due to elevated ALT or AST (see Section 4.7).

As indicated in the Guidance for Abnormal Liver Function Tests (Appendix C), additional laboratory tests may be ordered from Quintiles Laboratory as needed. The LFTs that the guidelines require to be repeated are AST, ALT, total bilirubin and alkaline phosphatase.

Additional tests may be ordered as required by investigators, these tests include: CPK, GGT, INR, PT, albumin, EBV, CMV, hepatitis A antibody, hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody.

Reason for addition: Increase patient safety.

8. Section 3.3.5

Changed to read:

All concomitant medications, **including herbal products**, used by the patient from randomization/entry through Study Day 350 will be recorded on the case report form. Patients may not receive the following concomitant medications from randomization through Study Day 350:

Reason for change: Increase patient safety.

9. Section 3.6

Added:

Patients who participate in this study may have the option of terminating early to enter the MI-CP212 study. This includes both MEDI-545 and placebo patients, but excludes patients who discontinued from previous MEDI-545 clinical studies for safety reasons. Patients must complete the treatment period and follow up through study Day 266 of this study to participate in MI-CP212. Patients will be considered terminated from this study upon signing the MI-CP212 informed consent form between study Day 266 and Day 350. If possible, patients should complete the Study Day 350 evaluations on their last study visit. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

Reason for addition: Define criteria for patient early termination in MI-CP152 study for enrollment into MI-CP212 study.

10. Section 4.6

Changed to read:

The MedImmune Medical Monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes immediate review of SAEs and timely review of other AEs reported during the study. The MedImmune Product

Safety Monitor has responsibility for the receipt, review, investigation, and follow-up of SAEs reported by the clinical study sites.

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

~~The MedImmune Medical Monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes immediate review of SAEs and timely review of other AEs reported during the study. The MedImmune Product Safety Monitor has responsibility for the day-to-day safety monitoring of the study, including the receipt, review, investigation, and follow-up of AEs and SAEs reported by the clinical study sites.~~

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

Reason for change: Clarify medical monitor and Safety Monitoring Committee responsibilities.

11. Section 4.7

Changed to read:

An individual patient will not receive any further study drug dosing if any of the following occur in the patient in question:

1. Withdrawal of consent;
2. Pregnancy;
3. Any life-threatening clinical event related to the study drug;
4. Severe hypersensitivity reaction (anaphylaxis) to the study drug, Grade 3 or higher;
5. Infusion reactions, Grade 3 or higher as defined in Table 2;
6. Serious clinical infections with a virus of the herpes family (including disseminated herpes infection, herpes encephalitis, or ophthalmic herpes infection) or with CMV or EBV; ~~or~~
7. **If 3 consecutive doses of study drug are missed due to abnormal LFTs (ALT, AST).**
8. **Two consecutive total bilirubin values taken at least 1 week apart > 2 x ULN not due to Gilbert's syndrome or hemolysis; or**

~~7.~~9. Any event ~~which~~ **that**, in the opinion of the investigator or the Medical Monitor, contraindicates further dosing such as illnesses or complications.

Patients who are permanently discontinued from study drug ~~dosing~~ **for any of these reasons, with the exception of withdrawal of consent,** will be followed for the full **follow-up** ~~study~~ period (through Study Day 350), including the collection of any mandated blood and urine specimens.

Reason for change: Increase patient safety.

12. Section 4.8

Changed to read:

1. ~~Death of any patient.~~**Death of any patient in which the cause is determined by the investigator or the sponsor to be related to study drug; or death of any patient which, in the opinion of the sponsor, contraindicates further dosing**

Reason for change: Clarification of death circumstances in regards to interruption of study dosing and randomization.

13. Section 5.1

Changed to read:

All data will be provided in data listings sorted by treatment group and patient number. All tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized by descriptive statistics including mean, standard deviation, median, minimum, and maximum. ~~Study Day 0~~ **Baseline values** will be defined as the ~~day of~~ last valid assessment prior to **the** first **administration of** study drug ~~administration~~. All data will be collected from Study Day 0 through Study Day 350.

Reason for change: Clarification of study baseline.

14. Section 5.3

Changed to read:

There will be 2 patient populations analyzed in this study. The primary patient population will include up to 164 new patients who receive study drug (excluding patients who received study drug prior to 10/Oct/2007). The secondary patient population will include the 22 patients who received study drug prior to 10/Oct/2007.

Efficacy data will be analyzed primarily based on the **modified** Intent-to-Treat Population including all randomized patients **who receive any study drug.** Safety and IM will be

analyzed in all patients who receive any study drug. Evaluability for analyses of MEDI-545 serum concentrations will be determined based upon the frequency and timing of the serum samples obtained.

Reason for change: Clarification of efficacy data analysis population.

15. Section 5.7

Changed to read:

- When ~~all~~ **at minimum 39** patients in Dose Cohort 4 complete Study Day 84~~and~~
- When all patients in Dose Cohort 4 complete Study Day 196.

Reason for change: Updated to reflect analyses conducted.

16. Section 10

Added:

Summary of Changes from Version 5.0 to Version 6.0 of the Study Protocol

Version 5.0 of the protocol (dated [redacted]) was amended to Version 6.0 (dated [redacted]). The major changes include: changing the medical monitor; updating the clinical experience with MEDI-545; including the option for patients to enter the long-term study MI-CP212; adding toxicity management guidelines for blood chemistry abnormalities; clarifying medical monitor and Safety Monitoring Committee responsibilities; including 2 additional conditions in which dosing should be discontinued; clarifying the circumstance of patient death as it applies to interruption of study dosing and randomization (ie, death of any subject which, in the opinion of the sponsor, contraindicates further dosing); changing the number of study sites from 40 to 50 to 30 to 40; changing the third interim analysis (which was to occur after all patients in Dose Cohort 4 completed Day 84) to when a minimum of 39 patients in Dose Cohort 4 complete Study Day 84; and providing guidance in Appendix C for the management of abnormal LFTs. Some of these changes occur in multiple places in the protocol including the Study Abstract, when applicable. Changes to the protocol are described in Appendix D.

Reason for addition: Update to summary of changes

17. Appendix C

Added:

Appendix C Guidance for Abnormal Liver Function Tests Management

This guidance is based on the October 2007 Draft Guidance of Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation.

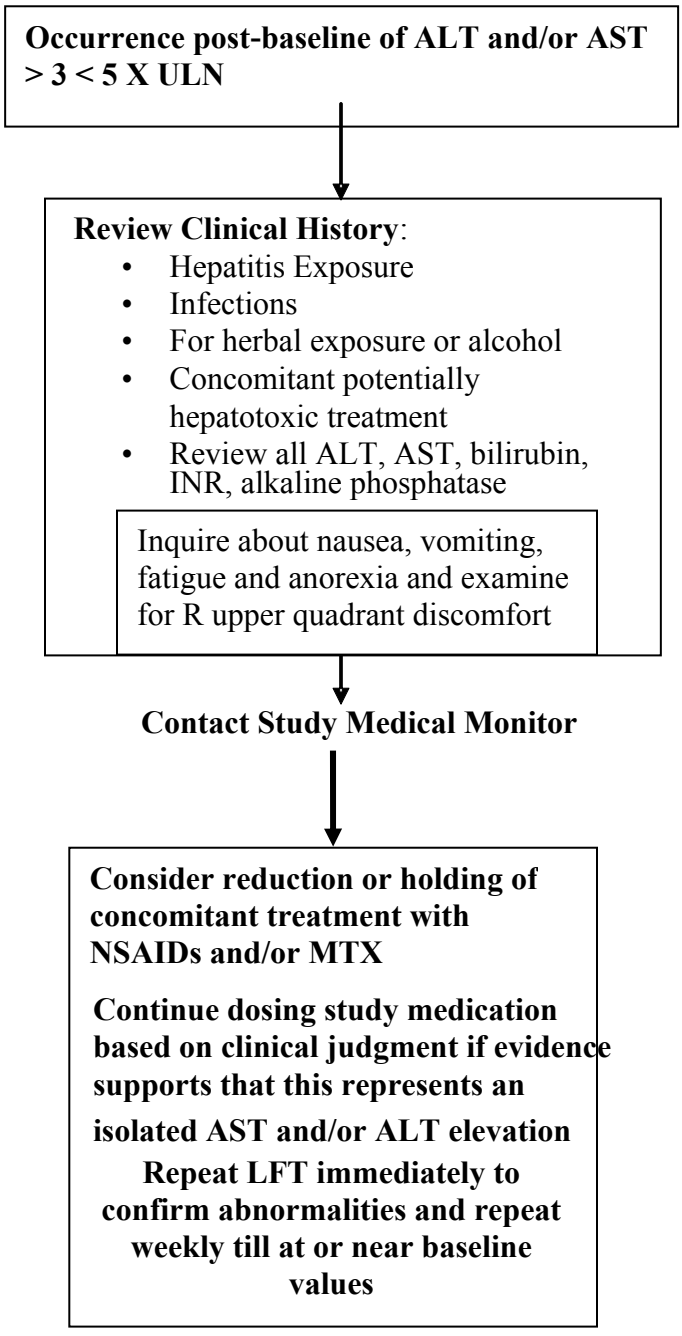
Section IV of the FDA document deals with the clinical evaluation of and monitoring of drug-induced liver injury, and this protocol-specific guidance has adopted the draft recommendations on detection of drug-induced liver disease, confirmation of abnormal ALT/AST with regard to retesting, follow-up observation, advice on appropriate history gathering and advice on the need for obtaining additional laboratory tests and consultations as needed. We have adopted a conservative approach to holding administration of study drug based on abnormal 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 study drug permanently. The 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-545 as well as input from the principle 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 study drug 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.

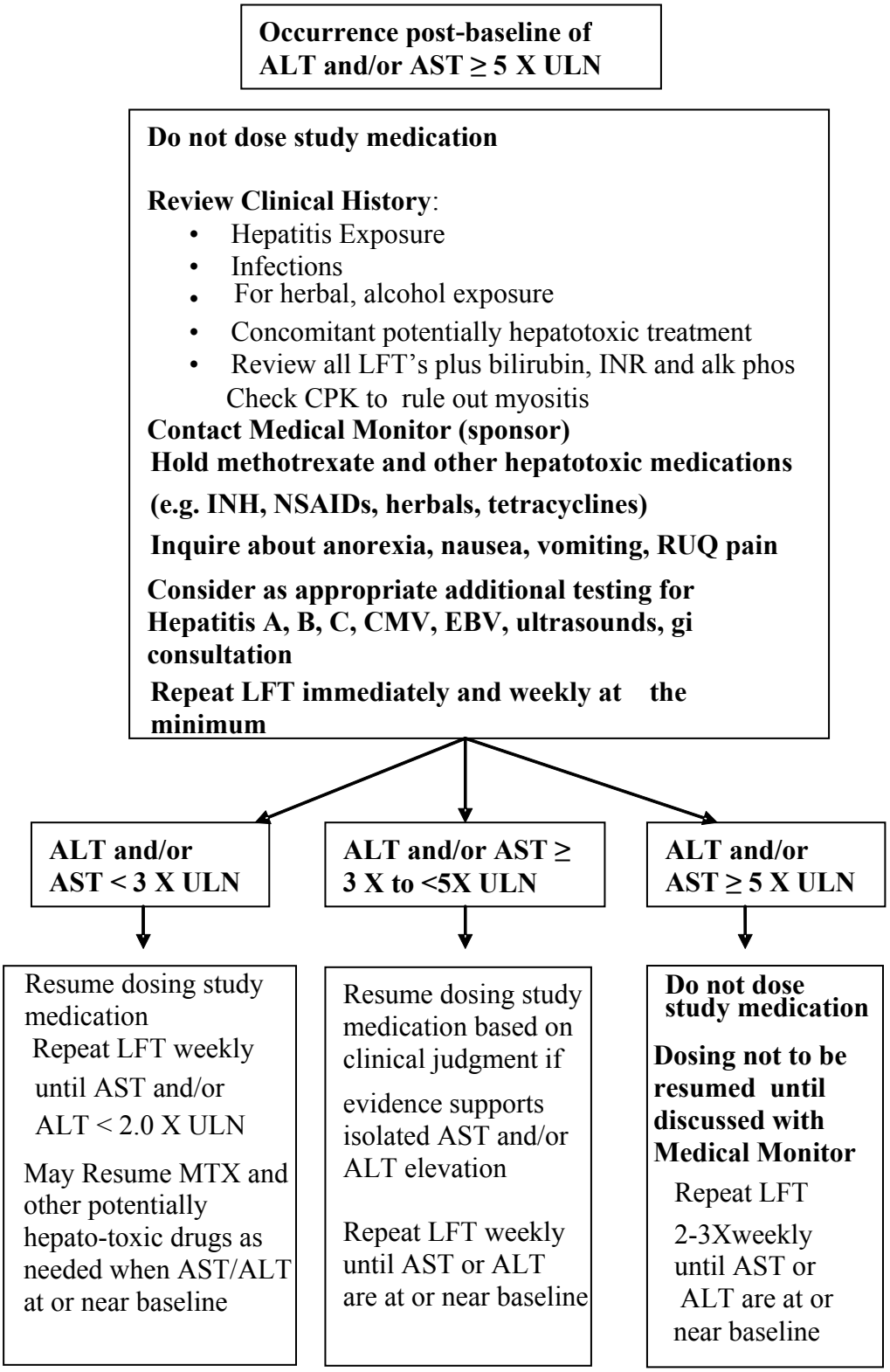
For the purpose of this document, LFTs will be AST, ALT, total bilirubin, and alkaline phosphatase.

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

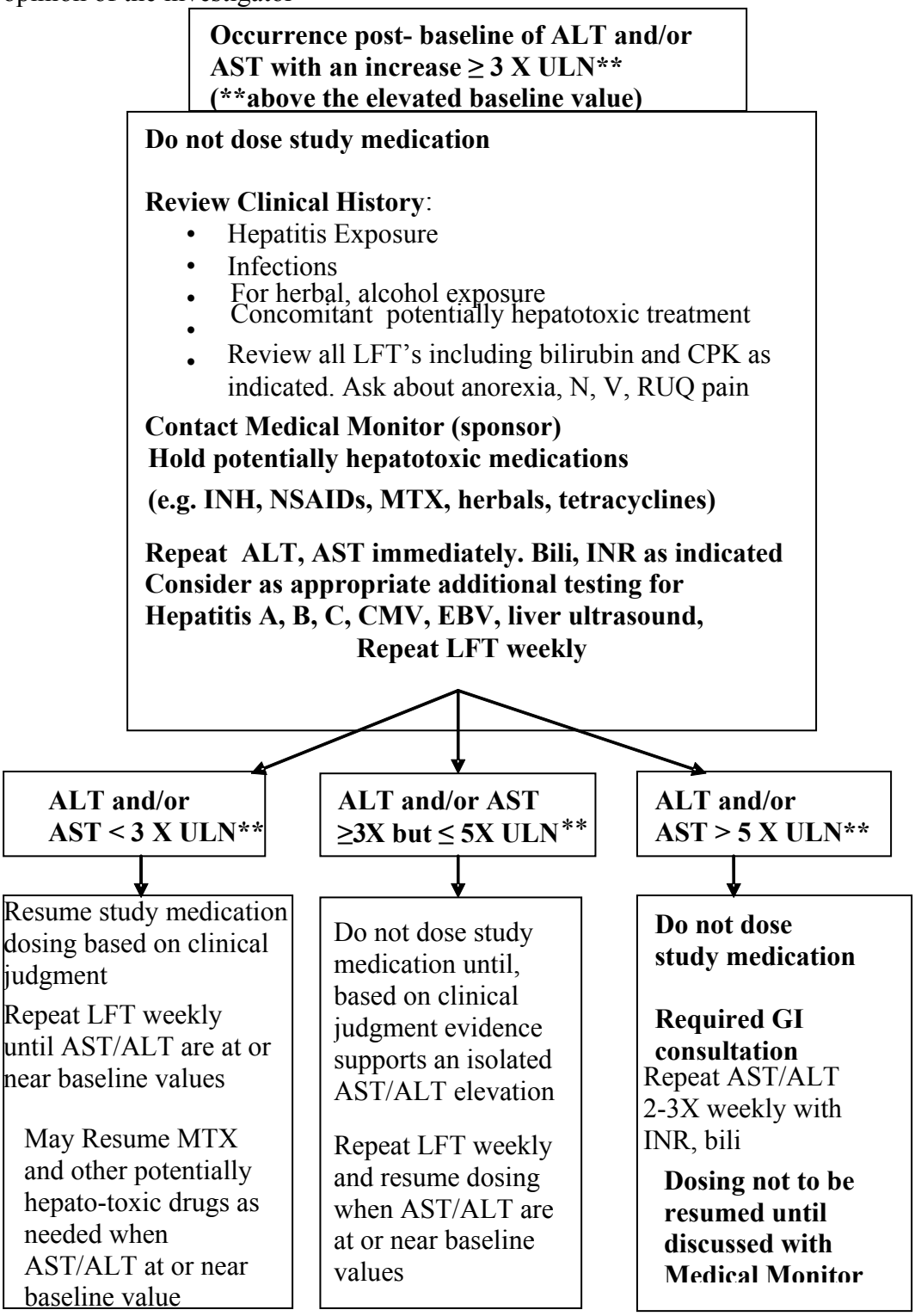
Copies of the document “Draft Guidance of Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation” can be located at http://www.fda.gov/cder/guidance/index/index.htm.

Guidance for abnormal Liver Function Tests during Study 152 or 179 that develop post-baseline in individuals with ALT or AST ≤2X ULN at baseline due to liver involvement by SLE in the opinion of the investigator.




Occurrence post-baseline of ALT and/or AST ≥ 5 X ULN
Do not dose study medication
Review Clinical History:
• Hepatitis Exposure
• Infections
• For herbal, alcohol exposure
• Concomitant potentially hepatotoxic treatment
• Review all LFT's plus bilirubin, INR and alk phos
Check CPK to rule out myositis
Contact Medical Monitor (sponsor)
Hold methotrexate and other hepatotoxic medications
(e.g. INH, NSAIDs, herbals, tetracyclines)
Inquire about anorexia, nausea, vomiting, RUQ pain
Consider as appropriate additional testing for Hepatitis A, B, C, CMV, EBV, ultrasounds, gi consultation
Repeat LFT immediately and weekly at the minimum
ALT and/or AST < 3 X ULN
ALT and/or AST ≥ 3 X to <5X ULN
ALT and/or AST ≥ 5 X ULN
Resume dosing study medication
Repeat LFT weekly until AST and/or ALT < 2.0 X ULN
May Resume MTX and other potentially hepato-toxic drugs as needed when AST/ALT at or near baseline
Resume dosing study medication based on clinical judgment if
evidence supports isolated AST and/or ALT elevation
Repeat LFT weekly until AST or ALT are at or near baseline
Do not dose study medication
Dosing not to be resumed until discussed with Medical Monitor
Repeat LFT
2-3Xweekly until AST or ALT are at or near baseline

Guidance for abnormal Liver Function Tests during Study 152 or 179 that develop post-baseline in individuals with ALT or AST > 2X ULN at baseline due to liver involvement by SLE in the opinion of the investigator



Reason for addition: To provide guidance for the management of abnormal LFTs.

ATTACHMENT 1 Toxicity Table

National Cancer Institute's Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE V3.0)

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

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

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever). ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death

ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis.						
ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death