A PHASE 1B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE SAFETY OF MULTIPLE-DOSE, INTRAVENOUSLY ADMINISTERED MEDI-545, A FULLY HUMAN ANTI-INTERFERON-ALPHA MONOCLONAL ANTIBODY, IN ADULT PATIENTS WITH DERMATOMYOSITIS OR POLYMYOSITIS

Study Agent: MEDI-545

MedImmune Protocol Number: MI-CP151

IND Number: IND 12751

Manufacturer: MedImmune
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Phone: [redacted]
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Sponsor: MedImmune

Medical Monitor: [redacted]
MedImmune
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Study Monitor: MedImmune

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

Signature_____ Date_____

Printed Name_____

[redacted]

LIST OF ABBREVIATIONS

βHCG	Beta human chorionic gonadotropin
λz	Terminal phase elimination rate constant
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANOVA	Analysis of variance
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
BUN	Blood urea nitrogen
C_{max}	Peak concentration
$C_{ss, max}$	Peak concentration within a dosing interval at steady state
$C_{ss, min}$	Trough concentration at steady state
CBC	Complete blood count
CDASI	Cutaneous dermatomyositis Disease Area and Severity Index
CK	Creatine kinase
CL_{ss}	Total body clearance at steady state
CLIA	Clinical Laboratory Improvement Amendments
CMV	Cytomegalovirus
CTMM	Clinical Trial Material Manager
DC	Dendritic cells
DLCO	Diffusion capacity for carbon monoxide
DM	Dermatomyositis
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECLA	Electrochemiluminescent assay
GLP	Good laboratory practice
CLINHAQ	Clinical Health Assessment Questionnaire
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HSV	Herpes simplex virus
IBM	Inclusion body myositis
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Institutional ethics committee
IFN	Interferon

[redacted]

Ig	Immunoglobulin
IgG1κ	Immunoglobulin G1 kappa
IHC	Immunohistochemical
IIM	Idiopathic inflammatory myopathies
IL	Interleukin
IM	Immunogenicity
IMACS	International Myositis Assessment and Clinical Studies
IND	Investigational new drug application
IRB	Institutional review board
IV	Intravenous
IVP	Intravenous Push
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
LFT	Liver function test
MAb	Monoclonal antibody
MDAAT	Myositis Disease Activity Assessment Tool
mDC	Myeloid dendritic cells
MDI	Myositis Damage Index
MHC	Major histocompatibility complex
mRNA	Messenger ribonucleic acid
MMT	Manual Muscle Test
MRT	Mean residence time
NCI CTCAE V3.0	National Cancer Institute's Common Terminology Criteria for Adverse Events Version 3.0
NK	Natural killer
OBGYN	Obstetrician/gynecologist
NOAEL	No-observable-adverse-effect level
PCR	Polymerase chain reaction
pDC	Plasmacytoid dendritic cells
PID	Patient identification number
PK	Pharmacokinetic(s)
PM	Polymyositis
RNA	Ribonucleic acid
RNP	Ribonucleoprotein
SAE	Serious adverse events
SF-36	Short Form 36 Health Survey
SLE	Systemic lupus erythematosus
SMC	Safety Monitoring Committee
SRP	Signal recognition particle
SSA	Sjögren’s Syndrome A

[redacted]

$T_{1/2}$	Terminal phase half-life
T_{max}	Time to peak concentration
$T_{ss, max}$	Time to peak concentration at steady state
TB	Tuberculosis
TCR	T cell receptor
TLR	Toll-like receptor
ULN	Upper limit of normal
VAS	Visual analog scale
Vd_{ss}	Steady state volume of distribution
Vdz	Terminal phase volume of distribution
WPAI: SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

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STUDY ABSTRACT

TITLE:

A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety of Multiple-Dose, Intravenously Administered MEDI-545, a Fully Human Anti-Interferon-Alpha Monoclonal Antibody, in Adult Patients with Dermatomyositis or Polymyositis

OBJECTIVES:

The primary objective of the study is to evaluate the safety and tolerability of multiple intravenous (IV) doses of MEDI-545 in adult patients with dermatomyositis (DM) or polymyositis (PM).

The secondary objective of the study is to assess the pharmacokinetics (PK) and immunogenicity (IM) of MEDI-545 in this patient population.

The exploratory objectives of the study are to:

1. Assess evidence of clinical activity and patient-reported outcomes of MEDI-545 in this patient population;
2. Assess the effects of MEDI-545 on levels of expression of type I IFN-inducible genes and proteins in the blood, skin, and muscle of patients with DM or PM and on levels of type I interferon (IFN) messenger ribonucleic acids (mRNAs) and proteins and other pharmacodynamic markers in blood and tissue samples in patients who have a median fold overexpression of the top 25 type I IFN inducible genes of 4-fold or greater in whole blood or muscle, compared to normals;
3. Assess the effect of MEDI-545 on cellular and tissue components using methods such as microarray analyses of blood, skin, and muscle; histologic and immunohistochemical (IHC) analyses of involved tissues; testing lymphocyte and dendritic cell subset in peripheral blood; testing autoantibody patterns and levels; and proteomic analyses; and
4. Explore the genetic variations in the patient population using single-nucleotide-polymorphism array profiling of whole blood DNA, if such analyses are warranted based on other exploratory analyses in this patient population.

DESIGN:

The study 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 DM or PM who have low/undetectable or high level of expression of mRNA for type I IFN-inducible genes in whole blood or muscle at the time of screening. Approximately 20 investigative sites in the United States of America (USA) will participate in the study. A total of 32 evaluable patients with high level of expression of mRNA for type I IFN-inducible genes (ie, gene signature positive) will be randomized in a 3:1 ratio to initially receive MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo every 2 weeks for 12 weeks for a total of 7 doses. An additional cohort (Dose Cohort 3B) of 8 evaluable patients with low/undetectable expression of type I IFN-inducible genes (ie, gene signature negative) will be randomized in a 3:1 ratio to initially receive MEDI-545 (3.0 mg/kg) or placebo every 2 weeks for 12 weeks for a total of 7 doses, with 6 patients receiving MEDI-545 and 2 patients receiving placebo. In each dose cohort, 6 patients

will receive MEDI-545 and 2 patients will receive placebo. Thereafter (2 weeks after the 7th dose), in each of the 5 dose cohorts, patients randomized to MEDI-545 will continue to receive the same dose of MEDI-545 over an additional 12 weeks (7 doses) and patients randomized to placebo will receive MEDI-545, at the dose specified in the dose cohort, every 2 weeks for an additional 12 weeks (7 doses) for a total of 26 weeks (14 doses).

All patients should receive their usual medications in unchanged doses during the entire treatment period. If a patient clinically deteriorates in the judgment of the investigator the investigator is permitted to add new or increase existing immunosuppressive medications, as long as no prohibited medications are added. Concurrent immunosuppressive therapy may be tapered and discontinued, according to the investigator's judgment, during the follow-up period.

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 at any time for safety reasons. Nonevaluable patients may be replaced to maintain a size of at least 8 patients per dose cohort. Data from all patients will be included in safety analyses. A dose cohort may be expanded by up to 4 additional patients (for a maximum of 20 additional patients in total) if eligible patients are in screening at the time 8 patients have been randomized into the dose cohort.

Study drug administration will start on Study Day 0 and continue through Study Day 182. At the end of the treatment period, patients will be followed for 24 weeks, through Study Day 350. Safety parameters including assessments of adverse events (AEs) and serious adverse events (SAEs) will be assessed at every study visit from the signing of informed consent through Study Day 350. The occurrence of treatment-emergent AEs and SAEs will be summarized from the first administration of study drug through Study Day 350. Disease activity will be assessed throughout the treatment period and during follow-up.

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 8 evaluable patients in each of the preceding lower dose cohorts.

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, 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 the study must be adults with probable or definite DM or PM according to the Bohan and Peter criteria (Bohan, 1975) and have active disease. Patients will either have low/undetectable or high level of expression of mRNA for type I IFN-inducible genes in whole blood or muscle at the time of screening. High level of expression, defined as a median fold

[redacted]

overexpression of the top 25 type I IFN inducible genes of 4-fold or greater, is referred to as gene signature positive, and low/undetectable level of expression is defined as gene signature negative.

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 or administration of study drug.

TREATMENT:

A total of 40 evaluable patients will participate in this study. A total of 32 evaluable patients with positive gene signature will be randomized in a 3:1 ratio to initially receive MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo using an infusion time of at least 60 minutes every 2 weeks for 12 weeks for a total of 7 doses. An additional cohort of 8 evaluable patients (Dose Cohort 3B) with negative gene signature will be randomized in a 3:1 ratio to initially receive MEDI-545 (3.0 mg/kg) or placebo every 2 weeks for 12 weeks for a total of 7 doses, with 6 patients receiving MEDI-545 and 2 patients receiving placebo. In each dose cohort, 6 patients will receive MEDI-545 and 2 patients will receive placebo. Thereafter (2 weeks after the 7th dose), in each of the 5 dose cohorts, patients randomized to MEDI-545 will continue to receive the same dose of MEDI-545 every 2 weeks for an additional 12 weeks (7 doses) and patients randomized to placebo will receive MEDI-545, at the dose specified in the dose cohort they are assigned, every 2 weeks for an additional 12 weeks (7 doses) for a total of 26 weeks (14 doses). MEDI-545 or placebo will be administered IV using an infusion pump over a period of at least 60 minutes.

PATIENT EVALUATION AND FOLLOW-UP:

Screening evaluations include the following: medical history; physical examination; 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); ECG; tuberculosis (TB) skin test; blood tests for hepatitis A, B, C, human immunodeficiency virus (HIV)-1 and HIV-2; serum β human chorionic gonadotropin (βHCG) for women (unless surgically sterile or 2 years after menopause); vital signs; serum chemistry (including Na, K, Cl, bicarbonate, blood urea nitrogen [BUN], creatinine, bilirubin, alkaline phosphatase, and random glucose); complete blood count (CBC) with differential and platelets; serum levels of muscle enzyme (including CK, aldolase, LDH, ALT, and AST); urinalysis; manual muscle testing (MMT); extramuscular activity assessment based on Myositis Disease Activity Assessment Tool (MDAAT); pulmonary function tests; physician global activity assessment; and clinical Health Assessment Questionnaire (CLINHAQ).

Safety assessments include AE and SAE evaluation, physical examination, vital signs, serum chemistry panel, CBC with differential and platelets, urinalysis, 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), and viral surveillance testing via oropharyngeal swabs for herpes simplex virus (HSV)-1 and HSV-2; vaginal swabs (women) for HSV-1, HSV-2, and human papillomavirus (HPV); blood tests for Epstein Barr virus (EBV) and cytomegalovirus (CMV).

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

Disease activity assessments, patient-reported outcomes, and exploratory analyses will be conducted using the following evaluations: serum levels of muscle enzymes (CK, aldolase, LDH, ALT, and AST), MMT, extramuscular activity assessment based on MDAAT scales, pulmonary function tests, physician global activity assessment, CLINHAQ (including patient global activity assessment), Myositis Damage Index, Short Form 36 Health Survey version 2 (SF-36v2™), Work Productivity and Activity Impairment Questionnaire: Specific Health Problem version 2.0 (WPAI: SHP), Cutaneous DM Disease Area and Severity Index (CDASI, DM patients only), pruritus VAS (DM patients only), Dermatology Life Quality Index (DLQI, DM patients only), skin photography (optional, DM patients only), blood samples for autoantibodies, exploratory research and storage, type I IFN gene expression, lymphocyte subset analysis using flow cytometry, muscle biopsies, and skin biopsies (optional, DM patients only). A whole blood sample for DNA analysis is obtained (optional).

ASSESSMENT OF ENDPOINTS:

The primary endpoints of the study are the safety and tolerability of MEDI-545, which 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 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 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. 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.

PK parameters after the first dose and at steady state will be estimated by non-compartmental analysis. MEDI-545 IM will be analyzed by summarizing the number and percentage of PM/DM patients who develop detectable anti-MEDI-545 antibodies by treatment and dose cohort.

The major clinical measures of myositis disease activity will include serum creatine kinase normalization, IMACS core set disease activity measures (physician's global activity assessment, patient global activity assessment, muscle strength assessed by MMT, physical function, muscle-associated enzymes, and extramuscular activity assessment), patients' need for new or increased doses of immunosuppressive therapy, changes in patients' immunosuppressive therapy during the follow-up period, photography of skin lesions, and pulmonary function testing. These assessments will be summarized descriptively by treatment group and time point.

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The biological activity and mechanism of action of MEDI-545 will be summarized descriptively by assessment.

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1 INTRODUCTION

1.1 Background

Idiopathic inflammatory myopathies (IIMs) are a group of rare, acquired, autoimmune diseases characterized by a chronic inflammatory infiltrate of the skeletal muscle that causes weakness (Rider, 2000; Dalakas 2003; Christopher-Stine, 2004; Dorph, 2002; Rider, 2004; Dalakas, 2006). On the basis of clinical, immunopathologic and demographic features, three major diseases can be identified: dermatomyositis (DM); polymyositis (PM); and inclusion body myositis (IBM) (Briani, 2006; Dalakas, 2006; Dalakas 2003; Rider, 2000; Dorph, 2002). The etiologies of these diseases are unknown, and their pathogenesis involves chronic immune activation in genetically susceptible individuals, possibly following exposure to environmental triggers (Plotz, 1995). IIMs, especially DM, are associated with malignancies (Dalakas, 2003; Lynn, 2005; Christopher-Stine, 2004). Type I interferons (IFNs) appear to be a part of the immunopathogenesis of each of these three diseases (Isenberg, 1986; Uzel, 2003; Crow, 2003; Greenberg, 2005; Greenberg, 2007; O'Connor, 2006; Wenzel, 2006).

Epidemiologic studies indicate peak onset in DM and PM in childhood (5-15 years) and midlife (30-50 years), whereas IBM peaks after age 50 years (Dalakas, 2003). Women are preferentially affected (about 3:1 ratio) in all forms of IIM, except IBM in which the female:male ratio is reversed, about 1:3. Genetic risk factors for IIM include certain human leukocyte antigen (HLA), cytokine and immunoglobulin (Ig) gene polymorphisms (O'Hanlon, 2005). Possible environmental triggers have been suggested (Plotz, 1995). The incidence of DM/PM is about 7-20 cases per million per year (Koh, 1993; Cherin, 2003a; Lynn, 2005). All forms of myositis (DM, PM, and IBM) affect about a total of 50,000 people in the United States (The Myositis Organization, www.myositis.org).

The diagnosis of DM is based on typical clinical presentation with progressive symmetrical proximal muscle weakness and pain, consistent skin lesions, and laboratory tests confirming inflammatory muscle disease. The skin lesions of DM can include a heliotrope rash (blue-purple discoloration) on the upper eyelids; a generalized flat red rash on the face, knees, elbows, malleoli, neck, anterior chest, back, and shoulders; a raised, violaceous, scaly eruption (Gottron's rash) at the knuckles; linear extensor erythema; subcutaneous calcifications; and severe vasculitis (Dalakas, 2006; Dalakas, 2003; Callen, 2006). Besides skin involvement, extramuscular manifestations of DM include constitutional symptoms (fever, fatigue, anorexia and weight loss), Raynaud's phenomenon, joint involvement, interstitial lung disease, and gastrointestinal involvement. Serum levels of sarcoplasmic enzymes are elevated, including creatine kinase (CK), aldolase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT) or aspartate aminotransferase (AST). Electromyographic abnormalities reflect inflammatory myopathy with sharp waves, fibrillations, polyphasic motor units and high frequency discharges. Muscle biopsies may show mononuclear cell infiltration, vascular endothelial thickening and inflammation, myofiber degeneration and regeneration with variation in muscle fiber size, and perifascicular atrophy.

The clinical presentation of PM is similar to that of DM except the presence of rashes (Dalakas, 2003). The presence of Gottron's papules or heliotrope rash alone is sufficient to distinguish

DM from PM (Oddis, 2005). Extramuscular manifestations are common in PM and similar to those seen in DM.

Previous studies of the immunopathogenesis of IIM have focused on adaptive immunity, with antigen-driven autoreactive T-cell and B-cell activation. Several lines of indirect evidence imply that autoreactive T cells play a central role in disease pathogenesis in myositis (Plotz, 1995). Increased proportions of lymphocytes expressing activation markers are detectable in the peripheral blood of patients with clinically active disease (Miller, 1990). Patients' peripheral blood mononuclear cells traffic to muscle in vivo (Miller, 1988) and show increased proliferative responses to autologous muscle in vitro (Holfield, 1991).

More recently, new focus has been placed on the potential contributions of innate immunity to IIM, with an immunopathogenesis characterized by plasmacytoid dendritic cell (pDC) infiltration, IFN-α/β inducible gene and protein expression, and direct injury to myofiber and capillaries by type 1 interferon-inducible proteins in DM (Greenberg, 2005). Another potential mechanism of tissue damage in PM and IBM may include subsequent maturation of myeloid dendritic cells (mDC), with loss of tolerance and expansion of autoreactive T and B cells. This new focus is based on new appreciation of the potential role of type I IFNs in the immunopathogenesis of IIM.

IFN-α subtypes are cytokines that belong to the type I IFN family, which includes α, β, ε, κ, and ω and are expressed from 13 functional IFN-α genes, one IFN-β gene, one IFN-ε gene, one IFN-κ gene, and one IFN-ω gene (Theofilopoulos, 2005). Type I IFNs are known to inhibit viral replication and contribute to immune system regulation (Belardelli, 1996; Theofilopoulos, 2005). Various types of cells including monocytes, macrophages, dendritic cells (DCs), lymphocytes, and other hematological cells, produce type I IFNs in response to pro-inflammatory cytokines and components of various pathogens.

Multiple cell types respond to type I IFN, leading to increased expression of immunologically important molecules such as major histocompatibility complex (MHC) class I, CD38, interleukins (BLyS, IL-6, IL-10 and IL-15), and chemokines (IL-8, MCP-1, MCP-2, MIG, MIP1α, MIP1β, and IP10) (Biron, 2001; Pogue, 2004; Salazar-Mather, 2003; Bussfeld, 2000; Asselin, 2001). Moreover, type I IFNs induce multiple biological functions in key components of the immune system including dendritic, T, B, and natural killer (NK) cells. For example, type I IFNs promote DC maturation, loss of tolerance, memory $CD8^+$ T cell proliferation, inhibition of $CD4^+$ T cell apoptosis, NK cell activation, and B cell differentiation (Banchereau, 2004; Taki, 2002; Mailliard, 2003).

Banchereau and Pascual (2006) have suggested that increased bioavailability of type I IFN contributes to peripheral tolerance breakdown through the activation of immature mDCs. Interferon induces the unabated activation of mDCs which select and activate autoreactive T cells rather than deleting them, thus failing to induce peripheral tolerance. These mDCs together with pDCs, help expand autoreactive B cells. Interferon-matured DCs also activate cytotoxic CD8+ T cells, possibly increasing apoptotic cell availability. The capture of apoptotic cells by mDCs and of nucleic acid-containing immune complexes by plasmacytoid DCs and B cells,

through binding to Toll-like receptors (TLRs) and FcγR, can amplify the autoimmune reaction leading to disease manifestations.

Type I IFNs appear to be a part of the immunopathogenesis of all three forms of IIM (Isenberg, 1986; Uzel, 2003; Crow, 2003; Greenberg, 2005; Greenberg, 2007; O'Connor, 2006; Wenzel, 2006) as summarized below:

- pDC, potent CD4+ cellular sources of type I IFN (Jego, 2003), are present in substantial numbers in muscle in DM and may account for most of the cells previously identified as CD4+ T helper cells (Greenberg, 2005). pDC appear to be an important source of type I IFNs in DM (Greenberg, 2005; Wenzel, 2006);
- Type I IFN is increased in muscle of patients with PM and is co-localized with infiltrating leukocytes and areas of increased expression of HLA Class I molecules on the sarcolemma, leading to hypothesis that IFNs are released by inflammatory infiltrates and induce increased MHC class I antigen expression (Isenberg, 1986). Perifascicular fibers express MHC class I antigens and various markers of regeneration, degeneration, or cytokine activation. Some of these markers are induced by IFN-α, β, or γ, indicating a stressor effect and local inflammatory response (Dalakas, 2006a);
- Expression of type I IFN inducible genes and proteins are increased in the blood and tissues of patients with IIM (O'Connor, 2006; Wenzel, 2006; Crow, 2003; Uzel, 2003; Greenberg, 2005; Tian, 2005);
- Expression of the type I IFN inducible protein myxovirus resistance protein A (MxA) in muscle is increased on perifascicular, and, sometimes all myofibers and on capillaries in DM patients (Greenberg, 2005). MxA expression is closely associated with expression of the IFN-inducible protein IP10/CXCL10 and the recruitment of CXCR3+ cells in DM (Wenzel, 2006);
- mDCs, whose differentiation from precursor cells is stimulated by type I IFNs (Banchereau, 2004), are present in substantial numbers in IBM and PM, frequently surrounded and sometimes invading otherwise intact myofibers (Greenberg, 2007). Dermatomyositis muscle has more pDCs than mDCs, whereas IBM and PM have greater numbers of mDCs. The stellate morphology of mDCs in dense collections of cells that include T cells suggests local intramuscular antigen presentation in IBM and PM (Greenberg, 2007);
- Only mDCs promote T cell proliferative responses to a unique amino-terminal fragment of the myositis-specific autoantigen Jo-1 (Ascherman, 2002);
- Gene expression profile data in juvenile DM patients with DQA1*0501 (present in 85% of patients) compared with age-matched control subjects show that the initial immune response is a type I IFN-induced cascade with secondary stimulation of IFN-γ (Uzel, 2003);
- Expression of type I IFN inducible gene MxA in peripheral blood mononuclear cells is associated with muscle involvement and increased disease activity in DM (O'Connor, 2006; Wenzel, 2006); and
- Patients who are treated with type I IFNs for other diseases can develop IIM (Falcone, 1998; Cirigliano, 1999; Hengstman, 2000; Dietrich, 2000; Lee, 2003; Venezia, 2005). The product label for recombinant IFN-α includes a black box warning for its use in patients with myositis (Product label).

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Therapy of IIM consists of immunosuppressives to decrease tissue inflammation and rehabilitation to strengthen remaining muscles (Plotz, 1995). Corticosteroids are the mainstay of treatment of DM and PM (Choy, 2005). Methotrexate, azathioprine and other immunosuppressives may be effective particularly if used early in DM and PM patients. However, chronic use of the aforementioned therapies is associated with a high side effect profile, and many remain refractory to treatment. Consequently, the discovery of novel therapeutic agents that are safe and effective for IIM is highly desirable.

The role of type I IFNs in IIM immunopathogenesis indicates that neutralization of type I IFNs may have an effect on disease mechanism and lead to potential treatment for IIM.

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 (PK) and immunogenicity (IM) 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

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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 6-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 MEDI-545 (0, 10 mg/kg, 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 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.

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).

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

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microscopic pathology data. Immunogenicity assay results found no anti-MEDI-545 antibody detected at any time point for any animal. There were no treatment-related effects in any of the 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 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. 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 one-to-one 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 humans are unknown. Theoretically, blockade of most subtypes of IFN-α could potentially impair host responses to viral infections. 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 myositis. As such, the most appropriate way to evaluate effect of MEDI-545 on viral infections is by careful clinical monitoring in humans.

Further details of the 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, and 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 study of MEDI-545 was a Phase 1, multicenter, randomized, double-blind, placebo-controlled, dose-escalation study with an open-label extension that evaluated the safety and tolerability of single IV doses of MEDI-545 ranging from 0.3 to 30 mg/kg in patients with SLE who were receiving 20 mg/day or less of prednisone orally or an equivalent dose of another oral corticosteroid (MI-CP126). As in IIM, type I IFN-α plays a role in the pathogenesis of SLE. Elevated levels of IFN-α in SLE was demonstrated more than 20 years ago and correlates with disease activity and severity (Hooks, 1979; Preble, 1982; Ytterberg, 1982; Bengtsson, 2000; Kirou, 2005). More recently, other studies have demonstrated the presence of type I IFN gene

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signatures in the blood and tissues of patients with SLE (Baechler, 2003; Bennett, 2003; Crow, 2003; Dall'era, 2005).

In MI-CP126, 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 effects were 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 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. Single-dose PK of MEDI-545 were similar between psoriasis and SLE patients. A total of 36 patients received study drug in this study. This study

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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, at least 0.75 mg/min. 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-CP152, is a Phase 1b, multicenter, multinational, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3 to 10.0 mg/kg) in adult subjects with SLE. In this study, MEDI-545 is administered every 2 weeks for a total of 14 doses over 26 weeks. The 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 27 weeks). The first 12 randomized subjects in each dose cohort provide safety data for dose escalation; the additional

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subjects 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 subjects for exploratory analyses of effect of MEDI-545 on the inhibition of type I IFN gene signature. On 28/Sep/2007, 1 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, ≥ 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 infusion reactions in each study were most likely due to MEDI-545 administered at a high rate of infusion (≥ 0.75 mg/min), 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 mg/kg to 10 mg/kg, and set the infusion volume and time to 100 mL and at least 60 minutes.

As of [redacted], 183 patients have been dosed in the MI-CP152 study. 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-545may 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) will be 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;

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(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 [redacted], 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.
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.

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

1.5 Rationale for Study

IIMs are a group of rare, acquired, autoimmune diseases characterized by a chronic inflammatory infiltrate of the skeletal muscle that causes weakness. On the basis of clinical, immunopathological, and demographic features, three major diseases can be identified: DM, PM, and IBM. Type I IFNs appear to be a part of the immunopathogenesis of all three forms of IIM. Therapy of IIM consists of immunosuppressives to decrease tissue inflammation and rehabilitation to strengthen remaining muscles. Corticosteroids are the mainstay of treatment of DM and PM. Methotrexate, azathioprine and other immunosuppressives may be effective particularly if used early in DM and PM patients. However, chronic use of the aforementioned therapies is associated with a high side effect profile, and many remain refractory to treatment. Consequently, the discovery of novel therapeutic agents that are safe and effective for IIM is highly desirable.

MEDI-545 is a fully human immunoglobulin IgG1κ antibody that binds to and neutralizes a 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 has been or is being investigated in patients with SLE (MI-CP126, MI-CP152, MI-CP179), psoriasis (MI-CP145), and myositis (this study, MI-CP151). Studies MI-CP126 and MI-

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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 will be 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-CP151, is a Phase 1b, multicenter, multinational, randomized, double-blind, placebo-controlled study to evaluate the safety of multiple IV doses of MEDI-545 in adult patients with DM or PM. This is a dose-escalation study designed to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo in 32 adult patients with DM or PM who have a high level of expression of mRNA for type I IFN-inducible genes in whole blood or muscle at the time of screening. MEDI-545 or placebo will be initially administered every 2 weeks for 12 weeks (7 doses) followed 2 weeks after the 7th dose by MEDI-545 every 2 weeks for another 12 weeks (7 doses) for a total of 26 weeks (14 doses). The planned starting dose of MEDI-545 (0.3 mg/kg) in MI-CP151 is less than one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated administrations every 2 weeks for 27 weeks). This 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 possibly related to study drug.

2 STUDY OBJECTIVES AND OVERVIEW

2.1 Primary Objective

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

2.2 Secondary Objectives

The secondary objective of the study is to assess the pharmacokinetics (PK) and immunogenicity (IM) of MEDI-545 in this patient population.

2.3 Exploratory Objectives

The exploratory objectives of the study are to:

1. Assess evidence of clinical activity and patient-reported outcomes of MEDI-545 in this patient population;
2. Assess the effects of MEDI-545 on levels of expression of type I IFN-inducible genes and proteins in the blood, skin, and muscle of patients with DM or PM and on levels of type I IFN mRNAs and proteins and other pharmacodynamic markers in blood and tissue samples

in patients who have a median fold overexpression of the top 25 type I IFN inducible genes of 4-fold or greater in whole blood or muscle, compared to normals;
3. Assess the effect of MEDI-545 on cellular and tissue components using methods such as microarray analyses of blood, skin, and muscle; histologic and immunohistochemical (IHC) analyses of involved tissues; testing lymphocyte and dendritic cell subset in peripheral blood; testing autoantibody patterns and levels; and proteomic analyses; and
4. Explore the genetic variations in the patient population using single-nucleotide-polymorphism array profiling of whole blood DNA, if such analyses are warranted based on other exploratory analyses in this patient population.

2.4 Overview

2.4.1 Study Design

The study 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 DM or PM who have low/undetectable or high level of expression of mRNA for type I IFN-inducible genes in whole blood or muscle at the time of screening. Approximately 20 investigative sites in the United States of America (USA) will participate in the study. A total of 32 evaluable patients with high level of expression of mRNA for type I IFN-inducible genes (ie, gene signature positive) will be randomized in a 3:1 ratio to initially receive MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo every 2 weeks for 12 weeks for a total of 7 doses. An additional cohort (Dose Cohort 3B) of 8 evaluable patients with low/undetectable or negative expression of type I IFN-inducible genes (ie, gene signature negative) will be randomized in a 3:1 ratio to initially receive MEDI-545 (3.0 mg/kg) or placebo every 2 weeks for 12 weeks for a total of 7 doses, with 6 patients receiving MEDI-545 and 2 patients receiving placebo. In each dose cohort, 6 patients will receive MEDI-545 and 2 patients will receive placebo. Thereafter (2 weeks after the 7th dose), in each of the 5 dose cohorts, patients randomized to MEDI-545 will continue to receive the same dose of MEDI-545 over an additional 12 weeks (7 doses) and patients randomized to placebo will receive MEDI-545, at the dose specified in the dose cohort, every 2 weeks for an additional 12 weeks (7 doses) for a total of 26 weeks (14 doses).

All patients should receive their usual medications in unchanged doses during the entire treatment period. If a patient clinically deteriorates in the judgment of the investigator the investigator is permitted to add new or increase existing immunosuppressive medications, as long as no prohibited medications are added (see Section 3.4.5). Concurrent immunosuppressive therapy may be tapered and discontinued, according to the investigator's judgment, during the follow-up period.

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 at any time for safety reasons. Nonevaluable patients may be replaced to maintain a size of at least 8 patients per dose cohort. Data from all patients will be included in safety analyses. A dose cohort may be expanded by up to 4 additional patients (for a maximum of 20 additional patients in total) if eligible patients are in screening at the time 8 patients have been randomized into the dose cohort.

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Study drug administration will start on Study Day 0 and continue through Study Day 182. At the end of the treatment period, patients will be followed for 24 weeks, through Study Day 350. Safety parameters including assessments of AEs and SAEs will be assessed at every study visit from the signing of the informed consent through Study Day 350. Disease activity will be assessed throughout the treatment period and during follow-up. Patient evaluations are described in Table 4 and Table 5.

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 8 evaluable patients in each of the preceding lower dose cohorts (Section 4.9).

The study schema is described in Figure 1.

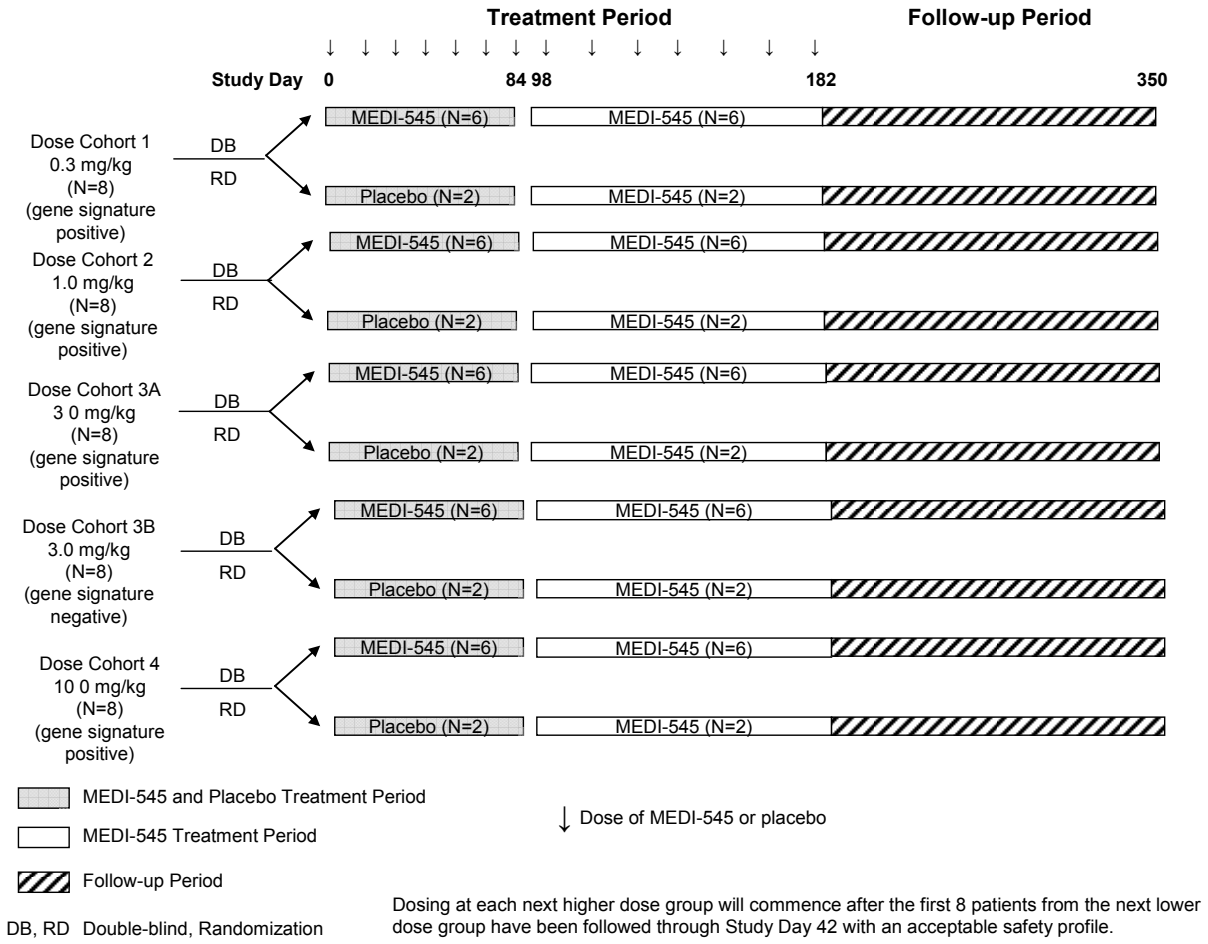

Figure 1 Study schematic

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, 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 the following: medical history; physical examination; 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); ECG; TB skin test; blood tests for hepatitis A, B, C, HIV-1 and HIV-2; serum βHCG for women (unless surgically sterile or 2 years after menopause); vital signs; serum chemistry (including Na, K, Cl, bicarbonate, BUN]creatinine,

bilirubin, alkaline phosphatase, and random glucose); CBC with differential and platelets, serum levels of muscle enzyme (including CK, aldolase, LDH, ALT, and AST); urinalysis; MMT, extramuscular activity assessment based on MDAAT, pulmonary function tests, physician global activity assessment; and CLINHAQ.

Safety assessments include AE and SAE evaluation, physical examination, vital signs, serum chemistry panel, CBC with differential and platelets, urinalysis, 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) and viral surveillance testing via oropharyngeal swabs for herpes simplex virus (HSV)-1 and HSV-2; vaginal swabs (women) for HSV-1, HSV-2, and human papillomavirus (HPV); blood tests for Epstein Barr virus (EBV) and cytomegalovirus (CMV).

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

Disease activity assessments, patient-reported outcomes, and exploratory analyses will be conducted using the following evaluations: serum levels of muscle enzymes (CK, aldolase, LDH, ALT, and AST), MMT, extramuscular activity assessment based on MDAAT scales, pulmonary function tests, physician global activity assessment, CLINHAQ (including Patient Global Activity Assessment), Myositis Damage Index, Short Form 36 Health Survey version 2 (SF-36v2™), Work Productivity and Activity Impairment Questionnaire: Specific Health Problem version 2.0 (WPAI: SHP), Cutaneous DM Disease Area and Severity Index (CDASI, DM patients only), pruritus VAS (DM patients only), Dermatology Life Quality Index (DLQI, DM patients only), skin photography (optional, DM patients only), blood samples for autoantibodies, exploratory research and storage, type I IFN gene expression, lymphocyte subset analysis using flow cytometry, muscle biopsies, and skin biopsies (optional, DM patients only). A whole blood sample for DNA analysis is obtained (optional).

3 STUDY PROCEDURES

3.1 Patient Selection

The patients in the study must be adults with probable or definite DM or PM according to the Bohan and Peter criteria (Bohan, 1975) and have active disease. Patients will either have low/undetectable or high level of expression of mRNA for type I IFN-inducible genes in whole blood or muscle at the time of screening. High level of expression, defined as a median fold overexpression of the top 25 type I IFN inducible genes of 4-fold or greater, is referred to as gene signature positive, and low/undetectable level of expression is referred to as gene signature negative.

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 or administration of study drug.

[redacted]

3.1.1 Inclusion Criteria

Patients must meet *all* of the following criteria:

1. Male or female adults at least 18 years of age at the time of randomization;
2. Written informed consent obtained from the patient or the patient's legal representative prior to receipt of any study medication or beginning study procedures;
3. Probable or definite PM or DM according to the Bohan and Peter criteria (Bohan, 1975);
4. For patients with PM, documentation of a muscle biopsy result that is consistent with the diagnosis of PM;
5. All patients including those with DM must meet at least two of the following criteria:
   a. Strength in MMT ≥ 80/150 but ≤ 125/150 using the MMT-8 muscle group testing (see Appendix A);
   b. Patient Global Activity Assessment by visual analog scale (VAS) ≥ 2.0 cm on a 10-cm scale, which is included as part of CLINHAQ (see Appendix B);
   c. Physician Global Activity Assessment by VAS ≥ 2.0 cm on a 10 cm scale, which is included as part of MDAAT (see Appendix C);
   d. CLINHAQ (see Appendix B) disability index ≥ 0.25;
   e. Global extramuscular activity assessment ≥ 1.0 cm on a 10-cm VAS scale (this measure is the physician's composite evaluation and is based on assessments of activity scores on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiovascular scales of the MDAAT [Appendix C]);
6. Subjects with PM must have an elevation of serum CK or aldolase at a minimum level of 1.3 × upper limit of normal (ULN) or serum CK or aldolase at least 2-fold higher than the patient's own lowest value since diagnosis;
7. Subjects with DM must have either an elevated CK or aldolase as above (per inclusion criterion #6) or other laboratory evidence of active myositis. This could include either abnormal signal on skeletal muscle MRI suggestive of inflammation or an electromyogram demonstrated muscle membrane irritability (e.g., fibrillation potentials, positive sharp waves, complex repetitive discharges) and short duration, small amplitude, polyphasic motor unit action potentials.
8. Patients randomized to Dose Cohorts 1, 2, 3A, and 4 must have median fold overexpression of the top 25 type I IFN-inducible genes of 4-fold or greater in whole blood or muscle at the time of screening; patients randomized to Dose Cohort 3B must have low/undetectable expression of type I IFN-inducible genes;
9. Sexually active women, unless surgically sterile (including tubal ligation) or at least 2 years postmenopausal, 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 end of study. Cessation of birth control after this point should be discussed with a responsible physician. Sexually active males, 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 end of study;
10. Ability to complete the study period, including follow-up period, of up to 350 days; and
11. Willing to forego other forms of experimental treatment during the study.

[redacted]

3.1.2 Exclusion Criteria

Patients must have *none* of the following criteria:

1. Receipt of MEDI-545 in any previous clinical study or prior randomization into the trial;
2. History of allergy or reaction to any component of the study drug formulation;
3. Inclusion body myositis, cancer-associated myositis, myositis associated with another connective tissue disease, environmentally-associated myositis, or drug-related myopathy;
4. A history of or a family history of noninflammatory myopathy, scapular winging, atrophy, or hypertrophy of the calf muscles;
5. Receiving prednisone > 35 mg/day (or an equivalent dose of another corticosteroid) within 14 days before Study Day 0;
6. Receiving the following dosages of medications within 28 days before Study Day 0: hydroxychloroquine > 600 mg/day, mycophenolate mofetil > 3 g/day, methotrexate > 25 mg/week, azathioprine > 3 mg/kg/day, or any dose of cyclophosphamide, cyclosporine, or thalidomide;
7. Have received fluctuating doses of antimalarials, mycophenolate mofetil, methotrexate, leflunomide, or azathioprine within 28 days before Study Day 0 or fluctuating doses of corticosteroids within 14 days before Study Day 0;
8. Have received leflunomide > 20 mg/day in the 6 months prior to Study Day 0.
9. Treatment with any investigational drug therapy within 28 days before Study Day 0 or biologic therapies (eg, rituximab) within 30 days or 5 half-lives of the biologic agent, whichever is longer, before Study Day 0;
10. In the investigator's opinion, evidence of clinically significant active infection, including ongoing, chronic infection, within 28 days before Study Day 0;
11. A history of severe viral infection as judged by the investigators, including severe infections of either CMV or the herpes family such as disseminated herpes, herpes encephalitis, ophthalmic herpes;
12. Herpes zoster ≤ 3 months prior to Study Day 0;
13. 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;
14. Vaccination with live attenuated viruses within 28 days before Study Day 0;
15. Pregnancy (sexually active women, unless surgically sterile or at least 2 years post-menopausal, must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to study drug administration on Study Day 0);
16. Breastfeeding or lactating women;
17. History of alcohol or drug abuse < 1 year prior to Study Day 0;
18. History of cancer, except for basal cell carcinoma or carcinoma in situ of the cervix treated with apparent success with curative therapy more than 1 year prior to Study Day 0;
19. History of active TB infection;
20. 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;

[redacted]

21. A history of coagulation disorders that in the opinion of the investigator would contraindicate skin or muscle biopsies;
22. Elective surgery planned from the time of screening through Study Day 196;
23. At screening blood tests (must be within 28 days before Study Day 0) any of the following:
    - Serum creatinine > 4.0 mg/dL,
    - Neutrophils < 1,500/mm^3,
    - Platelet count < 50,000/mm^3;
24. History of any disease, evidence of any current disease (other than DM or PM), 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
25. Any employee of the research site who is involved with the conduct of the study.

3.2 Patient Randomization Procedures and Treatment Allocation

Patients will be screened by investigators or qualified designees to assess eligibility for randomization into the study. Screening of patients will be managed so that about 40% to 60% of randomized patients will have DM and the remainder PM. A master log will be maintained of all consented patients and will document all screening failures, including the reason for screening failure.

Treatment assignments will be determined using a central randomization procedure through an interactive voice response system (IVRS). Patients with a median fold overexpression of the top 25 type I IFN inducible genes of 4-fold or greater in whole blood or muscle will be randomized to Dose Cohorts 1, 2, 3A, or 4, and patients with low/undetectable expression of type I IFN-inducible genes will be randomized to Dose Cohort 3B. Central randomization will be applied without regard to site.

The randomization procedure is as follows:

- Investigator or qualified designee confirms the patient meets all eligibility criteria and has signed an informed consent;
- 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;
- Investigator or qualified designee calls the IVRS on Study Day 0 and provides at a minimum the initials, date of birth, body weight of the patient, and the clinical diagnosis;
- 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.

When a patient is assigned a PID by the IVRS the patient is considered randomized into the study.

Patients will be dosed with either MEDI-545 or placebo on Study Day 0. In each of the 5 dose cohorts, if one of the first 8 patients is randomized but not treated, or not evaluable, the treatment assignment for this replaced patient will be used for the 9th patient enrolled in this cohort. If there are additional patients who are replaced, the replaced patient's treatment assignments will be used in order of enrollment. A dose cohort may be expanded by up to 4 additional patients (for a maximum of 20 additional new patients in total) if eligible patients are in screening at the time 8 patients 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). The safety data will also be reviewed on a regular basis by the Safety Monitoring Committee (SMC), which can stop study entry and dosing. The SMC includes physicians who are independent from MedImmune. The sponsor will notify the sites when randomization in each dose group is completed and when randomization into the next dose group is permitted.

3.3 Blinding

This study is double-blinded. 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. This includes the medical monitor, project management, statistician, site monitors, and data management. Patients and the study site staff, including the investigators, study nurses, coordinators, pharmacists, and the Clinical Trial Material Manager (CTMM) will remain blinded to the treatment during the study.

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.

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, will be unblinded during the study. In addition, once the last patient in 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 will be made after the first 2 cohorts complete Study Day 98, after all cohorts complete Study Day 98, and after all cohorts complete Study Day 196. These interim assessments are also for the purpose of making clinical development decisions. 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.

[redacted]

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

3.4 Study Drug

3.4.1 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): [redacted]

PLACEBO: [redacted]

The study 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 must be returned to the vendor designated by the sponsor.

3.4.2 Treatment Regimens

A total of 40 evaluable patients will participate in this study. A total of 32 evaluable patients with positive gene signature will be randomized in a 3:1 ratio to initially receive MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo infused over at least 60 minutes every 2 weeks for 12 weeks for a total of 7 doses (Table 1). An additional cohort (Dose Cohort 3B) of 8 evaluable patients with negative gene signature will be randomized in a 3:1 ratio to initially receive MEDI-545 (3.0 mg/kg) or placebo every 2 weeks for 12 weeks for a total of 7 doses, with 6 patients receiving MEDI-545 and 2 patients receiving placebo. In each dose cohort, 6 patients will receive MEDI-545 and 2 patients will receive placebo. Thereafter (2 weeks after the 7th dose), in each of the 5 dose cohorts, patients randomized to MEDI-545 will continue to receive the same dose of MEDI-545 every 2 weeks for an additional 12 weeks (7 doses) and patients randomized to placebo will receive MEDI-545, at the dose specified in the dose cohort they are assigned, every 2 weeks for an additional 12 weeks (7 doses) for a total of 26 weeks (14 doses). MEDI-545 or placebo will be administered IV over at least 60 minutes.

A dose cohort may be expanded by up to 4 additional patients (for a maximum of 20 additional patients in total) if eligible patients are in screening at the time 8 patients have been randomized into the dose cohort.

[redacted]

Table 1 Treatment Regimens

Dose Cohort	N	Treatment Period: Study Days 0-84	Treatment Period: Study Days 98-182
1 [a]	8	MEDI-545: 0.3 mg/kg × 7 doses (N=6)	MEDI-545: 0.3 mg/kg × 7 doses (N=6)
		Placebo × 7 doses (N=2)	MEDI-545: 0.3 mg/kg × 7 doses (N=2)
2 [a]	8	MEDI-545: 1.0 mg/kg × 7 doses (N=6)	MEDI-545: 1.0 mg/kg × 7 doses (N=6)
		Placebo × 7 doses (N=2)	MEDI-545: 1.0 mg/kg × 7 doses (N=2)
3A [a]	8	MEDI-545: 3.0 mg/kg × 7 doses (N=6)	MEDI-545: 3.0 mg/kg × 7 doses (N=6)
		Placebo × 7 doses (N=2)	MEDI-545: 3.0 mg/kg × 7 doses (N=2)
3B [b]	8	MEDI-545: 3.0 mg/kg × 7 doses (N=6)	MEDI-545: 3.0 mg/kg × 7 doses (N=6)
		Placebo × 7 doses (N=2)	MEDI-545: 3.0 mg/kg × 7 doses (N=2)
4 [a]	8	MEDI-545: 10.0 mg/kg × 7 doses (N=6)	MEDI-545: 10.0 mg/kg × 7 doses (N=6)
		Placebo × 7 doses (N=2)	MEDI-545: 10.0 mg/kg × 7 doses (N=2)

a This dose cohort consists of patients who are gene signature positive.
b This dose cohort consists of patients who are gene signature negative.

All patients should continue to receive medications they were taking at the time of consent in unchanged doses during the entire treatment; however, if clinical deterioration occurs and additional treatment is warranted in the opinion of the investigator, the investigator is permitted to add new or increase existing immunosuppressive medications, as long as no prohibited medications are added (see Section 3.4.5). Concurrent immunosuppressive therapy may be tapered and discontinued, according to the investigator's judgment, during the follow-up period.

3.4.3 Study Drug Ordering and Preparation

Study drug will be sent to the study sites before randomization in a blinded fashion. 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 infusion is calculated on the basis of the patient's weight (in kg) measured on Study Day 0 using the following formula:

$$\text{Dose (mL)} = \frac{\text{Pt. Wt (kg) x Dose (mg/kg)}}{\text{100 mg/mL of MEDI-545}}$$

For example: For an 80-kg patient dosed at 10.0 mg/kg MEDI-545, the volume of MEDI-545 required for IV administration would be 8.0 mL.

The MEDI-545 dose for administration must be prepared using aseptic technique. MEDI-545 will be diluted in 0.9% normal saline and the volume will be standardized to 100 mL. The study drug will be administered using an infusion pump over at least 60 minutes as described in Table 2.

[redacted]

Table 2 Summary of Infusion Volume, Duration, and Rate

Dose Cohort	Dose (mg/kg)	Infusion Volume [a] (mL)	Infusion Duration	Maximum Infusion Rate (mL/hr)	Infusion Rate (mg/kg/min)[b]
1	0.3	100	≥ 60 minutes	100	0.005
2	1.0	100	≥ 60 minutes	100	0.017
3A	3.0	100	≥ 60 minutes	100	0.05
3B	3.0	100	≥ 60 minutes	100	0.05
4	10.0	100	≥ 60 minutes	100	0.17

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. Infusion rate (mg/kg/min) is based on body weight.

The study drug dose will be prepared by the CTMM and administered to patients without blinding.

3.4.4 Administration of Study Drug

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

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be monitored before, approximately every 15 minutes during infusion, immediately after 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 safety and tolerability of the study drug. However, if reactions to the IV infusion occur during or after study drug administration, they should be treated appropriately.

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.

[redacted]

3.4.4.1 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 the first 24 hours after infusion, especially within minutes to a few hours, and will be distinguished from true anaphylactic reactions by absence of measurable antibodies against the 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 3, with suggested treatment options. Final treatment is at the discretion of the investigator and should reflect local standard of care.

[redacted]

Table 3 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

[redacted]

Table 3 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

[redacted]

If an 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 vital signs, for example every 5 to 10 minutes for Grade 1 or Grade 2 infusion reactions and every 2 to 5 minutes for Grade 3 or Grade 4 infusion reactions until stable;
- Collect serum for assessment of safety biomarkers (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies) for Grade 1 or higher infusion reactions as soon as possible after the event, at 60 minutes after the event, and at discharge.

3.4.4.2 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 J.

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

As indicated in the Guidance for Abnormal Liver Function Tests (Appendix J), 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.

3.4.5 Concomitant Medications

All concomitant medications, including herbal products, used by the patient from screening through Study Day 350 will be recorded on the case report form. The concomitant administration of IVIG is allowed.

Patients may not receive the following from screening through Study Day 350:
1. Investigational agents (eg, rituximab for myositis);
2. Any live attenuated virus vaccine;
3. Hydroxychloroquine > 600 mg/day, mycophenolate mofetil > 3 g/day, methotrexate > 25 mg/week, leflunomide > 20 mg/day, azathioprine > 3 mg/kg/day; or
4. Any dose of cyclophosphamide, cyclosporine, or thalidomide.

Corticosteroid doses may not exceed 35 mg/day of prednisone or an equivalent dose of another corticosteroid. Corticosteroid doses must remain constant from 14 days before Study Day 0 through Study Day 196. Thereafter, corticosteroid doses may be increased, tapered, and discontinued as considered appropriate by the investigator.

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

See Section 3.4.2 for guidance in handling clinical deteriorations.

3.5 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.

The schedule of patient evaluations for the screening and treatment periods can be found in Table 4, and the schedule of patient evaluations for the follow-up periods in the study can be found in Table 5. Eligibility screening will take place within 28 days before randomization into the study.

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.

[redacted]

Table 4 Schedule of Patient Evaluations (Screening and Treatment Period)

		Treatment Period													
Study Day		**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98 [a]**	**112**	**126**	**140**	**154**	**168**	**182**
Visit	**Screen [b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
ELIGIBILITY															
Written Informed Consent	X														
Verify Eligibility Criteria	X	X [c]													
Medical History [d]	X	X [c]													
Chest X-ray [e]	X														
Physical Examination	X	X [c]							X						
Body Weight		X							X						
ECG	X				X				X			X			
Tuberculosis Skin Test [f]	X														
HIV-1, HIV-2, Hepatitis A, B, C	X														
Serum βHCG [g]	X														
Urine βHCG [g]		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 [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry [i, j]	X	X [c]	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC & Differentials, Platelets [j]	X	X [c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis [j]	X	X [c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum for Safety Biomarkers [k]		X [c]													
Viral Surveillance Testing [j]		X [c]		X		X			X		X		X		
Record Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
DISEASE ACTIVITY AND DAMAGE															
Serum Levels of Muscle Enzymes [j, m]	X	X [c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Strength in MMT	X	X [c]		X		X			X		X		X		
Extramuscular Activity Assessment (MDAAT)	X	X [c]		X		X			X		X		X		
Pulmonary Function Tests [n]	X								X [o]						
Physician Global Activity Assessment [p]	X	X [c]		X		X			X		X		X		
CLINHAQ [q]	X	X [c]		X		X			X		X		X		
Patient Global Activity Assessment [q]	X	X [c]		X		X			X		X		X		
Myositis Damage Index		X [c]							X						
SF-36v2		X [c]							X						
WPAI:SHP Questionnaire		X [c]							X						
Pruritus VAS [r]		X [c]		X		X			X		X		X		
CDASI [r]		X [c]		X		X			X		X		X		
DLQI [r]		X [c]							X						
Skin Photographs [r, s, t,]		X[c]		X		X			X		X		X		

[redacted]

Table 4 Schedule of Patient Evaluations (Screening and Treatment Period)

		Treatment Period													
Study Day		**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98 [a]**	**112**	**126**	**140**	**154**	**168**	**182**
Visit	**Screen [b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
CORRELATIVE STUDIES															
Serum for Exploratory Research and Storage [j, s]		X [b]		X		X			X		X		X		
Serum for autoantibodies [j]		X [b]							X						
Whole Blood for IFN Gene Expression Analyses	X	X [b]		X		X			X		X		X		
Peripheral Blood for Flow Cytometry [j, u]		X [b]							X						
Muscle Biopsy [w]		X [b]							X						
Punch Skin Biopsy [r, s]		X [b]							X						
Whole Blood for DNA Sample [s]			X												
PK/IM															
MEDI-545 Serum Level [j]		X [v]	X	X	X	X	X	X	X [v]	X	X	X	X	X	X [v]
Anti-MEDI-545 Antibodies [j]		X		X		X			X		X		X		

Table 4 Footnotes:

a. If a patient discontinues his or her participation in the study prior to Study Day 98, the assessments designated for Study Day 98 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, except if follow-up muscle and skin biopsies have been done at any time, they need not be repeated. (If a patient discontinues after Day 98, see Table 5 footnotes a and b.)
b. Obtain within 28 days prior to Study Day 0.
c. Assessments may be performed up to 72 hours prior to dosing on Study Day 0, except muscle and skin biopsies and skin photographs, which may be performed up to 28 days prior to Study Day 0. The open muscle biopsy may be done as part of screening to meet inclusion criteria as long as the dose(s) of immunosuppressive medications have been stable for one month and will remain the same as that in Day 0.
d. Medical history includes history of viral reactivation events.
e. Chest x-ray taken within 6 months of screening is considered suitable for screening and need not be repeated.
f. Do not administer TB skin test if the patient is known to be positive.
g. Women, unless surgically sterile or at least 2 years postmenopausal, must have a negative serum pregnancy test within 28 days before randomization/entry, and a negative urine pregnancy test on all dosing visits before receiving the study drug.
h. 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 will be monitored up to 30 minutes before dosing, approximately every 15 minutes during administration of the drug, immediately after the 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. Blood pressure and heart rate will also be taken prior to discharge from the site on visits in which study drug is administered.
i. Includes Na, K, Cl, bicarbonate, BUN, creatinine, bilirubin, alkaline phosphatase, and random glucose.

j. Obtained prior to study drug administration, where applicable. Viral surveillance includes testing for EBV, CMV, HSV, and HPV. The patient will provide self-collected vaginal swabs for HSV and HPV testing; the 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.
k. A serum 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 a Grade 1 or higher infusion reaction as soon as possible after the event, 60 minutes after the event, and at discharge (see Section 3.4.4 for details).
l. At selected sites only.
m. Serum muscle enzymes include CK, aldolase, AST, ALT, and LDH.
n. Pulmonary function tests, a part of MDAAT, will assess lung volumes and diffusion capacity for carbon monoxide (DLCO).
o. Pulmonary function test on Study Day 98 should be done within 7 days before the visit.
p. Physician Global Activity Assessment is included as part of MDAAT.
q. Patient Global Activity Assessment is included as part of CLINHAQ.
r. DM patients only.
s. Optional procedures.
t. Photographs of up to two target skin lesions (if present) are requested. One photograph should be of the skin lesion that will be biopsied. It is preferred that the photographs are taken prior to the punch skin biopsy.
u. Flow cytometry will be performed on peripheral blood samples from selected sites in North America.
v. On Study Days 0, 98 and 182 only, serum samples for MEDI-545 concentrations are collected immediately before, immediately after (within 10 minutes after the infusion has stopped), and 2 hours after administration of the IV infusion.
w. Open muscle biopsy, unless otherwise approved by the sponsor.

[redacted]

Table 5 Schedule of Patient Evaluations (Follow-up Period)

	Follow-up Period								
Study Day	**185**	**189**	**196[a]**	**210**	**238**	**266**	**294**	**322**	**350[b]**
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
SAFETY ASSESSMENT									
Physical Examination			X						X
Body Weight			X						X
ECG			X						X
Urine βHCG						X			X
Vital Signs [c]	X	X	X	X	X	X	X	X	X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X
Serum Chemistry [d]			X	X	X	X	X	X	X
CBC & Differentials, Platelets			X	X	X	X	X	X	X
Urinalysis			X	X	X	X	X	X	X
Viral Surveillance Testing			X			X			X
Record Concomitant Medications			X	X	X	X	X	X	X
DISEASE ACTIVITY AND DAMAGE									
Serum Levels of Muscle Enzymes [f]			X	X	X	X	X	X	X
Strength in MMT			X		X		X		X
Extramuscular Activity Assessment (MDAAT)			X		X		X		X
Pulmonary Function Tests [g]			X						X
Physician Global Activity Assessment [h]			X		X		X		X
CLINHAQ [i]			X		X		X		X
Patient Global Activity Assessment [i]			X		X		X		X
Myositis Damage Index			X						X
SF-36v2			X						X
WPAI:SHP Questionnaire			X		X		X		X
Pruritus VAS [J]			X		X		X		X
CDASI [J]			X		X		X		X
DLQI [J]			X		X		X		X
Skin Photographs [j, k, l]			X		X		X		X
CORRELATIVE STUDIES									
Serum for Exploratory Research and Storage			X		X		X		X
Serum for Autoantibodies			X						X
Whole Blood for IFN Gene Expression Analyses			X		X		X		X
Peripheral Blood for Flow Cytometry [m]			X		X		X		X
PK/IM									
MEDI-545 Serum Level	X	X	X	X	X	X	X	X	X
Anti-MEDI-545 Antibodies			X		X		X		X

[redacted]

Table 5 Footnotes:

a. If a patient discontinues after Study Day 98 and prior to Study Day 196, the evaluations scheduled for Study Day 196 must be completed. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.
b. If a patient discontinues after Study Day 196 and prior to Study Day 350, the evaluations scheduled for Study Day 350 must be completed. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.
c. Vital signs include heart rate, blood pressure, respiratory rate and temperature.
d. Includes Na, K, Cl, bicarbonate, BUN, creatinine, bilirubin, alkaline phosphate, and random glucose.
e. At selected sites only.
f. Serum muscle enzymes include CK, aldolase, AST, ALT, and LDH.
g. Pulmonary function tests, a part of MDAAT, will assess lung volumes and DLCO.
h. Physician Global Activity Assessment is included as part of MDAAT.
i. Patient Global Activity Assessment is included as part of CLINHAQ.
j. DM patients only.
k. Optional procedures.
l. Photographs of up to two target skin lesions (if present) are requested. One photograph should be of the skin lesion that was biopsied.
m. Flow cytometry will be performed on peripheral blood samples from selected sites in North America.

Screening

Note: All screening laboratory assessments must be performed within 28 days before randomization (Study Day 0). The screening evaluations may be carried out over more than one visit. Chest x-ray taken within 6 months of screening is considered suitable for screening and need not be repeated.

1. Written informed consent
2. Verify eligibility criteria
3. Screening medical history
4. Chest x-ray
5. Screening physical examination
6. Screening ECG
7. TB skin test
8. Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
9. Urinalysis
10. Blood collection for screening
    - Chemistry panel (including Na, K, Cl, bicarbonate, BUN, creatinine, bilirubin, alkaline phosphatase, and random glucose)
    - CBC with differential and platelet count
    - Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody and HIV-1 and HIV-2 antibodies
    - Serum βHCG (for women who are sexually active and are not surgically sterile or at least 2 years postmenopausal; this test must be negative for study participation)
    - Serum levels of muscle enzymes (including CK, aldolase, LDH, ALT, and AST)
    - Whole blood for IFN gene expression analysis
11. Disease activity assessments:
    - MMT for strength
    - Extramuscular activity assessment (based on MDAAT scales)
    - Pulmonary function tests
    - Physician global activity assessment (included as part of MDAAT)
    - CLINHAQ (includes Patient global activity assessment)

Study Day 0: First Dose

Visit 1

1. Verify eligibility criteria
2. Update screening history and physical examination (any new findings since screening)
3. Body weight
4. Randomization and assignment of PID
5. Record concomitant medications
6. Urinalysis, includes collection of urine for βHCG (for women who are sexually active and are not surgically sterile or at least 2 years postmenopausal; this test must be negative for study participation)
7. Baseline blood collection
    - Chemistry panel

[redacted]

- CBC with differential and platelet count
- Serum for safety biomarkers
- Serum levels of muscle enzymes
- Serum for exploratory research (including IFN-α assay and proteomics) and storage
- Serum for autoantibodies (including ANA, anti-SSA, anti-RNP, anti-Jo-1, anti-SRP, anti-Mi-2 antibodies)
- Whole blood for IFN gene expression analysis
- Peripheral blood for flow cytometry
- MEDI-545 serum level
- Anti-MEDI-545 antibodies

8. Viral surveillance testing (including EBV, CMV, HSV, and HPV)
9. Disease activity assessments:
    - MMT
    - Extramuscular activity assessment
    - Physician global activity assessment (included as part of MDAAT)
    - CLINHAQ (includes Patient global activity assessment)
    - Myositis Damage Index
    - SF-36v2
    - WPAI: SHP questionnaire
    - Pruritus VAS (DM patients only)
    - CDASI (DM patients only)
    - DLQI (DM patients only)
10. Skin photographs (optional, DM patients only, preferably prior to the punch skin biopsy and within 28 days before the visit)
11. Muscle biopsy (within 28 days before the visit). The open muscle biopsy may be done during screening to address inclusion criteria as long as the dose(s) of immunosuppressive medications have been stable for one month and will remain the same as that in Day 0. Muscle for IFN gene expression analysis
12. Punch skin biopsy (optional punch biopsy, DM patients only, within 28 days before the visit). Skin for IFN gene expression analysis
13. Vital signs up to 30 minutes before administration of study drug
14. Administration of study drug
15. Monitor vital signs approximately every 15 minutes during administration of the drug, immediately after the infusion (within 10 minutes after the infusion has stopped), 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.
16. Post-dose blood collection (within 10 minutes after the infusion has stopped and 2 hours after study drug administration)
    - MEDI-545 serum level
17. AE/SAE assessment

Study Days 14, 42, 70, 84, 112, 140, 168 (± 3 Days): Treatment Period

Visits 2, 4, 6, 7, 9, 11, 13

1. Record concomitant medications

[redacted]

2. Urinalysis includes collection of urine for βHCG (for women who are sexually active and are not surgically sterile or at least 2 years postmenopausal)
3. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Serum levels of muscle enzymes
   - MEDI-545 serum level
   - Whole blood for DNA sample on Study Day 14 only (optional)
4. ECG (Study Days 42, 98, and 140)
5. Vital signs up to 30 minutes before administration of study drug
6. Administration of study drug
7. Monitor vital signs approximately every 15 minutes during administration of the drug, immediately after the infusion (within 10 minutes after the infusion has stopped), 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.
8. AE/SAE assessment

Study Days 28, 56, 126, 154 (± 3 Days): Treatment Period

Visits 3, 5, 10, 12

1. Record concomitant medications
2. Urinalysis includes collection of urine for βHCG (for women who are sexually active and are not surgically sterile or at least 2 years postmenopausal)
3. Baseline blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Serum levels of muscle enzymes
   - Serum for exploratory research (including IFN-α assay and proteomics) and storage
   - Whole blood for IFN gene expression analysis
   - MEDI-545 serum level
   - Anti-MEDI-545 antibodies
4. Viral surveillance testing
5. Disease activity assessments:
   - MMT
   - Extramuscular activity assessment
   - Physician global activity assessment (included as part of MDAAT)
   - CLINHAQ (includes Patient global activity assessment)
   - Pruritus VAS (DM patients only)
   - CDASI (DM patients only)
6. Skin photographs (optional, DM patients only, within 7 days of the visit)
7. Vital signs up to 30 minutes before administration of study drug
8. Administration of study drug
9. Monitor vital signs approximately every 15 minutes during administration of the drug, immediately after the infusion (within 10 minutes after the infusion has stopped), 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.
10. AE/SAE assessment

Unscheduled Visit

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

Study Day 98 (± 3 Days) or Discontinuation Visit

If a patient discontinues the study prematurely prior to Study Day 98, 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.

Visit 8

1. Record concomitant medications
2. Physical examination
3. Body weight
4. ECG
5. Urinalysis includes collection of urine for βHCG (for women who are sexually active and are not surgically sterile or at least 2 years postmenopausal)
6. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Serum levels of muscle enzymes
   - Serum for exploratory research (including IFN-α assay and proteomics) and storage
   - Serum for autoantibodies (including ANA, anti-SSA, anti-RNP, anti-Jo-1, anti-SRP, anti-Mi-2 antibodies)
   - Whole blood for IFN gene expression analysis
   - Peripheral blood for flow cytometry
   - MEDI-545 serum level
   - Anti-MEDI-545 antibodies
7. Viral surveillance testing
8. Disease activity assessments:
   - MMT
   - Extramuscular activity assessment
   - Pulmonary function tests (within 7 days before the visit)
   - Physician global activity assessment (included as part of MDAAT)
   - CLINHAQ (includes Patient global activity assessment)
   - Myositis Damage Index
   - SF-36v2
   - WPAI: SHP questionnaire
   - Pruritus VAS (DM patients only)
   - CDASI (DM patients only)
   - DLQI (DM patients only)

9. Skin photographs (optional, DM patients only, preferably prior to the punch skin biopsy and within 7 days before the visit))
10. Muscle biopsy (within 7 days before the visit). Open muscle biopsy for IFN gene expression analysis
11. Punch skin biopsy (optional punch biopsy, DM patients only, within 7 days before the visit). Skin for IFN gene expression analysis
12. Vital signs before administration of study drug
13. Administration of study drug (Study Day 98 only)
14. AE/SAE assessment
15. Post-dose blood collection (within 10 minutes after the infusion has stopped and 2 hours after study drug administration)
    - MEDI-545 serum level
16. Monitor vital signs up to 30 minutes before dosing, approximately every 15 minutes during administration of the drug, immediately after the infusion (within 10 minutes after the infusion has stopped), 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.

Study Day 182 (± 1 Day): Treatment Period

Visit 14

1. Record concomitant medications
2. Urinalysis includes collection of urine for βHCG (for women who are sexually active and are not surgically sterile or at least 2 years postmenopausal)
3. Blood collection
    - Chemistry panel
    - CBC with differential and platelet count
    - Serum levels of muscle enzymes
    - MEDI-545 serum level
4. Vital signs up to 30 minutes before administration of study drug
5. Administration of study drug
6. Monitor vital signs approximately every 15 minutes during administration of the drug, immediately after the infusion (within 10 minutes after the infusion has stopped), and approximately and every 30 minutes after the completion of the infusion until stable. Measure blood pressure and heart rate prior to discharge from the site.
7. AE/SAE assessment
8. Post-dose blood collection (within 10 minutes after the infusion has stopped and 2 hours after study drug administration)
    - MEDI-545 serum level

Study Days 185, 189 (± 1 Day): Follow-Up Period

Visits 15, 16
These visits must take place after the Study Day 182 visit.

1. Vital signs
2. AE/SAE assessment

3. Blood collection:
   - MEDI-545 serum level

Study Day 196 (± 3 Days): Follow-Up Period or Discontinuation Visit

If a patient discontinues the study prematurely after Study Day 98 and prior to Study Day 196, 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.

Visit 17

1. Record concomitant medications
2. Physical examination
3. ECG
4. Body weight
5. Vital signs
6. AE/SAE assessment
7. Urinalysis
8. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Serum levels of muscle enzymes
   - Serum for exploratory research (including IFN-α assay and proteomics) and storage
   - Serum for autoantibodies (including ANA, anti-SSA, anti-RNP, anti-Jo-1, anti-SRP, anti-Mi-2 antibodies)
   - Whole blood for IFN gene expression analysis
   - Peripheral blood for flow cytometry
   - MEDI-545 serum level
   - Anti-MEDI-545 antibodies
9. Viral surveillance testing
10. Disease activity assessments:
    - MMT
    - Extramuscular activity assessment
    - Pulmonary function tests
    - Physician global activity assessment (included as part of MDAAT)
    - CLINHAQ (includes Patient global activity assessment)
    - Myositis Damage Index
    - SF-36v2
    - WPAI: SHP Questionnaire
    - Pruritus VAS (DM patients only)
    - CDASI (DM patients only)
    - DLQI (DM patients only)
11. Skin photographs (optional, DM patients only, within 7 days of the visit)

Study Days 210, 266, 322 (± 7 Days): Follow-Up Period

Visits 18, 20, 22

1. Record concomitant medications
2. Vital signs
3. AE/SAE assessment
4. Viral surveillance testing (Study Day 266 only)
5. Urinalysis includes collection of urine for βHCG (for women who are sexually active and are not surgically sterile or at least 2 years postmenopausal) on Study Day 266 only
6. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Serum levels of muscle enzymes
   -
   - MEDI-545 serum level

Study Days 238, 294 (± 7 Days): Follow-Up Period

Visits 19, 21

1. Record concomitant medications
2. Vital signs
3. AE/SAE assessment
4. Urinalysis
5. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Serum levels of muscle enzymes
   - Serum for exploratory research (including IFN-α assay and proteomics) and storage
   - Whole blood for IFN gene expression analysis
   - Peripheral blood for flow cytometry
   - MEDI-545 serum level
   - Anti-MEDI-545 antibodies
6. Disease activity assessments:
   - MMT
   - Extramuscular activity assessment
   - Physician global activity assessment (included as part of MDAAT)
   - CLINHAQ (includes Patient global activity assessment)
   - WPAI: SHP Questionnaire
   - Pruritus VAS (DM patients only)
   - CDASI (DM patients only)
   - DLQI (DM patients only)
7. Skin photographs (optional, DM patients only)

[redacted]

Study Day 350 (± 7 days): Final Visit or Discontinuation Visit

If a patient discontinues the study prematurely after Study Day 196 and prior to Study Day 350, 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.

Visit 23

1. Record concomitant medications
2. Physical examination
3. Body Weight
4. ECG
5. Vital signs
6. AE/SAE assessment
7. Urinalysis includes collection of urine for βHCG (for women who are sexually active and are not surgically sterile or at least 2 years postmenopausal)
8. Blood collection
   - Chemistry panel
   - CBC with differential and platelet count
   - Serum levels of muscle enzymes
   - Serum for exploratory research (including IFN-α assay and proteomics) and storage
   - Serum for autoantibodies (including ANA, anti-SSA, anti-RNP, anti-Jo-1, anti-SRP, anti-Mi-2 antibodies)
   - Whole blood for IFN gene expression analysis
   - Peripheral blood for flow cytometry
   - MEDI-545 serum level
   - Anti-MEDI-545 antibodies
9. Viral Surveillance Testing
10. Disease activity assessments:
    - MMT
    - Extramuscular activity assessment
    - Pulmonary function tests
    - Physician global activity assessment (included as part of MDAAT)
    - CLINHAQ (includes Patient global activity assessment)
    - Myositis Damage Index
    - SF-36v2
    - WPAI: SHP Questionnaire
    - Pruritus VAS (DM patients only)
    - CDASI (DM patients only)
    - DLQI (DM patients only)
11. Skin photographs (optional, DM patients only)

[redacted]

3.6 Patient Evaluation Methods

3.6.1 Routine Laboratory and Clinical Evaluations

Clinical evaluations will be performed during screening and throughout the study as indicated in Table 4 and Table 5. Laboratory tests for serum chemistries, hematology, hepatitis serologies, viral infection, pregnancy and urinalysis with microscopic examination will be performed during screening and during the study by a central CLIA-certified laboratory in the United States. Urine pregnancy tests will be performed in female patients who are not postmenopausal or surgically sterile at the time of screening on Study Day 0, prior to study drug administration on Study Days 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, and 182, and on Study Days 266 and 350 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).

Additional studies to be performed include ECGs, and chest x-ray (anterior/posterior and lateral).

3.6.2 Viral Surveillance Testing

HSV-1, HSV-2, EBV, CMV, and HPV will be monitored by virus isolation in tissue culture and/or by molecular assays using PCR amplification as indicated in Table 4 and Table 5. The investigator or qualified designee will collect oropharyngeal swabs for HSV-1 and HSV-2 testing. The patient will provide self collect vaginal swabs for HSV-1, HSV-2, and HPV testing. The vaginal swabs may also be collected by an MD/OBGYN or qualified medical personnel such as an appropriately trained nurse practitioner, if previously approved by the sponsor. In addition, blood samples will be collected and tested for EBV and CMV by PCR molecular-based tests.

3.6.3 Tuberculosis Monitoring

At screening, patients will receive tuberculin skin test. Those who are known to have positive tuberculin skin test should not receive the skin test and should be confirmed by chest x-ray that they have no evidence of active TB. Reading of the tuberculin skin test should be performed 48 to 72 hours after administration by a trained person. A 10 mm cut point will be used to determine tuberculin skin test positivity for those patients not on systemic immunosuppressive medication and a 5 mm cut point will be used for those on systemic immunosuppressive medication. Patients who have latent TB must have completed an appropriate course of anti-TB treatment or be on prophylactic treatment.

3.6.4 Pharmacokinetic, Pharmacodynamic, and Immunogenicity Determinations

All PK and IM laboratory evaluations on samples from North American sites will be performed by MedImmune. MEDI-545 serum concentrations and anti-MEDI-545 antibody detection will be measured by ELISA or ECLA (electrochemiluminescent assay). Sera that are collected may be used for additional PK analyses (MEDI-545 characterization) and MEDI-545 antibody analyses.

3.6.5 Safety Biomarkers

Serum will be collected for assessment of safety biomarkers as described in Table 4. In addition, if a Grade 1 or higher infusion reaction occurs during or after study drug administration, serum for assessment of safety biomarkers will be collected as soon as possible after the event, at 60 minutes after the event, and at discharge (see Section 3.4.4 for details). Safety biomarkers include serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies.

3.6.6 Evaluations of Disease Activity

3.6.6.1 Serum Creatine Kinase Normalization

Creatine kinase has been the most useful serum enzyme for the diagnosis and assessment of adult patients with DM or PM. It is the most sensitive enzyme to muscle injury, is at times the only one elevated, and the degree of serum CK elevation is often greater than that seen with other muscle enzymes. As emphasized by Bohan and Peter (Bohan, 1975), trends in serum activity but not single values accurately reflect disease activity in individuals and are useful in the management of these patients. In fact, the trend of the CK has been frequently used in clinical practice to assess response to therapy and is reported in case studies to support evidence of clinical improvement. Preliminary data from MedImmune researchers suggest a correlation between CK values and level of type I IFN gene signature in peripheral blood.

Serum CK will be measured as described in Table 4 and Table 5. The relative normalization of serum CK will be derived from the serum CK ULN and the serum CK levels at baseline (Study Day 0 predose) and at the current visit (eg, Study Day 84) using the following formula:

$$\textit{Relative Serum CK Normalization} = \frac{\textit{Serum CK on Study Day 0} - \textit{Serum CK on Current Visit}}{\textit{Serum CK on Study Day 0} - \textit{Serum CK ULN}} \times 100\%$$

For example, if the serum CK is 1000 U/L on Study Day 0 and the serum CK on the Current Visit is 500 U/L, then the relative serum CK normalization is 62.5% based on a serum CK ULN of 200 U/L.

$$\frac{1000\ \text{U/L} - 500\ \text{U/L}}{1000\ \text{U/L} - 200\ \text{U/L}} \times 100\% = 62.5\%$$

However, if the serum CK on the Current Visit is less than the serum CK ULN, the relative CK normalization will be 100%.

3.6.6.2 IMACS Core Set Disease Activity Measures

The IMACS group proposed a core set of outcome measures to assess a clinical improvement in IIM clinical trials (Rider, 2004). The IMACS core set outcome measures includes the following domains:

1) Physician Global Activity Assessment
2) Patient Global Activity Assessment
3) Muscle Strength
4) Physical Function

[redacted]

5) Muscle-associated Enzymes
6) Extramuscular Activity Assessment

Table 6 summarizes the outcome measures for the 6 IMACS core set domains along with their validated methods of assessment. Clinical improvement (ie, IMACS-defined response) in myositis activity will be determined if 3 of the 6 core set measures improve by ≥ 20%, with no more than 2 worsening by ≥ 25% (excluding MMT).

Physician Global Activity Assessment is included as part of MDAAT, and Patient Global Activity Assessment is included as a part of CLINHAQ. In this study, the score for Patient Global Activity Assessment will be extracted from CLINHAQ, so that this indicator is measured only once at each time point.

Table 6 Myositis Core Set of Measures

IMACS Core Set Domain	Validated Method of Assessment
Physician Global Activity Assessment	Horizontal 10 cm VAS as part of MDAAT
Patient Global Activity Assessment	Horizontal VAS of 0 to 10 units as part of CLINHAQ
Muscle Strength	MMT including proximal, distal, and axial muscles assessed on 0-10 or expanded 0-5 point scale
Physical Function	CLINHAQ (Fries, 1980) to measure patient-reported functional status
Serum Muscle-associated Enzymes	At least 2 of CK, LDH[a], ALT, AST, or aldolase
Extramuscular Activity Assessment	Horizontal VAS of physician's composite evaluation based on assessments of activity scores on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiovascular scales of MDAAT

a. For LDH, the median percentage change to define clinical improvement is 25%.

3.6.6.3 Pulmonary Function Tests

Patients' pulmonary function will be tested as a part of the extramuscular portion of MDAAT assessments. Testing will be performed according to ATS/ERS guidelines (Miller, 2005). Prior to testing, patients will be required to withhold short-acting β2-agonists for at least 6 hours if possible.

3.6.6.4 Criteria for Disease Worsening

Disease worsening is defined as any of the following:

1. Worsening of the patient's global condition, as assessed by the physician, by ≥ 2 cm on a 10 cm VAS and worsening of muscle strength in MMT by ≥ 20%;
2. Worsening of global extramuscular activity assessment (an overall assessment of disease activity in extramuscular systems including constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiovascular activity) by ≥ 2 cm on a 10-cm VAS; or
3. Worsening of any 3 of 6 IMACS core set activity measures by ≥ 30%.

[redacted]

3.6.6.5 Myositis Damage Index

The myositis damage index is a comprehensive tool to assess the extent and severity of damage developing in different organs and systems (Appendix D). The index is composed of two portions. One portion counts the items of damage developing in different organs systems. The other portion, the myositis damage score, consists of a series of 10 cm VAS to quantitate the severity of damage in the same organ system.

3.6.6.6 Patient-Reported Outcomes

In addition to the Patient Global Activity Assessment and CLINHAQ evaluated as part of IMACS core set domains, the following patient-reported indicators will be evaluated: SF-36v2 Health Survey (Appendix E), WPAI: SHP questionnaire version 2.0 (Appendix F), pruritus VAS, CDASI (Appendix G), and DLQI (Appendix H). Pruritus VAS, CDASI, and DLQI will be performed in DM patients only.

SF-36v2 Health Survey is a validated instrument for measuring a person's general health status (Ware, 1992) over the past 4 weeks. It consists of two overall summary scores of physical component summary and mental component summary with eight domains: Physical Function, Role Limitations-Physical, Vitality, General Health Perceptions, Bodily Pain, Social Function, Role Limitations-Emotional, and Mental Health. Scores are calculated as from 0-100, in which higher scores indicate better health.

The WPAI: SHP (Reilly, 1993) consists of 6 items and measures work and activity impairment (including absenteeism, presenteeism, and impairment) over the past 7 days. Responses are expressed as impairment percentages (0-100), in which higher numbers indicate greater impairment, lower productivity, or less favorable outcomes.

Pruritus is an important treatable factor that significantly impacts quality of life for patients with DM (Hundley, 2006). A horizontal 10 cm VAS will be used to measure the severity of itching at a specific point in time. The patient-reported score ranges from 0 (no itching) to 10 (severe itching) (Ortonne, 2005).

Quain (2007) reported that the CDASI (Cutaneous DM Disease Area & Severity Index) scores are normally distributed, display greater reliability than the Cutaneous Assessment Tool, and correlate better with physician than patient global skin measures. This report suggested that the CDASI may be the optimal outcome measure for studies of cutaneous DM. The CDASI is scored from 0-76, in which higher scores indicate greater disease severity.

The DLQI (Findlay, 1994) consists of 10 questions related to symptoms and feelings, daily activities, leisure, work or school, personal relationships, and treatment over the past 7 days. Responses range from 0 (not at all) to 3 (very much) for a range of 0 to 30 with higher scores corresponding to greater impairment in quality of life. The DLQI exhibits good test-retest reliability and has been used extensively in clinical research worldwide (Lewis, 2004). Quality of life impairment in DM, as assessed using the DLQI, is greater than in other skin conditions including psoriasis and atopic dermatitis (Hundley, 2006).

[redacted]

3.6.6.7 Photography of Skin Lesions

Photographs of skin lesions in DM patients only will be requested at screening but are not required for study participation. For patients who have skin lesions at screening, up to two representative lesions will be chosen by the investigator and serial photographs will be taken. One of the two lesions will be the lesion selected for the punch skin biopsy. Preferably, the photographs will be taken prior to the punch skin biopsy. For patients who do not have skin lesions at screening but subsequently develop lesions during the study, up to two lesions will be selected by the investigators and serial photographs will be taken during the rest of the study period. See Appendix I for instructions.

3.6.7 Correlative Studies

Correlative studies include collection of serum for assessment of autoantibodies and proteomics, collection of serum for IFN-α assays and other exploratory research, peripheral blood for flow cytometry, and muscle and skin biopsies**.** It is preferred that the follow-up for the open muscle biopsy is done on the contralateral muscle, and the follow-up punch skin biopsy is done in close proximity to the first biopsy.

Other correlative studies include collection of whole blood and muscle for type I interferon inducible gene expression and whole blood for analysis of DNA. Collection of blood for DNA analysis is voluntary, and patients must sign a separate informed consent form (Informed Consent Form for Collection of Blood Samples for DNA Analysis) in order for this test to be done. Patients who do not wish to have the DNA test done will still be eligible for the study.

3.6.7.1 Serum for Exploratory Research and Storage

Serum samples will be obtained and analyzed for exploratory research, including IFN-α assays, analyses of autoantibodies, and proteomics. Analysis of the serum proteome will be carried out through the use of a large multiplex quantitative platform for known analytes. Exploratory studies for novel analytes may be carried out by 2-dimensional electrophoresis followed by high performance liquid chromatography and mass spectrophotometry or other methods.

Aliquots of serum may be frozen and stored for additional exploratory studies based on research findings.

3.6.7.2 Serum for Autoantibody Testing

As part of the disease activity and damage assessments, autoantibodies including ANA, anti-SSA, anti-RNP, anti-Jo-1, anti-SRP, and anti-Mi-2 antibodies will be measured in serum samples.

3.6.7.3 Open Muscle Biopsies

Open muscle biopsies will be performed at visits indicated in Table 4. The initial open muscle biopsy will be performed on an involved muscle within 28 days prior to Study Day 0. Involved muscle is defined as having a muscle strength of 4 to 4-/5 as assessed by MMT. The repeated open muscle biopsy will be performed on a muscle that was noted to be involved on Study Day

0. If involved on Study Day 0, the contralateral muscle is the preferred site of the repeated biopsy. The open muscle biopsy samples collected during the trial will undergo histopathological grading and IHC analysis of cellular infiltrates, including dendritic cell subtypes, B cells, and T cells. Additionally, gene expression will be analyzed, and changes in IFN-inducible protein levels within muscle specimens will be assessed by IHC methods.

3.6.7.4 Skin Biopsies

Skin lesions in patients with DM will be selected by the investigator for punch biopsy. Analysis of type 1 IFN-inducible gene expression, histologic evaluations, and IHC analyses of the punch skin biopsy samples will be performed. The procedure is requested but not required for study participation.

3.6.7.5 Flow Cytometry

Peripheral blood samples will be collected for flow cytometry at selected sites in North America. Phenotypic analysis of blood cell populations will be conducted using multicolor flow cytometry with a panel of markers specific to cell surface and intracellular markers. The panel of markers covers all major peripheral blood cell subsets including B cells, monocytes, neutrophils, blood dendritic cells, and various types of T cells. The longitudinal follow-up of the patients will help to determine if any changes in the characteristics of the cellular populations are correlated to the study drug and if the changes are associated with clinical effects.

3.6.7.6 Effects on Type I IFN-Inducible Gene Expression

The pharmacodynamics of MEDI-545 will be studied through analyses of its effects on type 1 IFN-inducible gene expression in whole blood, muscle, and skin. The levels of mRNA for type I IFN-inducible genes will be measured using genomic tests. PCR assay on selected panel of genes may be used to confirm the results. The analysis in whole blood is performed using Affymetrix whole genome expression array and taqMan-based assay on selected panel of genes. In muscle and skin, immunohistochemical methods will be used to stain for a pre-selected panel of genes that will allow further assessment of the pathogenesis of inflammatory muscle disease. Subsequent studies will be dependent upon the results obtained from our initial analyses.

3.6.7.7 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.

3.7 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 Study Day 350. It should be specified on the case report form whether or not the patient completed the study follow-up procedures through Study Day 350.

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 98, the patient should complete the evaluations scheduled for Study Day 98. If the patient discontinues after Study Day 98 and prior to Study Day 196, the patient should complete the evaluations scheduled for Study Day 196. If the patient discontinues after Study Day 196, the evaluations scheduled for Study Day 350 must be completed. 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 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), an AE is:

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

An AE includes but is not limited to:

- Any clinically significant worsening of a pre-existing condition;
- An AE occurring from overdose (ie, a dose higher than that prescribed by a healthcare professional for clinical reasons, or a dose higher than that described on the marketed product label) of an investigational or marketed product, whether accidental or intentional;
- An AE occurring from abuse (eg, use for non-clinical reasons) of an investigational or marketed product;
- An AE that has been associated with the discontinuation of the use of an investigational or marketed product; and
- Adverse changes from baseline, which are listed in the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE V3.0), which can be found in Attachment 1.

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

4.1.2 Study Reporting Period for Adverse Events

The reporting period for adverse events is the period from the signing of informed consent through Study Day 350. AEs will not be recorded for patients deemed screening failures.

4.1.3 Recording of Adverse Events

AEs will be reported using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational study product, possible etiologies and whether the event meets criteria as a SAE and therefore requires immediate notification of the Sponsor. See Sections 4.3 and 4.4 regarding guidelines

for assessment of severity and relationship, respectively, and Section 4.2.1 for the definition of SAEs. If an AE evolves into a condition which becomes "serious" the investigator will additionally report to the Sponsor on the ***SERIOUS ADVERSE EVENT (SAE) REPORT FORM***.

4.2 Serious Adverse Events

4.2.1 Definition of Serious Adverse Events

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

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

4.2.2 Study Reporting Period for Serious Adverse Events

The reporting period for SAEs is the period from the signing of informed consent 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.

[redacted]

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 a Serious Adverse Event, regardless of the presumed relationship to the Study Drug, 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 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 Food and Drug Administration (FDA), other applicable regulatory authorities, and participating investigators, in accordance with the U.S. Code of Federal Regulations (21 CFR 312.32 and 312.33) ICH Guidelines, and/or local regulatory requirements. MedImmune may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by MedImmune as soon as it becomes available.

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

The investigator must comply with the applicable regulatory requirements related to the reporting of serious adverse events to the Institutional Review Board or Independent Ethics Committee. The Institutional Review Board or Independent Ethics Committee must be informed in a timely manner by the principal investigator of serious adverse events occurring at their site during the study. Investigators must also submit safety information provided by MedImmune to the Institutional Review Board or Independent Ethics Committee 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 purpose of study analysis, if the event has not resolved at the end of the study reporting period it will be documented as ongoing. For purposes of regulatory safety monitoring the investigator is required to follow the event to resolution and report to the Sponsor the outcome of the event using the ***SERIOUS ADVERSE EVENT (SAE) REPORT FORM***.

4.3 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of adverse events and serious adverse events. The determination of severity should be made by a health care professional qualified to review AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment and the severity categories of *Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5*. Severity of toxicity will be graded according to the NCI CTCAE V3.0, as described in detail in Attachment 1.

4.4 Assessment of Relationship

An SAE is considered "product-related" for the purposes of regulatory reporting if the Investigator, the Medical Monitor, or the Product Safety Physician assesses the SAE as possibly, probably, or definitely related 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 SAE is treated as product-related for the purposes of reporting to regulatory authorities. An SAE may be deemed to be not related to the product for purposes of regulatory reporting only if the Investigator, Medical Monitor, and Product Safety Physician, if applicable, agree that the SAE is not product-related.

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

In addition to SAEs, 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. Patients who wish to become pregnant should be followed 3 months after the last dose of study drug*
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 event which, in the opinion of the investigator or the Medical Monitor, contraindicates further dosing such as illnesses or complications.

*Patients who 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 if any of the following occur in the patient in question:

- Withdrawal of consent;
- Pregnancy (Patients who become pregnant during the study period must not receive additional doses of study drug 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);
- Any life-threatening clinical event related to the study drug;
- Severe hypersensitivity (anaphylactic) reaction to the study drug, Grade 3 or higher;
- Infusion reactions, Grade 3 or higher as defined in Table 3;
- 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;
- If 3 consecutive doses of study drug are missed due to abnormal LFTs (ALT, AST);
- Two consecutive total bilirubin values taken at least 1 week apart > 2 x ULN not due to Gilbert's syndrome or hemolysis; or
- 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 study 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

If any of the following events occurs, no further administration of study drug will take place and no further patients will be entered or randomized into that cohort or any higher dose cohort until the event has been reviewed by the Medical Monitor and the SMC.

- 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;
- Any life-threatening clinical event related to the study drug, including anaphylactic reaction to study drug, Grade 4;
- 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 in any patient; or
- 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 modified, or

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 rules for dose escalation are as follows:

Dose Cohort 1 (single-dose, 0.3 mg/kg or placebo) will be started first. Dosing at each next higher dose cohort (Dose Cohort 2 [1.0 mg/kg or placebo], Dose Cohorts 3A and 3B [3.0 mg/kg or placebo], and Dose Cohort 4 [10.0 mg/kg or placebo] will commence after the Medical Monitor has reviewed the safety information including data through Study Day 42 from the first randomized 8 patients in each of the preceding lower dose cohorts and all cumulative safety data available in all cohorts, and has determined that the safety profile is acceptable (ie, Dose Cohort 2 will start only after safety data from the 8 patients in Dose Cohort 1 has been reviewed and it has been deemed safe; likewise, Dose Cohorts 3A and 3B will start only after the data from the 8 patients in Dose Cohort 2 has been reviewed and it has been deemed safe; Dose Cohort 4 will start only after safety data from the 8 patients from Dose Cohort 3A have been reviewed and it has been deemed safe). Dose Cohorts 3B and 4 will enter patients in parallel.

Available PK data from 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.

The SMC will independently review cumulative safety surveillance data throughout the study and make recommendations regarding the study progression. The SMC can stop study entry and dosing as it deems necessary.

4.10 Monitoring of Dose Administration

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

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. No formal statistical tests are planned. Missing data will be treated as missing. No data will be imputed unless otherwise specified. Study Baseline values will be defined as the last valid assessment prior to the first administration of study drug. All data will be collected from screening through Study Day 350.

5.2 Sample Size

For the study, 40 patients (5 dose cohorts of 8 patients each) will be randomized into the study. Within each dose cohort, 6 patients will initially receive MEDI-545 and continue receiving MEDI-545 for 14 doses in total; 2 patients will initially receive 7 doses of placebo followed by 7 doses of MEDI-545. In addition, a dose cohort may be expanded by up to 4 additional patients if eligible patients are already in screening at the time 8 patients have been randomized into the dose cohort. Sample size was not based on a formal statistical calculation, but based on clinical considerations as well as the primary objective of safety assessment.

Table 7 and Table 8 present the probability of observing at least one subject with an infrequently occurring AE when assuming a range of potential observed AE rates and exact binomial 95% confidence intervals to assess the precision of estimates of the AE rate for the MEDI-545 single cohort n=6 and for the combined cohorts (n= 12, 18, 24, and 30 respectively) before Study Day 98.

Table 7 Expected Numbers of Subjects with Adverse Events and Probabilities of Observing at Least 1 or 2 Subjects with Adverse Events Given The True Event Rates

N	True Event Rate (%)	Number of Subjects with Events Expected	Probability of Observing at Least One Subject with an Event (%)	Probability of Observing at Least Two Subjects with Events (%)
6	0.8	0	4.7	0.1
6	6.5	0	33.2	5.3
12	0.5	0	5.8	0.2
12	3.0	0	30.6	4.9
18	0.3	0	5.3	0.1
18	2.0	0	30.5	5.0
24	0.2	0	4.7	0.1
24	1.5	0	30.4	5.0
30	0.2	0	5.8	0.2
30	1.5	0	36.5	7.4

[redacted]

Table 8 Estimated Event Rates and 95% Exact Binomial Confidence Intervals Given The Numbers of Subjects with Adverse Events Observed

N	Number of Subjects with Events Observed	Estimated Event Rate (%)	95% Confidence Interval
6	0	0.0	(0.0%, 45.9%)
6	1	16.7	(0.4%, 64.1%)
6	2	33.3	(4.3%, 77.7%)
12	0	0.0	(0.0%, 26.5%)
12	1	8.3	(0.2%, 38.5%)
12	2	16.7	(2.1%, 48.4%)
18	0	0.0	(0.0%, 18.5%)
18	1	5.6	(0.1%, 27.3%)
18	2	11.1	(1.4%, 34.7%)
24	0	0.0	(0.0%, 14.2%)
24	1	4.2	(0.1%, 21.1%)
24	2	8.3	(1.0%, 27.0%)
30	0	0.0	(0.0%, 11.6%)
30	1	3.3	(0.1%, 17.2%)
30	2	6.7	(0.8%, 22.1%)

5.3 Patient Populations

The patient population analyzed will include all patients who receive at least one dose of study drug.

Safety results will be analyzed in all patients who receive any study drug. Evaluability for analyses of MEDI-545 serum concentrations and PK parameters will be determined based upon the frequency and timing of the serum samples obtained. IM analysis will be performed in all patients who have received at least one dose of MEDI-545. Efficacy results will be analyzed in all randomized patients who receive any study drug.

5.4 Study Endpoints

5.4.1 Primary Endpoints

The primary endpoints of the study are the safety and tolerability of MEDI-545, which 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. AEs and SAEs occurring after administration of study drug will be coded using the current version of MedDRA and will be summarized by system organ class and preferred terms, by severity, and by relationship to study drug. AEs and SAEs will be summarized for placebo, each of the MEDI-545 dose cohorts, and for all MEDI-545 doses combined. Since patients initially randomized to placebo will receive placebo for the first 7 doses and MEDI-545 for the next 7 doses, AEs and SAEs will also be reported with respect to different treatment periods. The rate of virus detection by surveillance testing will be summarized descriptively.

[redacted]

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

5.4.2 Secondary Endpoints

The secondary endpoints of the study are the PK and IM of multiple IV doses of MEDI-545 and evaluations of disease activity. 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 ($C_{ss,}$ C_{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 non-compartmental 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}.

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

5.4.3 Exploratory Endpoints

5.4.3.1 Clinical Activity

The major clinical measures of myositis disease activity will include serum creatine kinase normalization, IMACS core set disease activity measures (physician's global activity assessment, patient global activity assessment, muscle strength assessed by MMT, physical function, muscle-associated enzymes, and extramuscular activity assessment), patients' need for new or increased doses of immunosuppressive therapy, changes in patients' immunosuppressive therapy during the follow-up period, photography of skin lesions, and pulmonary function testing. These assessments will be summarized descriptively by treatment group and time point. A descriptive summary of the number and percent of patients who have reached any of the following: 1) complete CK normalization as indicated by relative normalization of 100% and 2) IMACS-defined response will be presented for placebo and each of the MEDI-545 dose group. The major patient-reported outcomes, including SF-36v2 Health Survey, pruritus VAS, CDASI, DLQI, and WPAI: SHP questionnaire will also be summarized descriptively.

5.4.3.2 Biological Activity and Mechanism of Action

Type I IFN-inducible genes will be used to measure the pharmacodynamics of MEDI-545. Whole blood samples and muscle and skin biopsies will be used to analyze the effects of MEDI-545 on levels of mRNA for type I IFN-inducible genes, using microarray analyses. PCR assay on selected panel of genes may be used to confirm the microarray results.

Other descriptive analyses may include levels of expression of type I IFN-inducible proteins and non-type I IFN-inducible genes in whole blood and muscle and skin biopsies, IHC of muscle and skin biopsies, serum IFN-α levels, proteomics and changes in autoantibody levels or profiles, flow cytometry results, and gene polymorphisms associated with response to MEDI-545.

5.5 Interim Analyses

Interim analysis of the type I inducible gene expression 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 in the study:

- After the first 2 cohorts complete the Study Day 98 evaluation;
- When at least 8 patients in Dose Cohort 4 complete the Study Day 98 evaluation; and
- After all cohorts complete Study Day 196 evaluation.

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 eCRFs, 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.

[redacted]

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 or the sponsor of the clinical trial. The principal investigator must also comply with all applicable privacy regulations (eg, Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

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

A list of IRB/IEC members should be obtained by the investigator and provided to the sponsor. Any documents that the IRB/IEC may need to fulfil 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

[redacted]

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.

[redacted]

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 ([redacted]) was amended to Version 2.0 (dated [redacted]) to provide more information about genetic testing; to include pregnancy testing before each dose of MEDI-545 and every 12 weeks thereafter; to exclude patients with a history of active tuberculosis; to clarify that Quantiferon-TB Gold assay for the diagnosis of latent tuberculous infection will be done at selected sites; to clarify that IVIG may be given in the study; to clarify other events requiring immediate reporting, and to correct typographical errors. The changes made to Version 1.0 of the protocol to create Version 2.0 are summarized in Appendix J.

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 reducing the starting dose of MEDI-545 from 1.0 to 0.3 mg/kg, reducing the highest dose of MEDI-545 from 30.0 to 20.0 mg/kg, and setting the infusion volume at 100 mL and the infusion time to 60 minutes. Other changes include updating the safety information on MEDI-545 and clarification of text. The changes made to Version 2.0 of the protocol to create Version 3.0 are summarized in Appendix J.

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 updating preclinical and clinical information; identification of specific safety biomarkers to analyze infusion reactions; addition of medically significant infusion reactions as an immediately reported event; and clarification of text. The changes made to Version 3.0 of the protocol to create Version 4.0 are summarized in Appendix J.

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 changing the medical monitor; updating preclinical

[redacted]

and clinical information; reducing the highest dose of MEDI-545 from 20.0 to 10.0 mg/kg; reducing the number of patients from 40 to 32; reducing the number of dose cohorts from five to four; indicating that CRPS will no longer be blinded to the study, although they will continue to be part of the project team, revisions to the inclusion and exclusion criteria; provided more detailed information regarding anaphylactic infusion reactions and suggested treatment procedures to the investigators, if any occur. Other revisions include changes to the statistical considerations section and clarification of text throughout the protocol. Finally, a new Table (number 3) was added and the rest of the tables were renumbered. The changes made to Version 4.0 of the protocol to create Version 5.0 are summarized in Appendix J.

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 preclinical and clinical information; moving the optional DNA analysis from Study Day 0 to Study Day 14; increasing the number of dose cohorts from 4 to 5 by adding Dose Cohort 3B, which will only include patients with low/undetectable gene signature; increasing the number of patients from 32 to 40; providing clarification that a physician must be present at the sites during all study drug administrations; 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; clarifying that patients will provide the vaginal self-collected swabs and clarification that these may also be collected by qualified medical personnel, if approved by the sponsor; providing clarification that patients who become pregnant during the study period must not receive additional doses of study product and should proceed to the follow-up phase beginning at Study Day 185. Other revisions include changes to the statistical considerations section and clarification of text throughout the protocol. The changes made to Version 5.0 of the protocol to create Version 6.0 are summarized in Appendix J.

Summary of Changes from Version 6.0 to Version 7.0 of the Study Protocol

Version 6.0 of the protocol (dated [redacted]) was amended to Version 7.0 (dated [redacted] The major changes include: 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 second interim analysis (which was to occur after all patients in Dose Cohort 4 completed Day 98) to when a minimum of 8 patients in Dose Cohort 4 complete Study Day 98; clarifying that complete clinical response and remission will not be assessed in this study (as the study duration is not long enough to do so); and providing guidance in Appendix J 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 K.

[redacted]

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APPENDIX A Manual Muscle Testing

MMT-8 is a set of 8 designated muscles tested unilaterally (score range 0-80) or bilaterally (score range 0-150) as follows:

Muscle Groups	**Right (0 – 10)**	**Left (0 – 10)**	**Axial (0 – 10)**
Axial Muscles (0 – 10)			
Neck Flexors	**X**	**X**	**0-10**
Proximal Muscles (0 – 100)			
Deltoid	**0-10**	**0-10**	**X**
Biceps brachii	**0-10**	**0-10**	**X**
Gluteus maximus	**0-10**	**0-10**	**X**
Gluteus medius	**0-10**	**0-10**	**X**
Quadriceps	**0-10**	**0-10**	**X**
Distal Muscles (0 – 40)			
Wrist Extensors	**0-10**	**0-10**	**X**
Ankle dorsiflexors	**0-10**	**0-10**	**X**
MMT-8 score (0 – 150)	**0-70**	**0-70**	**0-10**

[redacted]

APPENDIX B Clinical Health Assessment Questionnaire (CLINHAQ)

[redacted]

Protocol MI-CP151
Visit _ _ _
Subj Initials _ _ _

For Subject Completion ONLY

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

CLINICAL HEALTH ASSESSMENT QUESTIONNAIRE (CLINHAQ)

We are interested in learning how your illness affects your ability to function in daily life. Place an X in the box which best describes your usual abilities OVER THE PAST WEEK:

Are you able to:	Without ANY Difficulty (0)	With SOME Difficulty (1)	With MUCH Difficulty (2)	UNABLE To Do (3)
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
Stand up from a straight chair?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Cut your meat?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps	☐	☐	☐	☐

Please place an X in the box beside any aids or devices that you usually use for any of the above activities:

☐Cane (W) ☐Crutches (W) ☐Walker (W) ☐Wheelchair (W) ☐Built up or special utensils (E)
☐Devices used for dressing (button hook, zipper pull, long handled shoe horn) (D) ☐Special or built up chair (A)

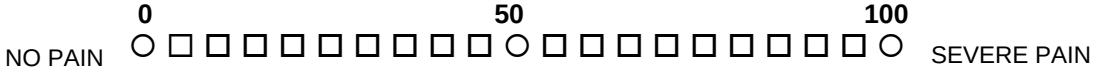
Place an X in the box beside any categories for which you usually need HELP FROM ANOTHER PERSON:

☐Dressing and Grooming (D) ☐Arising (A) ☐Eating (E) ☐Walking (W)

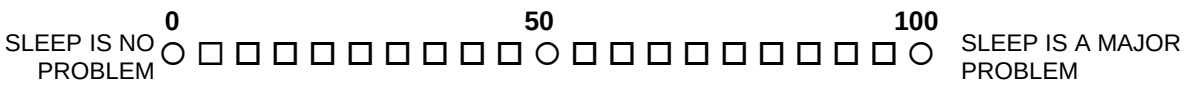
AT THIS MOMENT, are you able to:	Without ANY Difficulty (0)	With SOME Difficulty (1)	With MUCH Difficulty (2)	UNABLE To Do (3)
Walk two miles?	☐	☐	☐	☐
Participate in sports and games as you would like?	☐	☐	☐	☐
Get a good night's sleep?	☐	☐	☐	☐
Deal with feelings of anxiety or being nervous?	☐	☐	☐	☐
Deal with feelings of depression or feeling blue?	☐	☐	☐	☐

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

How much pain have you had because of your illness in the past week? Place an X in the box that best describes the severity of your pain on a scale of 0-100.



How much of a problem has sleep (i.e. resting at night) been for you IN THE PAST WEEK? Place an X in the box below that best describes how much of a problem sleep has been for you on a scale of 0-100.



Protocol MI-CP151
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PID _ _ _ _ _ _ _ _
Date _ _/ _ _ _/ _ _ _ _
(DD/ MON/ YYYY)

Considering ALL THE WAYS THAT YOUR ILLNESS AFFECTS YOU, RATE HOW YOU ARE DOING on the following scale. Place an X in the box below that best describes how you are doing on a scale of 0-10.

VERY WELL **0** ○ □ □ □ □ □ □ □ □ □ **5** ○ □ □ □ □ □ □ □ □ □ **10** ○ VERY POORLY

Place an X in the box which best describes your usual abilities OVER THE PAST WEEK:

Are you able to:	Without ANY Difficulty (0)	With SOME Difficulty (1)	With MUCH Difficulty (2)	UNABLE To Do (3)
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
Open jars which have been previously opened?	☐	☐	☐	☐
Open car doors?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Run errands and shop?	☐	☐	☐	☐
Do chores such as vacuuming or yardwork?	☐	☐	☐	☐

Please place an X in the box beside any AIDS or DEVICES that you usually use for any of these activities:

☐Bathtub bar (H) ☐Raised toilet seat (H) ☐Jar opener for jars previously opened (G)

☐Long-handled appliances for reach (R) ☐Long-handled appliances in bathroom (H)

☐Other _____

Please place an X in the box beside any categories for which you usually need HELP FROM ANOTHER PERSON:

☐Hygiene (H) ☐Reach (R) ☐Gripping and opening things (G) ☐Errands and Chores (E/C)

We are interested in knowing about any problems that you may have been having with fatigue. How much of a problem has fatigue or tiredness been for you IN THE PAST WEEK? Place an X in the box below that best describes the severity of your fatigue on a scale of 0-10.

FATIGUE IS NO PROBLEM **0** ○ □ □ □ □ □ □ □ □ □ **5** ○ □ □ □ □ □ □ □ □ □ **10** ○ FATIGUE IS A MAJOR PROBLEM

Protocol MI-CP151
Visit _ _ _
Subj Initials _ _ _

For Subject Completion ONLY
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PID _ _ _ _ _ _ _ _ _
Date _ _/ _ _ _/ _ _ _ _
(DD/ MON/ YYYY)

Please place an X in the box under the most appropriate answer for each question. Try to answer every question.

DURING THE PAST MONTH:	Always (0)	Very Often (1)	Fairly Often (2)	Some-times (3)	Almost Never (4)	Never (5)
1. How much of the time have you enjoyed the things you do?	☐	☐	☐	☐	☐	☐
2. How much of the time have you felt tense or "high strung"?	☐	☐	☐	☐	☐	☐
3. How much have you been bothered by nervousness, or your "nerves"?	☐	☐	☐	☐	☐	☐
4. How often did you find yourself having difficulty trying to calm down?	☐	☐	☐	☐	☐	☐
5. How much of the time have you been in low or very low spirits?	☐	☐	☐	☐	☐	☐
6. How much of the time did you feel relaxed and free of tension?	☐	☐	☐	☐	☐	☐
7. How much of the time have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
8. How often did you feel that nothing turned out for you the way you wanted it to?	☐	☐	☐	☐	☐	☐
9. How much of the time have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
10. How often did you feel that others would be better off if you were dead?	☐	☐	☐	☐	☐	☐
11. How much of the time were you able to relax without difficulty?	☐	☐	☐	☐	☐	☐
12. How often have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐

APPENDIX C Myositis Disease Activity Assessment Tool (MDAAT)

GLOSSARY FOR THE MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL (MDAAT)

CONSTITUTIONAL

1. *Pyrexia:* refers to a **documented** fever in excess of 38°C
2. *Weight loss*: unintentional weight loss of greater than 5% in body weight
3. *Fatigue:* sufficiently severe to interfere with normal daily activities not attributable to another cause

CUTANEOUS DISEASE ACTIVITY

4. *Cutaneous ulceration:* extensive injury to dermis or deeper due to dermatomyositis
5. *Erythroderma:* generalized, widespread confluent erythema involving both sun-exposed and non sun-exposed skin with >50% of body surface area involved
6. *Panniculitis:* tender erythematous or violaceous nodules or depressions due to inflammation in the subcutaneous fat
7. *Erythematous rashes* (includes malar rash, facial erythema, linear extensor erythema, V-sign, shawl sign, periungual erythema, sun-exposed or non sun-exposed erythema): (a) **Secondary change:** *erosions:* slightly depressed lesions with denuded epithelium; *vesiculobullous*: fluid-filled lesions ≤ 0.5cm (vesicles) or ≥ 0.5cm (bullae); *necrosis:* dead or devitalized tissue manifested as a black eschar, ulceration or wet or dry gangrene. (b) **Without secondary change:** erythema without accompanying changes to epidermis or dermis
8. *Heliotrope rash:* purple, lilac-colored or erythematous patches over eyelids or in a periorbital distribution, often associated with periorbital edema
9. *Gottron's papules or sign:* erythematous to violaceous papules, plaques or macules (sign) over extensor surfaces of joints, which are sometimes scaly
10. *Periungual capillary changes:* dilatation of periungual capillaries which may be accompanied by vessel dropout and which is visible by naked eye examination or by using additional magnification with otoscopy
11. *Alopecia:*
    a) Diffuse: non-scarring, non-erythematous widespread alopecia
    b) Focal: patchy alopecia with scaling and erythema localized to areas of inflammation (i.e. scalp rash of dermatomyositis)
12. *Mechanic's hands:* hyperkeratosis and scaling with frequent fissuring and cracking along the lateral and palmar aspects of the fingers

SKELETAL DISEASE ACTIVITY

13. *Arthritis:* active joint inflammation marked by tenderness, warmth or swelling
    a) Severe: arthritis of **two or more** joints with clinically significant loss of the functional range of movement and requiring assistance with activities of daily living
    b) Moderate: arthritis of **one or more** joints with some loss of functional range of movement, but not requiring assistance with activities of daily living
    c) *Mild*: arthritis of **one or more** joints with neither loss of range of motion nor impaired activities of daily living
14. *Arthralgia*: joint pain with or without stiffness but due to an inflammatory process in two or more joints

GASTROINTESTINAL DISEASE ACTIVITY

15. *Dysphagia*: difficulty swallowing, chewing or eating documented by clinical symptoms or by barium swallow examination, manometry, or other objective measure

    If dysphagia has been stable and unchanged and is present for > 6 months, this is most likely to represent a damage item and should be scored as such unless there is good evidence of reversibility.

    a) Severe: accompanied by aspiration pneumonia, nasal regurgitation, or difficulty in protecting the airway
    b) Moderate: frequent or moderate symptomatic difficulty swallowing, chewing or eating
    c) Mild: occasional dysphagia or asymptomatic dysphagia noted on objective testing; can eat regular diet
16. *Abdominal pain:* pain in the abdominal area related to the myositis disease process
    a) Severe: requiring hospitalization, treatment, or bowel rest with nothing per oral route (NPO)
    b) Moderate: requiring treatment, but not hospitalization or NPO
    c) Mild: no intervention required and does not interfere with function

PULMONARY DISEASE ACTIVITY

17. *Respiratory muscle weakness **without** interstitial lung disease (ILD):* Shortness of breath worsened with exertion or hypoventilation on pulmonary function testing in the absence of intrinsic lung disease

18. *Active reversible ILD:* Previously documented by radiography or pathology. Only active features are graded, not those based on pulmonary fibrosis or irreversible features.

    - In patients with new or significant deterioration in symptoms a complete evaluation with pulmonary function testing (PFTs) and radiography (chest x-ray or high resolution CT scan) is required. If further investigation is necessary to elucidate the cause of symptoms, then defer scoring until results are available.

    - 18a can always be answered clinically, but 18b and 18c may not be answered if radiography and PFTs (respectively) have not been recently performed.

    - If there has been no significant change since last visit - score 2. If results normalize - score 0. If patient is clinically better but no recent radiography/PFTs are available, score as NA.

    Any percentage change in PFTs is based on a change in the absolute value. As a guide a significant change in PFTs is defined as a ≥10% change in FVC (minimum 200 ml for adults) or ≥15% in DLCO (minimum 3ml/min/mmHg for adults). However, in some patients smaller changes in FVC or DLCO may be suggestive of worsening disease in the context of worsening symptoms or imaging studies.

19. *Dysphonia*: alteration in voice quality, resonance, articulation or speech rate from normal
    a) Moderate to severe: persistent voice symptoms or those that interfere with communication
    b) Mild: intermittent voice symptoms not interfering with communication

CARDIOVASCULAR DISEASE ACTIVITY

20. *Pericarditis:* Inflammation of the pericardium defined clinically or by electrocardiogram (EKG) or echocardiogram
21. *Myocarditis*: Inflammation of the myocardium defined clinically or with echocardiographic or other objective evidence
22. *Arrhythmia:* clinical or electrocardiographic evidence of irregular heart beat
    a) Severe arrhythmia: symptomatic and requiring therapy or other intervention, excluding sinus tachycardia
    b) Other cardiac arrhythmias: symptomatic, but not requiring intervention, excluding sinus tachycardia
23. *Sinus tachycardia:* resting heart rate > 100 beats per minute in an adult patient or greater than upper limit of age-appropriate normal value in a pediatric patient

OTHER DISEASE ACTIVITY

24. Specify feature that is felt to be due to the myositis disease process. Then on the VAS rate the severity of this feature: 'max' would be severe involvement with requirement for intensive care in the case of a systemic feature, or extensive/generalized cutaneous involvement.

EXTRAMUSCULAR GLOBAL ASSESSMENT

Overall evaluation for the disease activity in all extramuscular systems (**excluding** muscle disease activity). **This is an IMACS Core Set Measure.**

MUSCLE DISEASE ACTIVITY

25. *Myositis:* Muscle inflammation based upon manual muscle strength testing, functional assessments, laboratory or other testing. **In patients with stable muscle atrophy and damage only weakness attributable to active myositis is scored**
    a) *Severe muscle inflammation:* requiring assistance with activities of daily living and severe loss of function
    b) *Moderate muscle inflammation*: not requiring assistance with activities of daily living with some loss of function
    c) *Mild muscle inflammation:* little or no loss of function
26. *Myalgia*: muscle pain or tenderness

GLOBAL DISEASE ACTIVITY

Physician judgment of overall disease activity based on and laboratory assessments. **This is an IMACS Core Set Measure.**

IMACS FORM 07A: MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL (MDAAT) – 2005, VERSION 2

General Guidelines for Completion:

This is a combined tool that captures the physician's assessment of disease **activity** of various organ systems using (1) the 0-4 scale described below and (2) a visual analog scale (VAS). Please assess the clinical features (items 1-26) of each organ system based upon:

a) The presence of clinical features or symptoms **within the previous 4 weeks that are due to active disease** (i.e. use your clinical judgment to determine how active the myositis-associated clinical feature has been **within the previous 4 weeks**)

b) The judgment that the feature is due to the myositis disease process (i.e. clinical findings known or suspected to be due to another disease process or due to therapy should **NOT** be considered in this evaluation)

c) The concept that disease activity is defined as a potentially reversible finding

d) A clinical, functional, and laboratory assessment for each organ system:

NA = Cannot be assessed
0 = Not present in the last 4 weeks
1 = Improving - clinically significant improvement in the last 4 weeks compared to the previous 4 weeks
2 = The same - manifestations that have been present for the last 4 weeks without significant improvement or deterioration compared to the previous 4 weeks
3 = Worse - clinically significant deterioration over the last 4 weeks compared to the previous 4 weeks
4 = New - in the last 4 weeks (compared to the previous 4 weeks)

Also, rate your overall (global) assessment of the ongoing disease activity over the past 4 weeks for each organ system on the 0-10cm VAS scale (which precedes the listed clinical features) by drawing a **vertical** mark on the 10cm line according to the following guidelines:

- left end of line = no evidence of disease activity
- midpoint of line = moderate disease activity
- right end of line = extreme or maximum disease activity

Please review the glossary as you score each listed clinical feature. The VAS score for each organ system integrates the severity of activity based upon all of the clinical features listed for that particular organ system.

NOTE: The "Extramuscular Global Assessment" is very important as this is a Core Set Measure encompassing an overall evaluation for the disease activity in all the extramuscular organ systems and excludes muscle disease activity.

Guidelines for scoring mild, moderate, severe:

First, identify the category of mild-severe **using the glossary as a guide**. Then score what has happened in the last 4 weeks compared to the previous 4 weeks. Note that with worsening (3) or new (4) activity in the designated category, the same degree of activity should be ascribed in the items that are "less severe." For example:

- In a patient developing new moderate muscle inflammation (see glossary for definition) in the last 4 weeks, "moderate muscle inflammation" (25b) would score a 4 as would "mild muscle inflammation" (25c)
- If "severe muscle inflammation" worsened in the last 4 weeks, then the severe (25a), moderate (25b) and mild (25c) muscle inflammation categories would all score a 3

If a patient had severe muscle inflammation at last visit one month ago and improves to a moderate category over the past 4 weeks (based on the glossary definition), then score the severe category (25a) as a 1 (improving) and score moderate (25b) and mild (25c) as either a 1 or 2 (this would depend on just how much improvement has occurred over the last month so the glossary should be reviewed for this). If one month later the symptoms have further improved, then score the severe category (25a) as a 0 and the moderate (25b) and mild (25c) categories as a 1.

IMACS FORM 07a: MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL – 2005, Version 2

Subject's IMACS number: **ASSESSOR:** **Date Assessed:** **Assessment number:**

Constitutional Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Severe fatigue or malaise resulting in being bed bound and an inability to perform self care

1.	Pyrexia – documented fever > 38° Celsius	0	1	2	3	4	NA
2.	Weight loss – unintentional > 5%	0	1	2	3	4	NA
3.	Fatigue/malaise/lethargy	0	1	2	3	4	NA

Cutaneous Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** - Ulceration to muscle, tendon or bone; - Extensive erythroderma

4.	Cutaneous ulceration	0	1	2	3	4	NA
5.	Erythroderma	0	1	2	3	4	NA
6.	Panniculitis	0	1	2	3	4	NA
7.	Erythematous rashes:						
	a. **with** secondary changes (e.g. accompanied by erosions, vesiculobullous change or necrosis)	0	1	2	3	4	NA
	b. **without** secondary changes	0	1	2	3	4	NA
8.	Heliotrope rash	0	1	2	3	4	NA
9.	Gottron's papules/sign	0	1	2	3	4	NA
10.	Periungual capillary changes	0	1	2	3	4	NA
11.	Alopecia:						
	a. Diffuse hair loss	0	1	2	3	4	NA
	b. Focal, patchy with erythema	0	1	2	3	4	NA
12.	Mechanics hands	0	1	2	3	4	NA

Skeletal Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Severe arthritis with extreme loss of function (bedridden, inability for self care)

13. Arthritis:						
a. Severe active polyarthritis	0	1	2	3	4	NA
b. Moderately active arthritis	0	1	2	3	4	NA
c. Mild arthritis	0	1	2	3	4	NA
14. Arthralgia	0	1	2	3	4	NA

Gastrointestinal Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Major abdominal crisis requiring surgery or intensive care

15. Dysphagia:						
a. Moderate/severe dysphagia	0	1	2	3	4	NA
b. Mild dysphagia	0	1	2	3	4	NA
16. Abdominal pain related to the myositis disease process:						
a. Severe	0	1	2	3	4	NA
b. Moderate	0	1	2	3	4	NA
c. Mild	0	1	2	3	4	NA

Pulmonary Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Active interstitial lung disease or respiratory muscle weakness requiring ventilatory support

17. Respiratory muscle weakness **without** interstitial lung disease (ILD):						
a. Dyspnea at rest	0	1	2	3	4	NA
b. Dyspnea on exertion	0	1	2	3	4	NA
18. **Active reversible ILD** (i.e. not just ventilatory abnormalities due to pulmonary fibrosis): *Read glossary for scoring pulmonary function tests and score each item below (a,b and c).*						
a. Dyspnea or cough due to ILD	0	1	2	3	4	NA
b. Parenchymal abnormalities on chest x-ray or high resolution CT scan (HRCT) and/or ground glass shadowing on HRCT	0	1	2	3	4	NA
c. Pulmonary Function Tests: ≥ 10% change in FVC or DLCO	0	1	2	3	4	NA
19. Dysphonia:						
a. Moderate to severe	0	1	2	3	4	NA
b. Mild	0	1	2	3	4	NA

Cardiovascular Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Myocarditis, pericarditis or severe arrhythmia requiring intensive care unit

20. Pericarditis	0	1	2	3	4	NA
21. Myocarditis	0	1	2	3	4	NA
22. Arrhythmia:						
a. Severe arrhythmia	0	1	2	3	4	NA
b. Other arrhythmia, except sinus tachycardia	0	1	2	3	4	NA
23. Sinus tachycardia	0	1	2	3	4	NA

Other Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Extreme disease activity with major impact on function

24. Specify:_____	0	1	2	3	4	NA

Extramuscular Global Assessment	**(Absent)** ——— **(Maximum)** __ __ . __ cm	Overall evaluation for disease activity in all extramuscular systems **(EXCLUDING MUSCLE DISEASE ACTIVITY)**

Muscle Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Severe muscle weakness resulting in being bed bound and an inability to perform self care

25. Myositis:						
a. Severe muscle inflammation	0	1	2	3	4	NA
b. Moderate muscle inflammation	0	1	2	3	4	NA
c. Mild muscle inflammation	0	1	2	3	4	NA
26. Myalgia	0	1	2	3	4	NA

Global Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	Overall evaluation for the totality of disease activity in ALL systems, (**INCLUDING MUSCLE DISEASE ACTIVITY)**

APPENDIX D Myositis Damage Index

[redacted]

MYOSITIS DAMAGE INDEX (MDI) - 2001

Please see the instructions and Myositis Damage Index Glossary of Terms Prior to Assessment (pp. 5-8).

Subject's PID:_____ ASSESSOR:_____ Date Assessed:_____Assessment number:_____

MUSCLE DAMAGE	**(Absent)** ——— **(Maximum)**	**Maximum Value Guidelines (Examples of maximal score)**
		Severe muscle atrophy or weakness resulting in being bed bound and an inability to perform self care

1. Muscle atrophy (clinical)	0	1	NA
2. Muscle weakness not attributable to active muscle disease	0	1	NA
3. Muscle dysfunction: decrease in aerobic exercise capacity	0	1	NA
4. Muscle atrophy assessed by radiographic methods	*0*	*1*	*NA*
5. Low serum creatinine	*0*	*1*	*NA*

Creatinine value = ____ mg/dL or umol/L; lower limit normal value = _____mg/dL or umol/L

SKELETAL DAMAGE	**(Absent)** ——— **(Maximum)**	**Maximum Value Guidelines (Examples of maximal score)**
		-Life threatening fractures from osteoporosis -Avascular necrosis requiring arthroplasty

6. Joint contractures	0	1	NA
7. Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	0	1	NA
8. Avascular necrosis	0	1	NA
9. Deforming arthropathy (including reducible deformities, excluding avascular necrosis and contractures)	0	1	NA
10. Osteoporosis without clinical fracture, requiring treatment of osteoporosis	*0*	*1*	*NA*
11. Limitation of motion (Passive Joint ROM in degrees):			
a. Elbow extension (degrees): R_____L_____	*0*	*1*	*NA*
b. Hip flexion (degrees): R_____L_____	*0*	*1*	*NA*
c. Knee extension (degrees): R_____L_____	*0*	*1*	*NA*
d. Ankle dorsiflesion (degrees) R_____L_____	*0*	*1*	*NA*

CUTANEOUS DAMAGE	**(Absent)** ——— **(Maximum)**	**Maximum Value Guidelines (Examples of maximal score)**
		Calcinosis with extensive subcutaneous exoskeleton resulting in extreme loss of function (bedridden, inability for self care)

12. Calcinosis:	0	1	NA
a. Calcinosis, superficial plaques or nodules	*0*	*1*	*NA*
b. *Calcinosis, tumoral*	*0*	*1*	*NA*
c. Calcinosis, planar	*0*	*1*	*NA*
d. Calcinosis, exoskeleton/calcinosis universalis	*0*	*1*	*NA*
13. Alopecia	0	1	NA
14. Cutaneous scarring or atrophy	0	1	NA
15. Poikiloderma	0	1	NA
16. Lipodystrophy	0	1	NA

Subject's PID:_____ ASSESSOR:_____ Date Assessed:_____Assessment number:_____

GASTROINTESTINAL DAMAGE	**(Absent)** — **(Maximum)**	**Maximum Value Guidelines (Examples of maximal score)**
		Extreme dysfunction requiring total parenteral nutrition

17. Dysphagia	0	1	NA
18. Gastrointestinal dysmotility, constipation, diarrhea or abdominal pain	0	1	NA
19. Infarction or resection of bowel or other gastrointestinal organs	0	1	NA
20. Steatosis	*0*	*1*	*NA*

PULMONARY DAMAGE	**(Absent)** — **(Maximum)**	**Maximum Value Guidelines (Examples of maximal score)**
		- Fibrosis requiring ventilatory support; or -Pulmonary hypertension resulting in extreme loss of function (bedridden, inability for self care)

21. Dysphonia	0	1	NA
22. Impaired lung function due to respiratory muscle damage	0	1	NA
23. Pulmonary fibrosis	0	1	NA
24. Pulmonary hypertension	0	1	NA
25. Diminished lung function:			
a. DL-CO/Va (Carbon monoxide diffusing capacity corrected for alveolar volume)(% Predicted =_____%)	*0*	*1*	*NA*
b. FEV1 (forced expiratory volume in 1 second) (% predicted = _____%)	*0*	*1*	*NA*

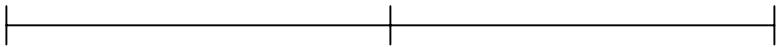
CARDIOVASCULAR DAMAGE	**(Absent)** — **(Maximum)**	**Maximum Value Guidelines (Examples of maximal score)**
		--Myocardial dysfunction resulting in extreme loss of function (bedridden, inability for self care)

26. Hypertension requiring treatment > 6 months	0	1	NA
27. Ventricular dysfunction / cardiomyopathy	0	1	NA
<u>Assessed in Adult Patients ≥ 18 years of age:</u>			
28. Angina or coronary artery bypass	0	1	NA
29. Myocardial infarction	0	1	NA

PERIPHERAL VASCULAR DAMAGE	**(Absent)** — **(Maximum)**	**Maximum Value Guidelines (Examples of maximal score)**
		- Limb loss; or -Thrombosis requiring intensive care unit (ICU) care; or-Severe disease resulting in extreme loss of function (bedridden, inability for self care)

30. Tissue or pulp loss	0	1	NA
31. Digit or limb loss or resection	0	1	NA
32. Venous or arterial thrombosis with swelling, ulceration or venous stasis	0	1	NA
<u>Assessed in Adult Patients ≥18 years of age:</u>			
33. Claudication	0	1	NA

Subject's PID:_____ ASSESSOR:_____ Date Assessed:_____Assessment number:_____

	(Absent) (Maximum)	Maximum Value Guidelines (Examples of maximal score)
ENDOCRINE DAMAGE		Extreme disease resulting in ICU care or life threatening complications, such as ICU stay for seizures or DKA; renal failure, amputation

Assessed in Patients with diagnosis before 18 years of age:

34. Growth failure	0	1	NA
35. Delay in development of secondary sexual characteristics	0	1	NA

Assessed in Both Pediatric and Adult Patients:

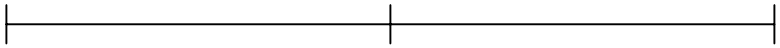
36. Hirsutism or Hypertrichosis	0	1	NA
37. Irregular menses	0	1	NA
38. Primary or Secondary Amenorrhea	0	1	NA
39. Diabetes	0	1	NA
40. Hyperlipidemia (regardless of treatment)	*0*	*1*	*NA*

Assessed in Adult Patients (> = 18 years of age and adolescent patients when applicable)

41. Infertility (female or male)	0	1	NA
42. Sexual dysfunction	0	1	NA

	(Absent) (Maximum)	Maximum Value Guidelines (Examples of maximal score)
OCULAR DAMAGE		Complete loss of vision in both eyes

43. Cataract resulting in visual loss	0	1	NA
44. Visual loss, other, not secondary to cataracts	0	1	NA

	(Absent) (Maximum)	Maximum Value Guidelines (Examples of maximal score)
INFECTION		Infection resulting in septic shock or life threatening complications

45. Chronic infection	0	1	NA
Specify:_____			
Specify:_____			
46. Multiple infections	0	1	NA
Specify:_____			
Specify:_____			

Subject's PID:_____ **ASSESSOR:**_____ **Date Assessed:**_____**Assessment number:**_____

MALIGNANCY (Absent) ——— (Maximum)

Maximum Value Guidelines (Examples of maximal score)

Malignancy resulting in ICU care or life threatening complications

47. Any form of cancer, Specify type, grade and stage:_____ 0 1 NA

OTHER DAMAGE, specify (Absent) ——— (Maximum)

Maximum Value Guidelines (Examples of maximal score)

Extreme disease damage resulting in ICU care or life threatening complications

48. *Death* *0 1 NA*
*Cause and date:*_____

49. Specify:_____

50. Specify:_____

GLOBAL DAMAGE (Absent) ——— (Maximum)

Maximum Value Guidelines (Examples of maximal score)

None

Derived from the IMACS MYOSITIS DAMAGE INDEX (MDI) - 2001
(Modification of the SLICC/ACR Damage Index, Brit J Rheum 1996; 35: 248-54)

Damage is defined as persistent changes in anatomy, physiology, pathology or function, which are present for at least 6 months. Damage may be the result of prior active disease (causing scarring, fibrosis and atrophy), complications of therapy, co-morbid conditions, or other events. A portion of disease damage is disease chronicity. Features of damage are ascertained by clinical assessment and must be present for at least 6 months (or the pathology that led to the feature must have been present for at least 6 months) despite prior immunosuppressive or other therapy, including exercise and rehabilitation. Only items present since date of diagnosis should be included. Damage is often permanent and cumulative. Damage scores most often increase over time, but in some cases may decline (i.e., a manifestation which was previously present which has currently resolved would receive a score of 0 in the present assessment).

For each organ system, please assess the severity and extent of damage exhibited by the patient at this time. To assess the severity, please rate your overall assessment of the current disease damage for each of the systems below by drawing a vertical mark on the 10-cm. line according to the following scale:
-Left end of line = no evidence of disease damage,
-Midpoint of line = moderate disease damage, and
-Right end of line = extreme or maximum disease damage.
-Please write in NA if the system cannot be assessed.

To assess the extent of damage in that organ system, please indicate the following for the specific items that are assessed:
-A score of 0 indicates the item has never been present.
-A score of 1 indicates the damage manifestation at a single point in time that has been present for at least six months.
-NA = cannot be assessed.

At the end of each organ system section, items in italics represent specialised objective testing items that are optional for the assessment and will be scored separately in an extended score. When absolute values are requested, please provide these even if they are within normal limits.

IMACS MYOSITIS DAMAGE INDEX Scoring System

The MDI has three proposed scores: an **extent of damage score**, a **severity of damage score** and an **extended damage score.**
The proposed scoring system for the **MDI extent of damage score** is the sum of all 0 or 1 scores for the eleven individual organ systems (MUSCLE, SKELETAL, CUTANEOUS, GASTROINTESTINAL, PULMONARY, CARDIOVASACULAR, PERIPHERAL VASCULAR, ENDOCRINE, OCULAR, INFECTION, MALIGNANCY) divided by the total possible score (range = 0 – 35 in children, 0-37 for adolescents and 0-38 in adults). If one or more items were not assessed, the resulting score would be divided by the maximum possible score of the assessed items. The categories of OTHER DAMAGE and GLOBAL DAMAGE are not included in the MDI extent of damage score but are scored separately.

The proposed **MDI severity of damage score** is the sum of the 10 cm visual analogue scale scores for each of the eleven individual organ systems (MUSCLE, SKELETAL, CUTANEOUS, GASTROINTESTINAL, PULMONARY, CARDIOVASACULAR, PERIPHERAL VASCULAR, ENDOCRINE, OCULAR, INFECTION, MALIGNANCY) divided by the total possible score (range = 0 – 110). If one or more organ systems were not assessed, the resulting score would be divided by the maximum possible score of the assessed items. The categories of OTHER DAMAGE and GLOBAL

DAMAGE are not included in the MDI severity score but are scored separately.
The proposed **MDI extended damage score** is the sum of the optional items listed in italics under the systems MUSCLE, SKELETAL, GASTROINTESTINAL, PULMONARY, ENDOCRINE divided by the total possible score. Each optional item is scored 0 or 1, providing a range of 0 – 16 for the extended damage score. If one or more items were not assessed, the resulting score would be divided by the maximum possible score assessed.

IMACS MYOSITIS DAMAGE INDEX Glossary of Terms

MUSCLE DAMAGE

1. *Muscle atrophy*: decreased muscle mass assessed by clinical exam
2. *Muscle weakness not attributable to active muscle disease:* weakness present for at least 6 months, demonstrated on clinical examination, not thought to be due to active muscle inflammation based on assessments of clinical and laboratory measures, such as serum muscle enzymes, magnetic resonance imaging, or repeat muscle biopsies.
3. *Muscle dysfunction*, decrease in aerobic exercise tolerance by clinical history **or** assessed by aerobic exercise testing, due to muscle damage and not attributable to cardiac, pulmonary, psychologic or other factors.
4. *Muscle atrophy:* assessed by radiographic methods, including T1 MRI, CT scan, DEXA scan (body composition) (OPTIONAL ASSESSMENT

SKELETAL DAMAGE

5. *Joint contractures*: fixed limitation in the normal range of motion of joints, in the absence of synovitis, excluding reducible deformities, avascular necrosis and deforming arthropathy.
6. *Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis):* demonstrated by any imaging technique.
7. *Avascular necrosis:* demonstrated by any imaging technique.
8. *Osteoporosis without clinical fracture:* requiring treatment of osteoporosis beyond calcium and vitamin D (prophylactic) therapy, demonstrated by any imaging technique (OPTIONAL ASSESSMENT)

CUTANEOUS DAMAGE

9. *Calcinosis:* dystrophic calcification, observed clinically or radiologically in the skin, subcutaneous tissue, fascia, or muscle. Calcinosis can be clinically or radiographically distinguished into 4 subtypes (Blane CE et al, 1984, AJR, 142: 397-400): (*the 4 subtypes are part of the OPTIONAL ASSESSMENT*)
    a. *Superficial plaques or nodules:* circumscribed lesions confined to the cutaneous or subcutaneous tissue
    b. *Tumoral:* large circumscribed nodules, which are intramuscular. Can ulcerate if subcutaneous.
    c. *Planar or fascial:* linear accumulations of calcinosis that are along the fascial plane of subcutaneous tissue or muscles.
    d. *Exoskeleton/calcinosis universalis:* widespread sheets of calcium in the muscle, fascia and subcutaneous tissue, often encasing the patient. Can ulcerate when subcutaneous.
10. *Alopecia:* hair loss with scarring present
11. *Cutaneous scarring or atrophy:* dermal or epidermal, with or without telangiectasia
12. *Poikiloderma:* fine speckled pattern of hyper- and hypopigmented macules interspersed with telangiectasias and cutaneous atrophy *(requires all 3 features)* usually in areas of photosensitivity
13. *Lipodystrophy:* loss of subcutaneous fat (localised or widely distributed) observed clinically or radiologically.

GASTROINTESTINAL DAMAGE

14. *Dysphagia:* persistent difficulty swallowing by history or persistent changes documented by radiography or other objective measures.
15. *Infarction or resection of bowel or other GI organs*, by history.
16. *Steatosis (OPTIONAL ASSESSMENT):* persistent fatty changes of liver, documented by ultrasound, CT scan or biopsy on at least 1 occasion, with persistent changes on reexamination

PULMONARY DAMAGE

17. *Dysphonia:* persistent alteration in voice quality, resonance, articulation or speech rate from normal.
18. *Impaired lung function due to respiratory muscle damage:* shortness of breath not thought to be due to active muscle inflammation or intrinsic pulmonary

disease

19. *Pulmonary fibrosis:* shortness of breath **or** rales on physical exam for at least 6 months, with previously documented abnormal chest radiograph, computed tomography scan, or biopsy evidence of interstitial lung disease (ILD)/pulmonary fibrosis.
20. *Pulmonary hypertension:* Right ventricular prominence, **or** loud P2, **or** by direct measurement of pulmonary pressures (greater than 10% above upper limit of normal).

CARDIOVASCULAR DAMAGE

21. *Hypertension:* Diagnosed by *b*lood pressure > 95% of upper limits of normal for age and gender, requiring treatment > 6 months
22. *Ventricular dysfunction/Cardiomyopathy:* ventricular dysfunction documented clinically or by echocardiography.

Assessed only in adult patients:

23. *Angina:* episodes of angina present for a period of at least 6 months.
24. *Myocardial infarction*: documented by electrocardiogram and enzymes.

PERIPHERAL VASCULAR DAMAGE

25. *Tissue or pulp loss:* tissue loss such as pulp space loss or loss less than entire digit.

Assessed only in adult patients:

26. *Claudication:* by history.

ENDOCRINE DAMAGE

Assessed only in Patients < 18 years of age:

27. *Growth failure:* Two of the following three features*:*
    a. Less than 3rd percentile height for age
    b. Growth velocity over 6 months less than 3rd percentile for age
    c. Crossing at least 2 centiles (5%, 10%, 25%, 50%, 75%, 95%) on growth chart
    (See http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm to obtain growth charts for U.S. patients)
28. *Delay in development of secondary sexual characteristics:* greater than 2 standard deviations beyond mean for age in Tanner staging (see Harriet Lane Handbook: A Manual for Pediatric House Officers, Ed. G.K. Sidberry, **or** Tanner, JM and Davies, PS, *J Pediatr* 1985; 107:317-29 for age-defined mean values for North American children).

Assessed in both pediatric and adult patients:

29. *Hirsutism:* excessive terminal hair growth in an adult male distribution, i.e., lip, chin, chest, back. This is to be assessed only in girls, women and pre-pubertal boys. *Hyptertrichosis:* Generalised increase in body hair.
30. *Irregular menses:* Missing more than one ovulatory menstrual cycle (i.e., 24 – 37 days in duration) in one year, assessed at least 3 years after menarche or before menopause.
31. *Primary amenorrhea:* the absence of any menstruation within 4.5 years of reaching puberty (i.e., in a girl without genital malformations who has reached her complete morphological development, including a bone age of at least 15 years, breasts for at least 2 years, and adult type pubic hair)
32. *Secondary amenorrhea*: cessation of menstrual periods before menopause, after initially menstruating
33. *Diabetes mellitus:* fasting glucose > 140 mg/dl or 2 hour glucose in Oral Glucose Tolerance Test > 200 mg/dl
34. *Hyperlipidemia (OPTIONAL ASSESSMENT):* Cholesterol or lipoprotein levels >95% of age appropriate reference ranges
35. References: *Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA. 1993; 269:3015-3023*; *"Report of the expert panel on blood cholesterol levels in children and adolescents" by the National Cholesterol Education program (NCEP), NIH Publication No 91-2732, September 1991.*

Assessed in adult patients and adolescents when applicable:

36. *Infertility (female or male):* no pregnancy after one year attempting to conceive via regular sexual intercourse

37. *Sexual dysfunction:* patient dissatisfaction with sexual function (female or male)

OCULAR DAMAGE

38. *Cataract:* lens opacity in either eye, ever, whether primary or secondary to steroid therapy, documented by ophthalmoscopy, and resulting in visual loss.
39. *Visual loss, other*: legal blindness, with vision less than or equal to 20/200.

INFECTION

40. *Chronic infection:* Infection (presumptive diagnosis with or without positive culture) requiring > 6 months of antimicrobial treatment, OR persisting with or without clinical symptoms > 6 months and associated with disability (absence from school, work, day-care)
41. *Multiple infections:* > 3 infections (at same or different sites, with same or different organisms) requiring antimicrobial treatment or disability (absence from school, work, day-care) over a 6 month period

MALIGNANCY

42. Documented by pathology, excluding dysplasias, including myositis associated malignancies.

OTHER

43. **Death** should be recorded under OTHER, and the date and cause of death noted (OPTIONAL ASSESSMENT)

44. Any other features of myositis damage not listed but felt to be of importance to the patient or physician. Please specify the feature in as much detail as possible. (These are not scored)

GLOBAL DAMAGE ASSESSMENT

45. Your expert clinical judgement of the totality of disease damage in all systems

APPENDIX E The SF-36v2 Health Survey

[redacted]

APPENDIX F Work Productivity and Activity Impairment Questionnaire: Specific Health Problems (WPAI: SHP) Version 2.0

[redacted]

Protocol MI-CP151 For Subject Completion ONLY PID _ _ _ _ _ _ _ _ _
Visit _ _ _ [redacted] Date _ _/ _ _ _/ _ _ _ _
Subj Initials _ _ _ (DD/ MON/ YYYY)

Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP) Muscle Disease

The following questions ask about the effect of your muscle disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your muscle disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your muscle disease. Do not include time you missed to participate in this study.*

_____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____HOURS

4. During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your muscle disease affect your productivity <u>while you were working</u>?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your muscle disease affected your work only a little, choose a low number. Choose a high number if your muscle disease affected your work a great deal.

Consider only how much your <u>muscle disease</u> affected productivity <u>while you were working</u>.

Muscle disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Muscle disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your muscle disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your muscle disease affected your activities only a little, choose a low number. Choose a high number if your muscle disease affected your activities a great deal.

Consider only how much your <u>muscle disease</u> affected your ability to do your regular daily activities, other than work at a job.

Muscle Disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Muscle Disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

APPENDIX G Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)

[redacted]

Version 8/20/2007 TIME START _____ TIME END _____

Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)

Select the score in each anatomical location that describes the most severely affected dermatomyositis-associated skin lesion

activity **damage**

Extent

Anatomical Location	Erythema	Scale	Excoriation	Ulceration	Poikiloderma (Dyspigmentation or Telangiectasia)	Calcinosis	Anatomical Location
	0-absent 1-pink; faint erythema 2-red 3-dark red; purple	0-absent 1-scale 2-crust; lichenification	0-absent 1-present	0-absent 1-present	0-absent 1-present	0-absent 1-present	
Scalp							Scalp
Malar Area							Malar Area
Periorbital							Periorbital
Rest of the face							Rest of the face
V-area neck (frontal)							V-area neck (frontal)
Posterior Neck							Posterior Neck
Upper Back & Shoulders							Upper Back & Shoulders
Rest of Back & Buttocks							Rest of Back & Buttocks
Abdomen							Abdomen
Lateral Upper Thigh							Lateral Upper Thigh
Rest of Leg & Feet							Rest of Leg & Feet
Arm							Arm
Mechanic's Hand							Mechanic's Hand
Dorsum of Hands (not over joints)							Dorsum of Hands (not over joints)
Gottron's – Not on Hands							Gottron's – Not on Hands

Gottron's – Hands

Examine patient's hands and double score if papules are present		Ulceration	Examine patient's hands and score if damage is present	
0-absent 1-pink; faint erythema 2-red erythema 3-dark red; purple erythema			0-absent 1-scarring 2-scarring + dyspigmentation	

Periungual

Periungual changes (examine)			
0-absent 1-pink; faint erythema 2-red erythema +/- cuticular dystrophy 3-telangiectasias +/- cuticular hemorrhage			

Alopecia

Recent Hair loss (within last 30 days as reported by patient)			
0-absent 1-present			

Total Activity Score
(For the activity score, please add up the scores of the left side, i.e. Erythema, Scale, Excoriation, Ulceration, Gottron's, Periungual, Alopecia)

Total Damage Score
(For the damage score, add up the scores of the right side, i.e. Poikiloderma, Calcinosis)

APPENDIX H Dermatology Life Quality Index (DLQI)

[redacted]

APPENDIX I Skin Photography

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 Canfield Scientific, Inc.
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.

[redacted]

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 website.

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]

[redacted]

APPENDIX J 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.

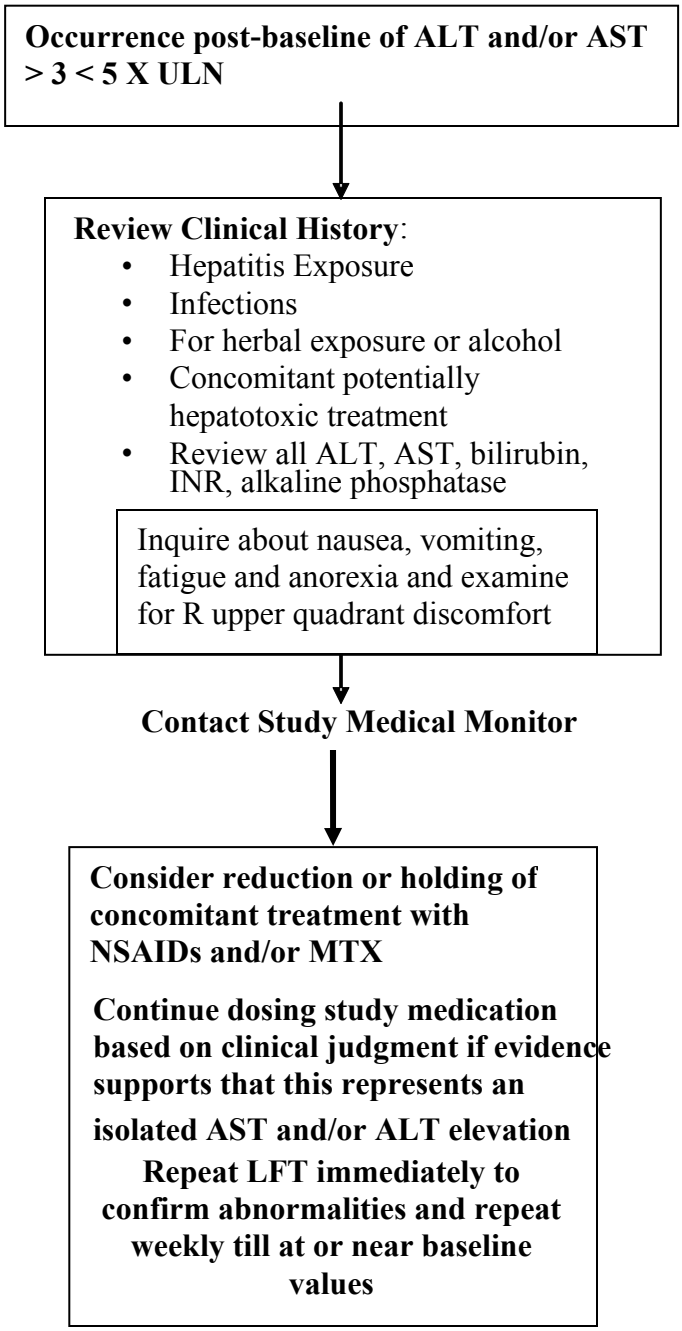
For the purpose of this document, LFTs will be AST, ALT, total bilirubin, and alkaline phosphatase.

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

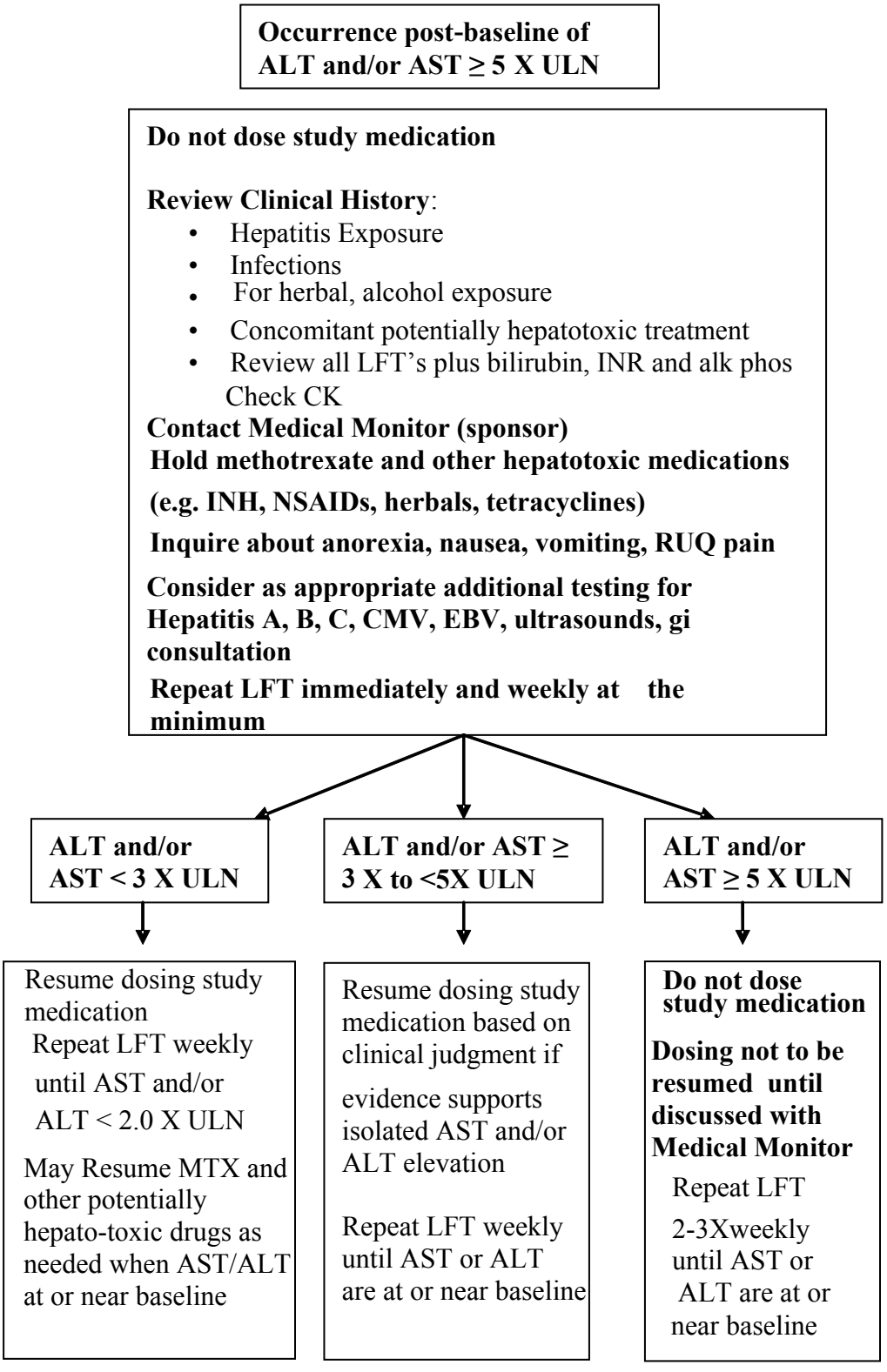
Copies of the document “Draft Guidance of Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation” can be located at http://www.fda.gov/cder/guidance/index/index.htm.

[redacted]

Guidance for abnormal Liver Function Tests during Study 151 that develop post-baseline in individuals with ALT or AST ≤2X ULN at baseline

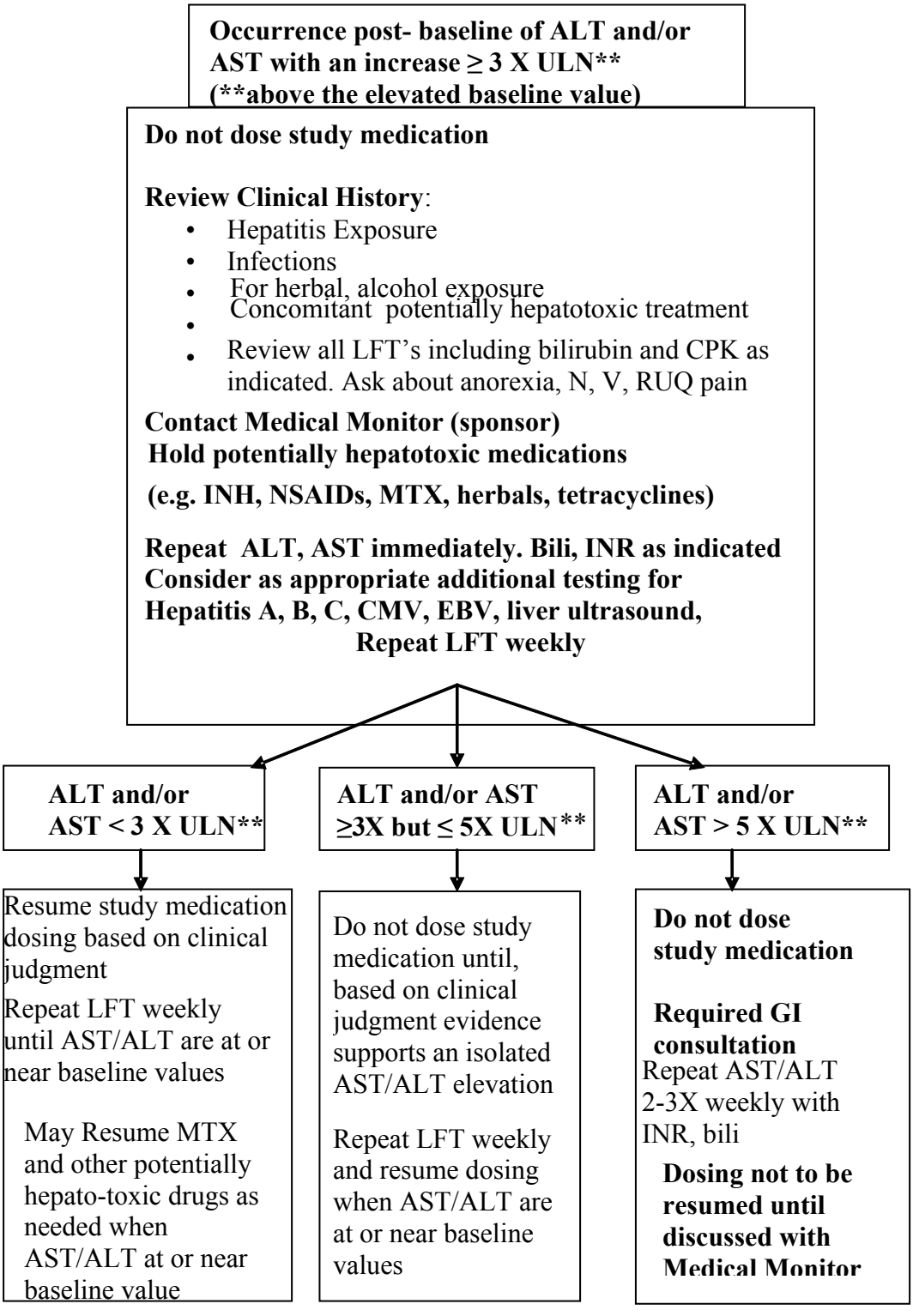


[redacted]



Guidance for abnormal Liver Function Tests during Study 151 that develop post-baseline in individuals with ALT or AST > 2X ULN at baseline

[redacted]


Occurrence post- baseline of ALT and/or AST with an increase ≥ 3 X ULN** (**above the elevated baseline value)
Do not dose study medication
Review Clinical History:
Hepatitis Exposure
Infections
For herbal, alcohol exposure
Concomitant potentially hepatotoxic treatment
Review all LFT's including bilirubin and CPK as indicated. Ask about anorexia, N, V, RUQ pain
Contact Medical Monitor (sponsor)
Hold potentially hepatotoxic medications
(e.g. INH, NSAIDs, MTX, herbals, tetracyclines)
Repeat ALT, AST immediately. Bili, INR as indicated
Consider as appropriate additional testing for
Hepatitis A, B, C, CMV, EBV, liver ultrasound,
Repeat LFT weekly
ALT and/or AST < 3 X ULN**
ALT and/or AST ≥3X but ≤ 5X ULN**
ALT and/or AST > 5 X ULN**
Resume study medication dosing based on clinical judgment
Repeat LFT weekly until AST/ALT are at or near baseline values
May Resume MTX and other potentially hepato-toxic drugs as needed when AST/ALT at or near baseline value
Do not dose study medication until, based on clinical judgment evidence supports an isolated AST/ALT elevation
Repeat LFT weekly and resume dosing when AST/ALT are at or near baseline values
Do not dose study medication
Required GI consultation
Repeat AST/ALT 2-3X weekly with INR, bili
Dosing not to be resumed until discussed with Medical Monitor

APPENDIX K 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]) to provide more information about genetic testing; to include pregnancy testing before each dose of MEDI-545 and every 12 weeks thereafter; to exclude patients with a history of active tuberculosis; to clarify that Quantiferon-TB Gold assay for the diagnosis of latent tuberculous infection will be done at selected sites; to clarify that IVIG may be given in the study; to clarify other events requiring immediate reporting, and to correct typographical errors. 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 strike-through.

1. Section 2.4.2 (also referenced in Study Abstract under Patient Evaluation and Follow-up)
   Changed to read:
   Screening evaluations include the following: medical history; physical examination; body weight; chest x-ray; ECG; tuberculosis skin test; blood tests for hepatitis A, B, C, human immunodeficiency virus (HIV)-1 and HIV-2; ~~**Quantiferon® TB Gold assay for tuberculosis;**~~ serum β human chorionic gonadotropin (βHCG) for women (unless surgically sterile or 2 years after menopause); vital signs; serum chemistry (including Na, K, Cl, bicarbonate, blood urea nitrogen [BUN], creatinine, bilirubin, alkaline phosphatase, and random glucose); complete blood count (CBC) with differential and platelets, serum levels of muscle enzyme (including CK, aldolase, LDH, ALT, and AST); urinalysis; manual muscle testing (MMT), extramuscular activity assessment based on Myositis Disease Activity Assessment Tool (MDAAT), pulmonary function tests, physician global activity assessment; and clinical Health Assessment Questionnaire (CLINHAQ).

   Safety assessments include AE and SAE evaluation, physical examination, vital signs, serum chemistry panel, CBC with differential and platelets, urinalysis, and viral surveillance testing via oropharyngeal swabs for herpes simplex virus (HSV)-1 and HSV-2; vaginal swabs (women) for HSV-1, HSV-2, and human papillomavirus (HPV); **Quantiferon®-TB Gold assay for tuberculosis (at selected sites);** and blood tests for Epstein Barr virus (EBV) and cytomegalovirus (CMV).

   Reason for Change: The Quantiferon®-TB Gold assay for tuberculosis will be performed at selected sites that have the facilities to perform this test. This assay has been moved from screening to Study Day 0.

2. Section 3.1.1
   Changed to read:
   5. All patients including those with DM must meet at least two of the following criteria:
      a. Strength in MMT greater ≥ 80/150 but ≤ 125/150 using the MMT-8 muscle group testing (see Appendix A);

[redacted]

b. Patient Global Activity Assessment by visual analog scale (VAS) ≥ 2.0 cm on a 10 cm scale, **which is included as part of CLINHAQ (see Appendix B)**;
c. Physician Global Activity Assessment by VAS ≥ 2.0 cm on a 10 cm scale, **which is included as part of MDAAT (see Appendix C);**
d. CLINHAQ (see Appendix B) disability index ≥ 0.25;
e. Global extramuscular activity assessment ≥ 1.0 cm on a 10-cm VAS scale (this measure is the physician's composite evaluation and is based on assessments of activity scores on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiovascular scales of the MDAAT [Appendix C]);

Reason for Change: Clarification of text.

3. Section 3.1.2
Changed to read:
19. History of active ~~**or latent**~~ tuberculous infection ~~**without completion of an appropriate course of treatment and with evidence of active infection on chest x-ray**~~;

Added:
20. **History of latent tuberculous infection without completion of an appropriate course of treatment**;

Reason for Change: Exclusion of patients with a history of active tuberculosis infection.

4. Section 3.2
Changed to read:
- MedImmune calls and informs the ~~**IVRS**~~ **investigator** of patient eligibility to participate based on the expression of mRNA for type I IFN-inducible genes;

Reason for Change: Clarification of text.

5. Section 3.4.2
Added cross-reference to Table 1 for clarification of text.

6. Section 3.4.5
Changed to read:
All concomitant medications used by the patient from screening through Study Day 350 will be recorded on the case report form. **The concomitant administration of intravenous immunoglobulin (IVIG) is allowed**.

Patients may not receive the following from screening through Study Day 350:
1. Investigational agents (eg, rituximab for myositis);
2. Any live attenuated virus vaccine;
3. Hydroxychloroquine > 600 mg/day, mycophenolate mofetil > 3 g/day, methotrexate > 25 mg/week, leflunomide > 20 mg/day, azathioprine > 3 mg/kg/day; or
4. Any dose of cyclophosphamide, cyclosporine, or thalidomide.

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

Corticosteroid doses may not exceed 35 mg/day of prednisone or an equivalent dose of another corticosteroid. Corticosteroid doses must remain constant from 14 days before Study Day 0 through Study Day 196. Thereafter, corticosteroid doses may be increased, tapered, and discontinued as considered appropriate by the investigator.

Reason for Change: Clarification of allowed concomitant medications.

7. Section 3.5
Deleted
~~**Patients who withdraw consent during the study should**~~

Reason for Change: Correction of typographical error.

8. Section 3.5 (Table 2 and Table 3) and Description of Visits
Added ECGs at Study Days 42 and 140 for additional safety information.

Added urine pregnancy testing (urine βHCG) on Study Days 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, 182, 266, and 350.

Reason for Change: Increased frequency of pregnancy testing as an additional assessment of safety.

Moved Quantiferon-TB Gold assay from screening to Study Day 0.

Changed Footnote "g" and corresponding visits for consistency of vital signs monitoring as follows:

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. ~~**On Study Days 0 and 98,**~~ Vital signs will be monitored before **and immediately after** study drug administration and every 30 minutes after study drug administration ~~**for at least 2 hours or**~~ until stable ~~**and at discharge**~~. ~~**On all other treatment visits, vital signs will be monitored before study drug administration and at least 30 minutes after study drug administration or until stable.**~~

Added Footnote "q" to state that Quantiferon-TB Gold assay will be done at selected sites.

Reason for Change: The Quantiferon®-TB Gold assay for tuberculosis will be performed at selected sites that have the facilities to perform this test.
Added Footnote "r" stating that chest x-rays taken within 6 months of screening will be considered suitable for screening and need not be repeated.

Reason for Change: To allow use of prior chest x-rays for screening purposes.

[redacted]

Added Footnotes "s" and "t" to clarify that Physical Global Activity Assessment is included as part of MDAAT and Patient Global Activity Assessment is included as part of CLINHAQ.

Reason for Change: Clarification of text.

9. Section 3.5 (Description of Visits)
Changed to read (Screening Visit):
- Serum βHCG **(for women who are sexually active and are not surgically sterile or at least 2 years postmenopausal; this test must be negative for study participation)**

Changed to read (Study Day 0, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, 182, 266, and 350 Visits):
6. Urinalysis, **includes collection of urine for βHCG (for women who are sexually active and are not surgically sterile or at least 2 years postmenopausal; this test must be negative for study participation)**

Reason for Change: Clarification of text.

10. Section 3.6.1
Changed to read:
Urine pregnancy tests will be performed in female subjects who are not postmenopausal or surgically sterile at the time of screening on **Study Day 0, prior to study drug administration on Study Days 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, and 182, and on Study Days 266 and 350** 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).

Reason for Change: Clarification of text.

11. Section 3.6.3
Changed to read:
At screening, patients will receive tuberculin skin test. Those who are known to have positive tuberculin skin test should not receive the skin test and should be confirmed by chest x-ray that they have had no evidence of active tuberculosis. **Reading of the tuberculin skin test should be performed 48 to 72 hours after administration by a trained health professional. The 10 mm cut point will be used to determine tuberculin skin test positivity.** Those who have ~~**had a history of active or**~~ latent tuberculosis ~~**in the past**~~ must have completed an appropriate course of anti-tuberculosis treatment. During the study, **at selected sites,** patients will receive Quantiferon-TB Gold tests as described in CDC guidelines to monitor for tuberculosis (Mazurek, 2005).

Reason for Change: Added information describing positive tuberculin skin test, and clarified language regarding latent tuberculosis.

12. Section 3.6.5.2
Changed to read:

[redacted]

Physician Global Activity Assessment is included as part of MDAAT, and Patient Global Activity Assessment is included as a part of CLINHAQ.

Changed Table 4 to be consistent with the text.

Reason for Change: Clarification of text.

13. Section 3.6.5.4
Changed to read:
Lack of evidence of active myositis is defined as assessed by global and extramuscular assessments **~~using IMACS forms~~**, stable muscle strength and function (defined as equivalent to < 15% change in the semiquantitative scoring of the measures of these domains over at least a 6-month period), and normal muscle enzyme levels.

Reason for Change: Clarification of text.

14. Section 3.6.5.8
Corrected publication year (Ware, **1992**).

15. Section 3.6.6
Changed to read:
Correlative studies include collection of serum for assessment of autoantibodies and proteomics, collection of serum for IFN-α assays and other exploratory research, **~~whole blood for gene expression analyses,~~** peripheral blood for flow cytometry, and muscle and skin biopsies**~~, and whole blood for DNA analysis~~**. The follow-up muscle biopsy should be done on the contralateral muscle, and the follow-up skin biopsy should be done in close proximity to the first biopsy.

Other correlative studies include collection of whole blood for type I interferon inducible gene expression and analysis of DNA. Collection of blood for DNA analysis is voluntary, and patients must sign a separate informed consent form (Informed Consent Form for Collection of Blood Samples for DNA Analysis) in order for this test to be done. Patients who do not wish to have the DNA test done will still be eligible for the study.

Reason for Change: To provide more information on the analysis of whole blood for type I interferon inducible gene expression and analysis of DNA.

[redacted]

16. Section 3.6.6.3

Changed to read:

~~**Open**~~ **Muscle biopsies** will be performed at visits indicated in Table 2**. The initial muscle biopsy will be performed on an involved muscle within 7 days prior to Study Day 0. Involved muscle is defined as having a muscle strength of 4 to 4-/5 as assessed by MMT. The repeated muscle biopsy will be performed on a muscle that was noted to be involved on Study Day 0. If involved on Study Day 0, the contralateral muscle is the preferred site of the repeated biopsy.** Muscle biopsy samples collected during the trial will undergo histopathological grading and IHC analysis of cellular infiltrates, including dendritic cell subtypes, B cells, and T cells. Additionally, gene expression will be analyzed, and changes in IFN-inducible protein levels within muscle specimens will be assessed by IHC methods.

Reason for Change: Specified the use of involved muscle for the muscle biopsies.

17. Section 3.6.6.6

Changed to read:

The pharmacodynamics of MEDI-545 will be studied through analyses of its effects on type 1 IFN-inducible gene expression in whole blood, muscle, and skin. The levels of mRNA for type I IFN-inducible genes will be measured using genomic tests. PCR assay on selected panel of genes may be used to confirm the results. **The analysis in whole blood is performed using Affymetrix whole genome expression array and taqMan-based assay on selected panel of genes. In muscle and skin, immunohistochemical methods will be used to stain for a pre-selected panel of genes that will allow further assessment of the pathogenesis of inflammatory muscle disease. Subsequent studies will be dependent upon the results obtained from our initial analyses.**

Reason for Change: To provide more information on the analysis of whole blood for type I interferon inducible gene expression.

18. Section 3.6.6.7

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 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, request that the blood collected for DNA analysis be destroyed.**

[redacted]

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: To provide more information and clarification of text on the analysis of whole blood for analysis of DNA.

19. Section 4.4

Changed to read:

An **S**AE is considered "product-related" for the purposes of regulatory reporting if the Investigator, the Medical Monitor, or the Product Safety Physician assesses the SAE as possibly, probably, or definitely related 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 **S**AE is treated as product-related for the purposes of reporting to regulatory authorities. An **S**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 **S**AE is not product-related.

Reason for Change: Clarification of text.

20. Section 4.5

Changed to read:

In addition to SAEs, 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. Severe hypersensitivity reaction to the study drug, Grade 3 or higher
4. Severe viral infection, Grade 3 or higher
5. **Any event which, in the opinion of the investigator or the Medical Monitor, contraindicates further dosing such as illnesses or complications**.

*Patients who become pregnant during the study period must not receive additional doses of study product 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 text.

[redacted]

21. Section 4.8
    Deleted:
    ~~**Patients who are in lower dose cohorts may continue to be dosed:**~~

    Reason for Change: Clarification of text.

22. Section 11
    Deleted references not cited in protocol, and **corrected** and **added** references that were noted in the text but not in the reference section.

    Reason for Change: Clarification of text.

23. Appendix C
    Replaced Appendix C with a modified version of the MDAAT stipulating that assessments of muscle disease involvement must be made in the absence of muscle enzyme laboratory test results. This change was made to prevent unblinding of the study.

24. Appendix H
    Replaced Appendix H with a validated version of the CDASI.

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 reducing the starting dose of MEDI-545 from 1.0 to 0.3 mg/kg, reducing the highest dose of MEDI-545 from 30.0 to 20.0 mg/kg, and setting the infusion volume at 100 mL and the infusion time to 60 minutes. Other changes include updating the safety information on MEDI-545 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 strike-through. Changes that are similar in nature throughout the text are listed only once.

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 40
   - Serum for safety biomarkers was added prior to dose administration and after any dose administration during which an AE such as infusion reaction occurs

2. Section 1.4
Changed to read:
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.

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

Changed to read:
This is a dose-escalation study designed to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, 10.0, or ~~30~~**20.0** mg/kg) or placebo in ~~32~~ **40** adult patients with DM or PM who have a high level of expression of mRNA for type I IFN-inducible genes at the time of screening. MEDI-545 or placebo will be 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 planned starting dose of MEDI-545 (~~1.0~~**0.3** mg/kg) in MI-CP151 is **less than** one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated administrations every 2 weeks for 27 weeks).

Similar statements of changes in number of patients and doses are included thereafter in the text where appropriate. In addition, the study schema in Figure 1 now includes the new 0.3 mg cohort.

Reason for Change: Number of patients and doses were updated.

4. Section 2.4.2 (also referenced in Study Abstract under Patient Evaluation and Follow-up)
Changed to read:
Safety assessments include AE and SAE evaluation, physical examination, vital signs, serum chemistry panel, CBC with differential and platelets, urinalysis, **serum for safety biomarkers such as inflammatory proteins**;

Reason for Change: Safety assessment added.

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

Changed to read:
19. History of active tuberculous infection or **newly positive TB skin test (defined as reaction ≥ 10 mm in diameter)**;

Reason for Change: Clarification of exclusion of patients with a history of active tuberculosis infection.

6. Section 3.2
Changed to read:
Patients will be dosed with either MEDI-545 or placebo on Study Day 0. In each of the ~~four~~**five** dose cohorts.

Reason for Change: Clarification of text.

7. Section 3.3
Changed to read:

A limited number MedImmune personnel, independent of the project team, who will perform and interpret assays such as gene expression signature analyses on blood samples, will be unblinded during the study. In addition, once the last patient in 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 will be made after the first 2 cohorts complete Study Day 98, after all cohorts complete Study Day 98, and after all cohorts complete Study Day 196. These interim assessments are also for the purpose of making clinical development decisions. 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 effect individuals involved in the clinical conduct of the study will be communicated, ie, the actual results of the interim analyses will not be communicated. 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.

Reason for Change: Clarification of blinding.

8. Section 3.4.2
Changed to read:

Up to 20 additional patients may be enrolled (4 patients in each of 5 cohorts), if those patients are in screening at the time 8 patients have been randomized to each cohort. In each dose cohort, 6 patients will receive MEDI-545 and 2 patients will receive placebo. Thereafter (2 weeks later), in each dose cohort, patients randomized to MEDI-545 will continue to receive the same dose of MEDI-545 every 2 weeks for an additional 12 weeks (7 doses) and patients randomized to placebo will receive MEDI-545, at the dose specified in the dose cohort they are assigned, every 2 weeks for an additional 12 weeks (7 doses) for a total of 26 weeks (14 doses). MEDI-545 or placebo will be administered IV **over 60 minutes.**

[redacted]

In addition, changes are made in Table 1 to reflect changes in doses.

Reason for Change: Clarification of text and stipulation of infusion time. Similar text is added in several places thereafter in the text, to clarify that additional patients, up to 4 per cohort, may be added if in screening at the time 32 patients are enrolled in the same cohort and to clarify that infusion duration is 60 minutes.

9. Section 3.4.3 (Study Drug Ordering and Preparation)
Changed to Read:
Study drug will be prepared for IV infusion as follows:

1. **Initially dilute study drug to a volume of 20 mL using 0.9% Sodium Chloride for Injection, USP;**
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 (see Table 2).**

Table 2 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/kg/min)[a]
1	0.3	100	60 minutes	100	0.005
2	1.0	100	60 minutes	100	0.017
3	3.0	100	60 minutes	100	0.05
4	10.0	100	60 minutes	100	0.17
5	20.0	100	60 minutes	100	0.33

a. Maximum infusion rated is based on the maximum allowable weight of 120 kg per cohort.

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, but will not exceed 20.0 mg/kg. The study drug dose will be prepared by the CTMM and administered to patients without blinding.

Reason for Change:
Clarification of dilution of study drug and infusion duration and rate.

10. Section 3.4.4 (Administration of Study Drug)
Changed to Read:
The study drug should be dispensed by the pharmacist or qualified designee and administered as a an IV infusion over 60 minutes using an infusion pump according to the directions provided in the Clinical Trial Material Manual. Do not administer by IV push 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**~~.

[redacted]

Patients should not be premedicated unless they have had a prior infusion reaction, since the primary objective of this study is to evaluate the safety and tolerability of the study drug. However, if reactions to the IV infusion occur during or after study drug administration, they should be treated appropriately.

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) 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.

If an 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 transferred to an emergency or hospital facility is deemed warranted for a more severe reaction:

- **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**;

Reason for Change:
Clarification of infusion rate, premedication, timing of vital signs during and after infusion and handling of infusion reactions.

11. Section 3.5 (Table 3 and Table 4) and Description of Visits

Changes:
Tables renumbered here and throughout rest of text to reflect insertion of new Table 2. in Section 3.4.3.

Reason for Change: Correction of numbering.

12. Section 4.1.2 (Study Reporting Period for Adverse Events)

Changed to read:
The reporting period for adverse events is the period from the **~~day of randomization~~signing of informed consent** through Study Day 350.

Reason for Change: Clarification of text.

13. Section 4.10 (Monitoring of Dose Administration)

Changed to read:
As with any antibody, **infusion reactions and IgE-mediated** allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat **infusion reactions and** acute **~~anaphylactic~~ allergic** reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Reason for Change: Clarification of text.

14. Section 5.4 (Sample Size)
    Changed to read:
    For example, if the event rate in the placebo-to-MEDI-545 group is **10%, the difference is 23.3%, and the 95% confidence interval is between -3.2% and 46.7%**.

    Information in Tables 6 and 7 is update to reflect change in sample size from 32 to 40.

    Reason for Change: Added and corrected information.

15. Section 5.5 (Interim Analyses)
    Changed to read:
    Interim analysis of the type I inducible gene expression will be performed after all patients in each dose cohort complete Study Day 28 evaluations.

    Reason for Change: Clarification of text.

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 updating preclinical and clinical information; identification of specific safety biomarkers to analyze infusion reactions; addition of infusion reactions as an immediately reported event; 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 strike-through. Changes that are similar in nature throughout the text may be listed only once.

1. Overall Changes

   - The medical monitor was changed from [redacted] to [redacted].
   - AEs and SAEs will be monitored from the singing of informed consent and not from time of randomization.
   - The safety results of MI-CP126, MI-CP145, and MI-CP152 were updated
   - The statement regarding the collection of serum for safety biomarkers was revised to include serum levels of mast cell tryptase, cytokines/chemokines, and IgE.
   - Typographical errors were corrected.

2. Section 1.2

   Changed to read:

   MEDI-545 is a fully human Mab that binds to and neutralizes **majority of the subtypes of human IFN-α** ~~all human IFN-α subtypes~~ without neutralizing other type I IFNs.

[redacted]

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 and to provide more background on MEDI-545

3. Section 1.5

Changed to read:

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 in adult patients with DM or PM. This is a dose-escalation study designed to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, 10.0, or ~~30.0~~ **20.0** mg/kg) or placebo in ~~32~~ 40 adult patients with DM or PM who have a high level of expression of mRNA for type I IFN-inducible genes at the time of screening. MEDI-545 or placebo will be 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 planned starting dose of MEDI-545 (~~1.0~~ **0.3** mg/kg) in MI-CP151 is **less than** one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated administrations every 2 weeks for 27 weeks)

Similar statements of changes in number of patients and doses are included thereafter in the text where appropriate. In addition, the study schema in Figure 1 now includes the new 0.3 mg cohort.

Reason for Change: Number of patients and doses were updated

4. Section 2.4.1

Changed to read:

The study 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 DM or PM who have a high level of expression of mRNA for type I IFN-inducible genes at the time of ~~randomization~~ **screening**.

Safety parameters including assessments of AEs and SAEs will be assessed at every study visit from the day of ~~randomization~~ **informed consent** through Study Day 350.

Reason for Change: Clarification of text

[redacted]

5. Section 2.4.2

Changed to read:

Safety assessments include AE and SAE evaluation, physical examination, vital signs, serum chemistry panel, CBC with differential and platelets, urinalysis, serum for safety biomarkers **in any patient who has an infusion reaction (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies)** ~~such as inflammatory proteins~~ and viral surveillance testing via oropharyngeal swabs for herpes simplex virus (HSV)-1 and HSV-2; vaginal swabs (women) for HSV-1, HSV-2, and human papillomavirus (HPV); Quantiferon®-TB Gold assay for tuberculosis (at selected sites); and blood tests for Epstein Barr virus (EBV) and cytomegalovirus (CMV).

Reason for Change: FDA requirement

6. Section 3.1.1

Changed to read:

2. Written informed consent obtained from the patient **or the patient's legal representative** prior to receipt of any study medication or beginning study procedures;
7. Median fold overexpression of the top 25 type I IFN inducible genes of five fold or greater in whole blood at the time of ~~randomization~~ **screening**;
8. Sexually active women, unless surgically sterile **(including tubal ligation)** or at least 2 years
10. In the investigator's opinion, evidence of clinically significant active infection, including ongoing, chronic infection, within ~~21~~ **28** days before Study Day 0;
14. Vaccination with live attenuated viruses within ~~21~~ **28** days before Study Day 0;
23. At screening blood tests (must be within ~~21~~ **28** days before Study Day 0) any of the following:
    - Serum creatinine > 4.0 mg/dL,
    - Neutrophils < 1,500/mm^3,
    - Platelet count < 50,000/mm^3;

Reason for Change: Clarification of text

7. Section 3.2

Changed to read:

Treatment assignments will be determined using a central randomization procedure through an interactive voice response system (IVRS). For each of the ~~four~~ **five** dose cohorts, patients with a median fold overexpression of the top 25 type I IFN inducible genes on whole blood of five fold or greater will be randomized in a 3:1 ratio to initially receive MEDI-545 or placebo. Central randomization will be applied without regard to site.

[redacted]

- **MedImmune calls the IVRS before Study Day 0 to provide the results of type I IFN gene signature in the patient**
- ~~MedImmune calls and informs the investigator of patient eligibility to participate based on the expression of mRNA for type I IFN inducible genes;~~
- **The IVRS notifies the investigator or qualified designee that the patient may be randomized into the study;**

Reason for Change: Clarification of text

8. Section 3.4.1

MEDI-545 (100 mg/mL): [redacted]

Reason for Change: Correction and clarification of text

9. Section 3.4.3

Changed to read:

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

1. ~~Initially dilute study drug to a volume of 20 mL using 0.9% Sodium Chloride for Injection, USP;~~
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 (see Table 2).~~

The MEDI-545 dose for administration must be prepared using aseptic technique. MEDI-545 will be diluted in 0.9% normal saline and the volume will be standardized to 100 mL. The study drug will be administered using an infusion pump over 60 minutes as described in Table 2.

The study drug dose will be prepared by the CTMM and administered to patients without blinding.

Reason for Change: Clarification of text

[redacted]

10. Section 3.4.4

Changed to read:

The study drug should be dispensed by the pharmacist or qualified designee and administered as ~~a~~ an IV infusion over 60 minutes using an infusion ~~pump according to the directions provided in the Clinical Trial Material Manual~~. Do not administer by **intravenous push (**IV) 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 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 transferred to an emergency or hospital facility is deemed warranted for a more severe reaction:

- **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**
- ~~Collect serum for assessment of safety biomarkers as soon as possible after the event, at 60 minutes after the event, and at discharge; and~~

Reason for Change: FDA requirement and clarification of text

11. Section 3.5

Changed to read:

Eligibility screening will take place within ~~21~~ **28** days before randomization into the study.

Table 3

The serum for safety biomarkers row was corrected to include only the pre-dose serum collection on Day 0.

Footnotes for Table 3

a. **Obtain** within ~~21~~ **28** days prior to Study Day 0.
f. Women, unless surgically sterile or at least 2 years postmenopausal, must have a negative serum pregnancy test within ~~21~~ **28** days before randomization/entry, and a negative urine pregnancy test on ~~Study Day 0~~ **all dosing visits** before receiving the study drug.

[redacted]

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 will be monitored **before dosing**, every 15 minutes during administration of the drug, **at the end of infusion**, and every 30 minutes after the completion of the infusion until stable.

u. Pulmonary function test on Study Day 98 should be done within 7 days before the visit.

v. A serum 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 as soon as possible after the event, 60 minutes after the event, and at discharge (see Section 3.4.4 for details)

w. 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 98, the patient should complete the evaluations scheduled for Study Day 98. If the patient discontinues on or after Study Day 98 and prior to Study Day 182.

Footnote for Table 4

u. If the patient discontinues on or after Study Day 182 and prior to Study Day 350, the evaluations scheduled for Study Day 350 must be completed. If a particular assessment has been performed within 2 weeks before the discontinuation visit, it need not be repeated.

Reason for Change: FDA requirement and clarification of text

12. Section 3.5

Changed to read:

Study Day 0: First dose

15. Monitor vital signs every 15 minutes during administration of the drug, **at end of infusion**, and every 30 minutes after the completion of the infusion until stable

Study Days 14, 42, 70, 84, 112, 140, 168 (± 3 Days): Treatment Period
Visits 2, 4, 6, 7, 9, 11, 13

4. ECG (Study Days 42, 98, and 140)

7. Monitor vital signs **before dosing**, every 15 minutes during administration of the drug, **at end of infusion**, and every 30 minutes after the completion of the infusion until stable

Study Day 98 (± 3 Days) or Discontinuation Visit

If a patient discontinues the study prematurely prior to Study Day 98, 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.

Study Day 182 (± 3 Days) or **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.

Study Day 196 (± 3 Days): Follow-Up Period or Discontinuation Visit

17. **Muscle biopsy (within 7 days before the visit), if not performed at the time of discontinuation**
18. **Skin biopsy (optional, DM patients only, within 7 days before the visit), if not performed at the time of discontinuation**

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

Reason for Change: Clarification of text

13. Section 3.6.1

Changed to read:

Laboratory tests for serum chemistries, hematology, hepatitis serologies, viral infection, pregnancy and urinalysis with microscopic examination will be performed during screening and during the study by a central CLIA-certified laboratory in the United States. o~~r in a laboratory with local CLIA-equivalent certification or accreditation~~

Reason for Change: Only US laboratories will be used.

14. Section 3.6.5

Changed to read:

Whole blood will be collected for assessment of safety biomarkers as described in Table 3. 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 3.4.4 for details). Safety biomarkers include serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies.

[redacted]

Reason for Change: FDA requirement

15. Section 3.7

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 98, the patient should complete the evaluations scheduled for Study Day 98. If the patient discontinues after Study Day 98 and prior to Study Day 182, the patient should complete the evaluations scheduled for Study Day 182. If the patient discontinues after Study Day 182, the evaluations scheduled for Study Day 350 must be completed. 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. Section 4.1.3

Changed to read:

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

Reason for Change: Clarification of text

17. Section 4.5

Changed to read:

5. **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)**

Reason for Change: FDA requirement

[redacted]

18. Section 5.2

Changed to read:

Table 6 demonstrates the calculated 95% confidence intervals that correspond to various differences in potential rates of adverse events between the two combined treatment groups: patients who initially receive MEDI-545 (regardless of dose) and patients who initially receive placebo (regardless of MEDI-545 dose from Study Days 98 to 182). For example, if the event rate in the MEDI-545-treated group is 33.3% and the rate in the placebo-to-MEDI-545 group is 10%, the difference is 23.3%, and the 95% confidence interval is between -**1**3.2% and 45.7%.

Reason for Change: Correction of data

19. Section 5.4.1

Changed to read:

The primary endpoints of the study are the safety and tolerability of MEDI-545, which 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.

Reason for Change: Clarification

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 electronic case report forms (eCRFs) provided by MedImmune or designee. Completed eCRFs will be reviewed by the sponsor or designee. A copy of each completed eCRF will be retained by the investigator.~~

Reason for Change: Clarification

[redacted]

21. Section 10

Changed to read:

The changes made to the protocol are summarized in Appendix J.

Reason for Change: Moved detailed list of changes to Appendix J.

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 changing the medical monitor; updating preclinical and clinical information; reducing the highest dose of MEDI-545 from 20.0 to 10.0 mg/kg; reducing the number of patients from 40 to 32; reducing the number of dose cohorts from five to four; indicating that CRPS will no longer be blinded to the studies, although they will continue to be part of the project team, revisions to the inclusion and exclusion criteria; provided more detailed information regarding anaphylactic infusion reactions and suggested treatment procedures to the investigators, if any occur. Other revisions include changes to the statistical considerations section and clarification of text throughout the protocol. Finally, a new Table (number 3) was added and the rest of the tables were renumbered. 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. 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 ~~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
[redacted]

Reason for change: [redacted] is the new Medical Monitor for this study.

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.

[redacted]

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 (also referenced in Study Abstract under Rationale and Section 2.4.1)

   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.

   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 in adult patients with DM or PM. This is a dose-escalation study designed to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, **or** 10~~ or 20.0~~ mg/kg) or placebo in ~~40~~ **32** adult patients with DM or PM who have a high level of expression of mRNA for type I IFN-inducible genes at the time of screening. MEDI-545 or placebo will be initially administered every 2 weeks for 12 weeks (7 doses) followed 2 weeks after the 7th dose by MEDI-545 every 2 weeks for another 12 weeks (7 doses) for a total of 26 weeks (14 doses). The planned starting dose of MEDI-545 (0.3 mg/kg) in MI-CP151 is less than one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated administrations every 2 weeks for 27 weeks).

   Reason for Change: The description of MEDI-545 was clarified; a number of patients and doses were updated.

5. Section 3.1

   Changed to read:

   The patients in the study must be adults with probable or definite DM or PM according to the Bohan and Peter criteria (Bohan, 1975) and~~ have elevated serum CK of ≥ 1.3 × the upper limit of normal (ULN)~~ **and have active disease**. Patients must have a median fold

[redacted]

overexpression of the top 25 type I IFN inducible genes of ~~five~~ **4-**fold or greater in whole blood **or muscle**, compared to normals.

Reason for Change: Clarification of inclusion of patients with a history of active disease.

6. Section 3.1.1

Changed to read:

6. **Subjects with PM must have an** elevation of serum CK **or aldolase** at a minimum level of 1.3 × **upper limit of normal** (ULN) **or serum CK or aldolase at least 2-fold higher than the patient's own lowest value since diagnosis**;

7 Subjects with DM must have either an elevated CK or aldolase as above (per inclusion criterion #6) or other laboratory evidence of active myositis. This could include either abnormal signal on skeletal muscle MRI suggestive of inflammation or an electromyogram demonstrated muscle membrane irritability (e.g., fibrillation potentials, positive sharp waves, complex repetitive discharges) and short duration, small amplitude, polyphasic motor unit action potentials.

8~~7~~. Median fold overexpression of the top 25 type I IFN inducible genes of ~~five~~ **4-**fold or greater in whole blood **or muscle** at the time of screening;

Reason for Change: Clarification of inclusion of patients with a history of active disease.

7. Section 3.1.2

Changed to read:

~~3. Weight ≥ 120 kg~~;

19. ~~20~~. 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**;

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

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.

[redacted]

8. Section 3.2

Changed to read:

Treatment assignments will be determined using a central randomization procedure through an interactive voice response system (IVRS). For each of the ~~five~~ **four** dose cohorts, patients with a median fold overexpression of the top 25 type I IFN inducible genes **of 4-fold or greater** in whole blood **or muscle** will be randomized in a 3:1 ratio to initially receive MEDI-545 or placebo. Central randomization will be applied without regard to site.

Reason for Change: The number of dose cohorts was changed from five to four; clarification of patient population.

9. Section 3.3

Changed to read:

A limited number of MedImmune personnel **will be unblinded during the conduct of the study**. **With the exception of CRPS, unblinded personnel will be independent of the project team, and** will perform and interpret assays such as gene expression signature analyses on blood samples, will be unblinded during the study.

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

10. Section 3.4.4

Changed to read:

PLACEBO: [redacted]

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.

[redacted]

11. Section 3.4.4

Changed to read:

The study drug should be dispensed by the pharmacist or qualified designee and administered as an IV infusion over **at least** 60 minutes using an infusion pump. Do not administer by intravenous push (IV) or bolus injection.

Reason for Change: Clarification of the duration of infusion time.

Changed to read:

~~If study drug is not administered within 1 hour after preparation, it should be stored at +2°C to +8°C~~ **(36°F to 46°F)** ~~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 details~~ **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.**

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

Changed to read:

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be monitored before, **approximately** every 15 minutes during infusion, immediately after infusion, and **approximately** every 30 minutes after completion of the infusion until stable. **If an anaphylactoid-like infusion reaction or true IgE-mediated 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 with the administration~~ **been reported with the administration of IV gamma globulin 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 **the** first 24 hours after infusion, **especially within minutes to a few hours, and will be distinguished from true anaphylactic reactions by absence of measureable 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 3, with suggested treatment options. Final treatment is at the discretion of the physician and should reflect local standard of care**.

[redacted]

Table 3 Classification and Suggested Treatments for Infusion Reactions

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

Table 3 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**n** ~~medically significant~~ 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;**

[redacted]

- **Close monitoring of vital signs, for example every 5-10 minutes for Grade 1 or Grade 2 infusion reactions and every 2-5 minutes for Grade 3 or Grade 4 infusion reactions until stable;**
- Collect serum for assessment of safety biomarkers (including serum levels of mast cell tryptase, cytokines/chemokines, and IgE antibodies) **for Grade 1 or higher infusion reactions** as soon as possible after the event, at 60 minutes after the event, and at discharge.

Reason for Change:

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

12. Table 4

Changed to read:

Footnote a to table 4: If a patient discontinues his or her participation in the study **prior to Study Day 98**, the assessments designated for Study Day 98 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, except if follow-up muscle and skin biopsies have been done at any time, they need not be repeated. **(If a patient discontinues after Day 98, see Table 4 footnotes a and b.)**

Footnote c to table 4: Assessments may be performed up to 72 hours prior to dosing on Study Day 0, except muscle and skin biopsies **and skin photographs**, which may be performed up to ~~7~~ **28** days prior to Study Day 0~~ and 98~~. **Muscle biopsy may be done as part of screening to meet inclusion criteria as long as the dose(s) of immunosuppressive medications have been stable for one month and will remain the same as that in Day 0.**

Footnote h to table 4: 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 will be monitored **up to 30 minutes** before dosing, **approximately** every 15 minutes during administration of the drug, **immediately after the** ~~at the end of~~ infusion, and **approximately** every 30 minutes after the completion of the infusion until stable. **Blood pressure and heart rate will also be taken prior to discharge from the site on visits in which study drug is administered.**

Footnote t to table 4: Photographs of up to two target skin lesions (if present) are requested. One photograph should be of the skin lesion that will be biopsied. **It is preferred that the photographs are taken prior to the punch skin biopsy.**

Reason for Change: Clarification and timing of procedures.

[redacted]

13. Study Day 0 Procedures

Changed to read:

10. Skin photographs (optional, DM patients only~~)~~, **preferably prior to the punch skin biopsy and within 28 days before the visit)**

11. Muscle biopsy (within **28** ~~7~~ days before the visit). **Muscle biopsy may be done during screening to address inclusion criteria as long as the dose(s) of immunosuppressive medications have been stable for one month and will remain the same as that in Day 0.**

15. Monitor vital signs **approximately** every 15 minutes during administration of the drug, **immediately after the** ~~at 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.**

Reason for Change: Clarification and timing of procedures.

14. Section 3.6.3

Changed to read:

At screening, patients will receive tuberculin skin test. Those who are known to have positive tuberculin skin test should not receive the skin test and should be confirmed by chest x-ray that they have no evidence of active TB. Reading of the tuberculin skin test should be performed 48 to 72 hours after administration by a ~~health professional~~ **trained person**. ~~The~~ **A** 10 mm cut point will be used to determine tuberculin skin test positivity **for those patients not on systemic immunosuppressive medication and a 5 mm cut point will be used for those on systemic immunosuppressive medication**. ~~Those~~ **Subjects** who have latent ~~tuberculosis~~ **TB** must have completed an appropriate course of anti-TB treatment **or be on prophylactic treatment**. During the study, at selected sites, patients will receive Quantiferon-TB Gold tests as described in CDC guidelines to monitor for **tuberculosis** TB (Mazurek, 2005).

Reason for Change: Clarification of TB monitoring and screening.

15. Section 3.6.6.6

Changed to read:

~~3.3.6.6 Unilateral Function Index-2~~
~~The Unilateral Function Index-2 is a disease-specific measure of impairment of the upper and lower limbs and neck in patients with DM and PM (Appendix D). The content this index has been confirmed by extensive analysis of the original functional index and by patients and health professionals. It is a valid, reliable, and feasible outcome measure of muscle~~

[redacted]

~~impairment that has been proposed as a complement to the IMACS core set outcome measures to assess muscle endurance.~~

Reason for Change: The Unilateral Function Index is being eliminated for this study.

16. Section 3.6.6.7

Changed to read:

3.6.6.**7**~~8~~. Patient Reported Outcomes

In addition to the Patient Global Activity Assessment and CLINHAQ evaluated as part of IMACS core set domains, the following patient-reported indicators will be evaluated: SF-36v2 Health Survey (Appendix ~~F~~ **E**), WPAI: SHP questionnaire version 2.0 (Appendix ~~G~~ **F**), pruritus VAS, CDASI (Appendix ~~H~~ **G**), and DLQI (Appendix ~~I~~ **H**). Pruritus VAS, CDASI, and DLQI will be performed in DM patients only.

Reason for Change: Reorganization of appendices (removal of the Unilateral Function Index, formerly Appendix D).

17. Section 3.6.6.8

Changed to read:

3.6.6.**8**~~9~~. Photography of Skin Lesions

Photographs of skin lesions in DM patients only will be requested at screening but **are** ~~is~~ not required for study participation. For patients who have skin lesions at screening, up to two representative lesions ~~may~~ **will** be chosen by the investigator and serial photographs will be taken. One of the two lesions ~~should~~ **will** be the lesion selected for **the punch skin** biopsy. **the photographs will be taken prior to the punch skin biopsy .** For patients who do not have skin lesions at screening but subsequently develop lesions during the study, up to two lesions may be selected by the investigators and serial photographs ~~may~~ **will** be taken during the rest of the study period. See Appendix ~~J~~ **I** for instructions.

Reason for Change: Clarification of procedure and reorganization of appendices (removal of the Unilateral Function Index, formerly Appendix D).

18. Section 4.5

Changed to read:

3. Severe hypersensitivity **(anaphylactic)** reaction to the study drug, Grade 3 or higher
4. Infusion reaction, Grade 3 or higher

Reason for Change: To enhance safety monitoring of patients.

[redacted]

19. Section 4.7

Changed to read:

- **Severe hypersensitivity (anaphylactic) reaction to the study drug, Grade 3 or higher**
- ~~Anaphylactic reaction to study drug;~~
- **Infusion reactions, Grade 3 or higher**

Reason for Change: To enhance safety monitoring of patients.

20. Section 4.8

Changed to read:

- Any life-threatening clinical event related to the study drug**, including** anaphylactic reaction to study drug**, Grade 4**;

Reason for Change: To enhance safety monitoring of patients.

21. Section 5.2

Changed to read:

For the study, ~~40~~ **32** patients (~~5~~ **4** dose cohorts of 8 patients each) will be randomized into the study. Within each dose cohort, 6 patients will initially receive MEDI-545 and continue receiving MEDI-545 for 14 doses in total; 2 patients will initially receive 7 doses of placebo followed by 7 doses of MEDI-545. In addition, a dose cohort may be expanded by up to 4 additional patients if eligible patients are already in screening at the time 8 patients have been randomized into the dose cohort. Sample size was not based on a formal statistical calculation, but based on clinical considerations as well as the primary objective of safety assessment.

Table 7 and Table 8 present the probability of observing at least 1 infrequently occurring event when assuming a range of potential observed event rates and exact binomial 95% confidence intervals to assess the precision of estimates of the event rate for the MEDI-545 cohort n=6 and for the combined cohorts (n= 12, 18, 24, respectively).

Reason for Change: Change in number of patients and cohorts.

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 preclinical and clinical information; moving the optional DNA analysis from Study Day 0 to Study Day 14; increasing the number of dose cohorts from 4 to 5 by adding Dose Cohort 3B, which will only include patients with low/undetectable gene signature; increasing the number of patients from 32 to 40; providing clarification that a physician must be present at the sites during all study drug administrations; 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; clarifying that patients will provide the vaginal self-collected swabs and clarification that these may also be collected by qualified medical personnel, if approved by the sponsor; providing clarification that patients who become pregnant during the study period must not receive additional doses of study product and should proceed to the follow-up phase beginning at Study Day 185. Other revisions include changes to the statistical considerations section and clarification of text throughout the protocol. The changes made to Version 5.0 of the protocol to create Version 6.0 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 ~~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]

   Reason for change: Change in Medical Monitor.

2. List of Abbreviations
   Updated list of abbreviations.

3. 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.

[redacted]

4. 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.

5. Section 1.5

   The clinical experience with MEDI-545 in study MI-CP151 was updated to reflect the status of current clinical trial.

   Reason for Change: This section was updated to provide current information on study MI-CP151.

6. Section 2.3

   Changed to read:

   2. Assess the effects of MEDI-545 on levels of expression of type I IFN-inducible genes and proteins in the blood, skin, and muscle of patients with DM or PM and on levels of type I IFN mRNAs and proteins and other pharmacodynamic markers in blood and tissue samples **in patients who have a median fold overexpression of the top 25 type I IFN inducible genes of 4-fold or greater in whole blood or muscle, compared to normals**;

   Reason for Change: Clarification of text since patients with low/undetectable levels of expression of type I IFN-inducible genes were being added to the study.

7. Section 2.4.1

   Changed to read:

   The study 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 DM or PM who have ~~a~~ **low/undetectable or** high level of expression of mRNA for type I IFN-inducible genes in whole blood or muscle at the time of screening. Approximately 20 investigative sites in the United States of America (USA) ~~and Canada~~ will participate in the study. A total of 32 evaluable patients **with high level of expression of mRNA for type I IFN-inducible genes (ie, gene signature positive)** will ~~participate, with 8 patients~~**be** randomized in a 3:1 ratio to initially receive MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo every 2 weeks for 12 weeks for a total of 7 doses. **An additional cohort (Dose Cohort 3B) of 8 evaluable patients with low/undetectable or negative expression of type I IFN-inducible genes (ie, gene signature negative) will be randomized in a 3:1 ratio to initially receive MEDI-545 (3.0 mg/kg) or placebo every 2 weeks for 12 weeks**

[redacted]

for a total of 7 doses, with 6 patients receiving MEDI-545 and 2 patients receiving placebo. In each dose cohort, 6 patients will receive MEDI-545 and 2 patients will receive placebo. Thereafter (2 weeks after the 7th dose), in each **of the 5** dose cohort**s**, patients randomized to MEDI-545 will continue to receive the same dose of MEDI-545 over an additional 12 weeks (7 doses) and patients randomized to placebo will receive MEDI-545, at the dose specified in the dose cohort, every 2 weeks for an additional 12 weeks (7 doses) for a total of 26 weeks (14 doses).

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 at any time for safety reasons. Nonevaluable patients may be replaced to maintain a size of at least 8 patients per dose cohort. Data from all patients will be included in safety analyses. A dose cohort may be expanded by up to 4 additional patients (for a maximum of ~~16~~ **20** additional patients in total) if eligible patients are in screening at the time 8 patients have been randomized into the dose cohort.

Figure 1 was modified to include the changes made to the study design.

Reason for Change: Change in study design to add additional dose cohort containing patients with low/undetectable expression of type I IFN-inducible genes. This change increased the number of total patients to 40, necessitating the need for 4 additional patients for cohort expansion.

8. Section 2.4.2

Changed to read:

Screening evaluations include the following: medical history; physical examination; 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)**; ECG; TB skin test; blood tests for hepatitis A, B, C, HIV-1 and HIV-2; serum βHCG for women (unless surgically sterile or 2 years after menopause); vital signs; serum chemistry (including Na, K, Cl, bicarbonate, BUN]creatinine, bilirubin, alkaline phosphatase, and random glucose); CBC with differential and platelets, serum levels of muscle enzyme (including CK, aldolase, LDH, ALT, and AST); urinalysis; MMT, extramuscular activity assessment based on MDAAT, pulmonary function tests, physician global activity assessment; and CLINHAQ.

Deletion of Quantiferon®-TB Gold assay in the study.

Clarification that the CLINHAQ includes the Patient Global Activity Assessment.

Reason for Change: Clarification of chest x-ray or CT scan use for screening, and the CLINHAQ includes the Patient Global Activity Assessment. In addition, the use of the Quantiferon®-TB Gold assay was deleted.

[redacted]

9. Section 3.1

Changed to read:

The patients in the study must be adults with probable or definite DM or PM according to the Bohan and Peter criteria (Bohan, 1975) and have active disease. **Patients will either have low/undetectable or high level of expression of mRNA for type I IFN-inducible genes in whole blood or muscle at the time of screening. High level of expression, defined as** ~~Patients must have~~ a median fold overexpression of the top 25 type I IFN inducible genes of 4-fold or greater**, is referred to as gene signature positive, and low/undetectable level of expression is referred to as gene signature negative**~~in whole blood or muscle, compared to normals~~.

Reason for Change: Clarification of text since patients with low/undetectable levels of expression of type I IFN-inducible genes will be included in the study.

10. Section 3.1.1

Changed to read:

8. **Patients randomized to Dose Cohorts 1, 2, 3A, and 4 must have m**~~M~~edian fold overexpression of the top 25 type I IFN-inducible genes of 4-fold or greater in whole blood or muscle at the time of screening**; patients randomized to Dose Cohort 3B must have low/undetectable expression of type I IFN-inducible genes**;

Reason for Change: Clarification of text since patients with low/undetectable levels of expression of type I IFN-inducible genes will be included in the study.

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

11. Section 3.2

Changed to read:

Treatment assignments will be determined using a central randomization procedure through an interactive voice response system (IVRS). ~~For each of the 4 dose cohorts, p~~**P**atients with a median fold overexpression of the top 25 type I IFN inducible genes of 4-fold or greater in whole blood or muscle will be randomized ~~in a 3:1 ratio to initially receive MEDI-545 or placebo~~**to Dose Cohorts 1, 2, 3A, or 4, and patients with low/undetectable expression of type I IFN-inducible genes will be randomized to Dose Cohort 3B**. Central randomization will be applied without regard to site.

Reason for Change: Clarification of text.

[redacted]

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

12. Section 3.4.2

Changed to read:

A total of 40 evaluable patients will participate in this study. A total of 32 evaluable patients with positive gene signature will ~~participate in the study, with 8 patients~~**be** randomized in a 3:1 ratio to initially receive MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo infused over at least 60 minutes every 2 weeks for 12 weeks for a total of 7 doses (Table 1). **An additional cohort (Dose Cohort 3B) of 8 evaluable patients with negative gene signature will be randomized in a 3:1 ratio to initially receive MEDI-545 (3.0 mg/kg) or placebo every 2 weeks for 12 weeks for a total of 7 doses, with 6 patients receiving MEDI-545 and 2 patients receiving placebo.** ~~Up to 20 additional patients may be enrolled (4 patients in each of the 5 dose cohorts), if those patients are in screening at the time 8 patients have been randomized to each cohort.~~ In each dose cohort, 6 patients will receive MEDI-545 and 2 patients will receive placebo. Thereafter (2 weeks after the 7th dose), in each **of the 5** dose cohort**s**, patients randomized to MEDI-545 will continue to receive the same dose of MEDI-545 every 2 weeks for an additional 12 weeks (7 doses) and patients randomized to placebo will receive MEDI-545, at the dose specified in the dose cohort they are assigned, every 2 weeks for an additional 12 weeks (7 doses) for a total of 26 weeks (14 doses). MEDI-545 or placebo will be administered IV over at least 60 minutes.

A dose cohort may be expanded by up to 4 additional patients (for a maximum of 20 additional patients in total) if eligible patients are in screening at the time 8 patients have been randomized into the dose cohort.

Table 1 Treatment Regimens

		Treatment Period	
Dose Cohort	**N**	**Study Days 0-84**	**Study Days 98-182**
1 [a]	8	MEDI-545: 0.3 mg/kg × 7 doses (N=6)	MEDI-545: 0.3 mg/kg × 7 doses (N=6)
		Placebo × 7 doses (N=2)	MEDI-545: 0.3 mg/kg × 7 doses (N=2)
2 [a]	8	MEDI-545: 1.0 mg/kg × 7 doses (N=6)	MEDI-545: 1.0 mg/kg × 7 doses (N=6)
		Placebo × 7 doses (N=2)	MEDI-545: 1.0 mg/kg × 7 doses (N=2)
3**A** [a]	8	MEDI-545: 3.0 mg/kg × 7 doses (N=6)	MEDI-545: 3.0 mg/kg × 7 doses (N=6)
		Placebo × 7 doses (N=2)	MEDI-545: 3.0 mg/kg × 7 doses (N=2)
3B [b]	**8**	**MEDI-545: 3.0 mg/kg × 7 doses (N=6)**	**MEDI-545: 3.0 mg/kg × 7 doses (N=6)**
		Placebo × 7 doses (N=2)	**MEDI-545: 3.0 mg/kg × 7 doses (N=2)**
4 [a]	8	MEDI-545: 10.0 mg/kg × 7 doses (N=6)	MEDI-545: 10.0 mg/kg × 7 doses (N=6)
		Placebo × 7 doses (N=2)	MEDI-545: 10.0 mg/kg × 7 doses (N=2)

a **This dose cohort consists of patients who are gene signature positive.**
b **This dose cohort consists of patients who are gene signature negative.**

[redacted]

Reason for Change: Change in study design to add additional dose cohort containing patients with low/undetectable expression of type I IFN-inducible genes. This change increased the number of dose cohorts to 5 and the total number of patients to 40.

13. Section 3.4.3

Changed to read:

Table 2 Summary of Infusion Volume, Duration, and Rate

Dose Cohort	Dose (mg/kg)	Infusion Volume [a] (mL)	Infusion Duration	Maximum Infusion Rate (mL/hr)	Infusion Rate (mg/kg/min) [b]
1	0.3	100	≥ 60 minutes	100	0.005
2	1.0	100	≥ 60 minutes	100	0.017
3**A**	3.0	100	≥ 60 minutes	100	0.05
3B	**3.0**	**100**	**> 60 minutes**	**100**	**0.05**
4	10.0	100	≥ 60 minutes	100	0.17

a. ~~It is expected that s~~**S**ome 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. Infusion rate (mg/kg/min) is based on body weight.

Reason for Change: Clarification of text.

14. Section 3.4.4

Changed to read:

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

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be monitored before, approximately every 15 minutes during infusion, immediately after 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.

Reason for Change: Clarification of text.

15. Section 3.5

Deleted Quantiferon TB Gold Assay from Table 4 and Table 5 and made the respective changes for the individual study visits.

Added Patient Global Activity Assessment as a separate evaluation to Table 4 and Table 5 and made the respective changes for the individual study visits.

Changed collection of blood sample for DNA analysis from Study Day 0 to Study Day 14 and made the respective changes for the individual study visits.

Clarified the muscle biopsy was open (footnote c) and made the respective changes for the individual study visits.

Clarified the vital sign monitoring (footnote h) and made the respective changes for the individual study visits.

Clarified that the patient will provide self-collected vaginal swabs for HSV and HPV testing or via an MD/OBGYN or qualified medical personnel, if approved by the sponsor (footnote j).

Clarified that serum samples for MEDI-545 concentrations were collected within 10 minutes after the infusion has stopped (footnote v).

16. Sections 3.6.1 and 3.6.3

    Deleted the Quantiferon TB Gold assay for the diagnosis of latent TB infection (at selected sites).

17. Section 3.6.2

    Changed to read:

    HSV-1, HSV-2, EBV, CMV, and HPV will be monitored by virus isolation in tissue culture and/or by molecular assays using PCR amplification as indicated in Table 4 and Table 5. The investigator or qualified designee will collect oropharyngeal swabs for HSV-1 and HSV-2 testing**. The patient will provide** ~~, and women will~~ self collect vaginal swabs for HSV-1, HSV-2, and HPV testing. **The vaginal swabs may also be collected by an MD/OBGYN or qualified medical personnel such as an appropriately trained nurse practitioner, if previously approved by the sponsor.** In addition, blood samples will be collected and tested for EBV and CMV by PCR molecular-based tests.

    Reason for Change: Clarification of text.

18. Section 3.6.7.3

    Changed to read:

    ### 3.6.7.3 Open Muscle Biopsies

[redacted]

~~Muscle~~ **Open muscle** biopsies will be performed at visits indicated in Table 4. The initial **open** muscle biopsy will be performed on an involved muscle within ~~7~~ **28** days prior to Study Day 0. Involved muscle is defined as having a muscle strength of 4 to 4-/5 as assessed by MMT. The repeated **open** muscle biopsy will be performed on a muscle that was noted to be involved on Study Day 0. If involved on Study Day 0, the contralateral muscle is the preferred site of the repeated biopsy. **The open** ~~M~~**m**uscle biopsy samples collected during the trial will undergo histopathological grading and IHC analysis of cellular infiltrates, including dendritic cell subtypes, B cells, and T cells. Additionally, gene expression will be analyzed, and changes in IFN-inducible protein levels within muscle specimens will be assessed by IHC methods.

Reason for Change: Clarification of text that an open muscle biopsy will be performed.

19. Section 3.7

Added:

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: Added option for patients to enter a long-term, open-label, safety study with MEDI-545.

20. Section 4.1.2

Changed to read:

The reporting period for adverse events is the period from the signing of informed consent through Study Day 350. **AEs will not be recorded for patients deemed screening failures.**

Reason for Change: Clarification of text regarding reporting adverse events for screening failures.

21. Section 4.2.2

Changed to read:

The reporting period for SAEs is the period from the signing of informed consent 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.

Reason for Change: Clarification of text regarding reporting serious adverse events for screening failures.

[redacted]

22. Section 4.5

Changed to read:

2. Pregnancy or intent to become pregnant. **Patients who wish to become pregnant should be followed 3 months after the last dose of study drug***

*Patients who 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.

23. Section 4.7

Changed to read:

Pregnancy **(Patients who become pregnant during the study period must not receive additional doses of study drug 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)**;

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

24. Section 4.9

Changed to read:

Dose Cohort 1 (single-dose, 0.3 mg/kg or placebo) will be started first. Dosing at each next higher dose cohort (Dose Cohort 2 [1.0 mg/kg or placebo], Dose Cohort**s** 3**A and 3B** [3.0 mg/kg or placebo], and Dose Cohort 4 [10.0 mg/kg or placebo] will commence after the Medical Monitor has reviewed the safety information including data through Study Day 42 from the first randomized 8 patients in each **of the** preceding lower dose cohort**s** and all cumulative safety data available in all cohorts, and has determined that the safety profile is acceptable **(ie, Dose Cohort 2 will start only after safety data from the 8 patients in Dose Cohort 1 has been reviewed and it has been deemed safe; likewise, Dose Cohorts 3A and 3B will start only after the data from the 8 patients in Dose Cohort 2 has been reviewed**

[redacted]

and it has been deemed safe; Dose Cohort 4 will start only after safety data from the 8 patients from Dose Cohort 3A have been reviewed and it has been deemed safe). Dose Cohorts 3B and 4 will enter patients in parallel.

Reason for Change: Clarification of dose escalation text in light of the additional dose cohort (Dose Cohort 3B).

25. Section 5.2

Changed to read:

For the study, ~~32~~ **40** patients (4 **5** dose cohorts of 8 patients each) will be randomized into the study. Within each dose cohort, 6 patients will initially receive MEDI-545 and continue receiving MEDI-545 for 14 doses in total; 2 patients will initially receive 7 doses of placebo followed by 7 doses of MEDI-545. In addition, a dose cohort may be expanded by up to 4 additional patients if eligible patients are already in screening at the time 8 patients have been randomized into the dose cohort. Sample size was not based on a formal statistical calculation, but based on clinical considerations as well as the primary objective of safety assessment.

Table 7 and Table 8 present the probability of observing at least one **subject with an** infrequently occurring ~~event~~ **AE** when assuming a range of potential observed ~~event~~ **AE** rates and exact binomial 95% confidence intervals to assess the precision of estimates of the ~~event~~ **AE** rate for the MEDI-545 cohort n=6 and for the combined cohorts (n= 12, 18, 24, **and 30** respectively).

Reason for Change: Clarification of text. In addition, increase in sample size resulted in a modification of the probability of observing at least one infrequently occurring adverse event in Tables 7 and 8.

Summary of Changes from Version 6.0 to Version 7.0 of the Study Protocol

Version 6.0 of the protocol (dated [redacted]) was amended to Version 7.0 (dated [redacted] The major changes include: 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 second interim analysis (which was to occur after all patients in Dose Cohort 4 completed Day 98) to when a minimum of 8 patients in Dose Cohort 4 complete Study Day 98; clarifying that complete clinical response and remission will not be assessed in this study (as the study duration is not long enough to do so); and providing guidance in Appendix J for the management of abnormal LFTs.

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 strike-through. Changes that are similar in nature throughout the text may be listed only once.

1. List of Abbreviations
   Updated list of abbreviations.

2. 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 G_1 kappa ($IgG_1\kappa$) monoclonal antibody (Mab) that binds to and neutralizes a majority of the subtypes of human interferon α (IFN α).~~

   ~~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.~~

   ~~MEDI-545 is currently being investigated in the autoimmune disease systemic lupus erythematosus (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 provides an acceptable safety profile as well as evidence of clinical activity. Because the IIMs have a similar magnitude of type I IFN inducible genes in whole blood as 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.~~

   Reason for change: MEDI-545 description updated.

[redacted]

3. Section 1.4

Changed to read:

In MI-CP126, 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**s** ~~was~~ were 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 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 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**

[redacted]

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. Single-dose PK of MEDI-545 were similar between psoriasis and SLE patients. A total of 36 patients received study drug 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, at least 0.75 mg/min. 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.** ~~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-CP152, is a Phase 1b, multicenter, multinational, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3 to 10.0 mg/kg) in adult subjects with SLE. In this study, MEDI-545 is administered every 2 weeks for a total of 14 doses over 26 weeks. The 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 27 weeks). The first 12 randomized subjects in each dose cohort provide safety data for dose escalation; the additional subjects 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 subjects 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 patients, 22.7%), blood potassium decreased (4 patients, 18.2%), urinary tract infection (3 patients, 13.6%), and nausea (3 patients, 13.6%).~~ On [redacted], 1 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, ≥ 0.75 mg/min. After thorough review, the Medical Monitor judged this event to be an infusion reaction. This study was stopped on [redacted] due to an SAE of anaphylactic reaction associated with Grade 4 hypotension in MI-CP145 and restarted in [redacted].

A review of the safety data from both MI-CP145 and MI-CP152 concluded the aforementioned SAEs **of infusion reactions in each study** were most likely due to MEDI-545 administered at a high rate of infusion (≥ 0.75 mg/min), 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 mg/kg to 10 mg/kg, and set the infusion volume and time to 100 mL and at least 60 minutes.

As of [redacted], 183 patients have been dosed in the MI-CP152 study. 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

[redacted]

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-545may 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 reinitiation of the MI-CP152 study and as of [redacted], the most frequently reported AEs (incidence > 10%) were hemoglobin decreased and systemic lupus erythematosus (flares) (13 patients each; 16.7%); blood potassium decreased (11 patients; 14.1%); lymphocyte count decreased and arthralgia (10 patients each; 12.8%); blood bicarbonate decreased (9 patients; 11.5%); blood alkaline phosphatase increased 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 reinitiation of the study and as of [redacted], 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, which included 1 patient (respiratory failure, renal failure, thrombocytopenia, diabetes mellitus, and cellulitis); 1 patient (dehydration); 1 patient (blindness transient); 1 patient (chest pain); 1 patient (costochondritis); 1 patient (constipation); 1 patient (abdominal pain); 1 patient (psychotic disorder); 1 patient (angioplasty); and 1 patient (sepsis).~~

A third study of MEDI-545 in patients with SLE (MI-CP179) will be 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 [redacted], 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. ~~As of [redacted], 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 [redacted], 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.~~

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

4. Section 1.5

Changed to read:

The current study, 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 in adult patients with DM or PM. This is a dose-escalation study designed to evaluate the safety and tolerability of multiple IV doses of MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo in 32 adult patients with DM or PM who have a high level of expression of mRNA for type I IFN-inducible genes in whole blood or muscle at the time of screening. MEDI-545 or placebo will be initially administered every 2 weeks for 12 weeks (7 doses) followed 2 weeks after the 7th dose by MEDI-545 every 2 weeks for another 12 weeks (7 doses) for a total of 26 weeks (14 doses). The planned starting dose of MEDI-545 (0.3 mg/kg) in MI-CP151 is less than one-hundredth of the highest dose tested (100 mg/kg) in cynomolgus monkeys (repeated administrations every 2 weeks for 27 weeks). **This 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 possibly related to study drug.** ~~As of [redacted], 9 patients had 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, hyponatremia, 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), Grade 3 (2 patients), and Grade 1 (2 patients). As of [redacted], one patient reported an SAE of chest pain, which was judged by the investigator as not related to the study drug (MEDI-545 or placebo).~~

Reason for Change: This section was updated to provide current information on study MI-CP151.

5. Section 2.4.1

Added:

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, 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.

Reason for addition: This section was added to provide clarification on what patients may qualify to enter the CP212 open label extension study.

6. Section 3.4.1

Changed to read:

MEDI-545 (100 mg/mL): [redacted]

PLACEBO: [redacted]

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

7. Section 3.4.4.2

Added:

3.4.4.2 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.**

[redacted]

- **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 J.

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

As indicated in the Guidance for Abnormal Liver Function Tests (Appendix J), 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 3.4.5

Changed to read:

All concomitant medications**, including herbal products,** used by the patient from screening through Study Day 350 will be recorded on the case report form. The concomitant administration of IVIG is allowed.

Reason for change: Increase patient safety.

9. Section 3.6.6.4

Removed:

[redacted]

~~**Complete Clinical Response and Clinical Remission**~~

~~The IMACS group also provided definitions for complete clinical response and clinical remission (Oddis, 2005). A complete clinical response will be defined as the lack of evidence of active myositis for a 6-month continuous period while receiving drug therapy for IIM. A complete clinical remission will be defined as the lack of evidence of active myositis for a 6-month continuous period while not receiving drug therapy for IIM.~~

~~Lack of evidence of active myositis is defined as assessed by global and extramuscular assessments, stable muscle strength and function (defined as equivalent to < 15% change in the semiquantitative scoring of the measures of these domains over at least a 6-month period), and normal muscle enzyme levels.~~

Reason for change: Complete clinical response and remission is defined as lack of evidence of active disease for a 6-month continuous period. As the study duration for continuous dosing is only 5 months, complete clinical response and remission have been removed from the list of descriptive summaries.

10. Section 3.7

Changed to read:

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.

~~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: Define criteria for patient early termination in MI-CP151 study for enrollment into MI-CP212 study.

11. 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

[redacted]

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 Specialist has responsibility for the day-to-day safety monitoring of the study, including the receipt, review, investigation, and follow-up of SAEs reported by the clinical study sites.~~

~~An SMC will independently review cumulative safety surveillance data, as well as the decisions of the MedImmune 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 adverse events felt to be medically significant by the Medical Monitor. The SMC is composed of at least two MedImmune physicians who are not directly involved in the day-to-day operations of the study, and two physicians who are not employees of MedImmune.~~

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

12. Section 4.7

Changed to read:

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

- Withdrawal of consent;
- Pregnancy (Patients who become pregnant during the study period must not receive additional doses of study drug 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);
- Any life-threatening clinical event related to the study drug;
- Severe hypersensitivity (anaphylactic) reaction to the study drug, Grade 3 or higher;
- Infusion reactions, Grade 3 or higher as defined in Table 3;
- 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; If 3 consecutive doses of study drug are missed due to abnormal LFTs (ALT, AST);

- **Two consecutive total bilirubin values taken at least 1 week apart > 2 x ULN not due to Gilbert's syndrome or hemolysis; or**
- **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 **for any of these reasons, with the exception of withdrawal of consent,** will be followed for the full study period (through Study Day 350), including the collection of any mandated blood and urine specimens.

Reason for change: Increase patient safety.

13. **Section 4.8**

Changed to read:

- 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.

14. 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. No formal statistical tests are planned. Missing data will be treated as missing. No data will be imputed unless otherwise specified. Study ~~Day 0~~ **Baseline values** will be defined as the **last valid assessment prior to the** ~~day of~~ first **administration of** study drug ~~administration~~. All data will be collected from screening through Study Day 350.

Reason for change: Clarification of study baseline.

15. Section 5.3

Changed to read:

Safety results will be analyzed in all patients who receive any study drug. Evaluability for analyses of MEDI-545 serum concentrations and PK parameters will be determined based upon the frequency and timing of the serum samples obtained. IM analysis will be performed in all patients who have received at least one dose of MEDI-545. **Efficacy results will be analyzed in all randomized patients who receive any study drug.**

[redacted]

Reason for change: Clarification of efficacy data analysis population.

16. Section 5.4.3.1

Changed to read:

The major clinical measures of myositis disease activity will include serum creatine kinase normalization, IMACS core set disease activity measures (physician's global activity assessment, patient global activity assessment, muscle strength assessed by MMT, physical function, muscle-associated enzymes, and extramuscular activity assessment), patients' need for new or increased doses of immunosuppressive therapy, changes in patients' immunosuppressive therapy during the follow-up period, photography of skin lesions, and pulmonary function testing. These assessments will be summarized descriptively by treatment group and time point. A descriptive summary of the number and percent of patients who have reached any of the following: 1) complete CK normalization as indicated by relative normalization of 100% **and** 2) IMACS-defined response~~, 3) complete clinical response, or 4) clinical remission~~ will be presented for placebo and each of the MEDI-545 dose group. The major patient-reported outcomes, including SF-36v2 Health Survey, pruritus VAS, CDASI, DLQI, and WPAI: SHP questionnaire will also be summarized descriptively.

Reason for change: Complete clinical response and remission is defined as lack of evidence of active disease for a 6-month continuous period. As the study duration for continuous dosing is only 5 months, complete clinical response and remission have been removed from the list of descriptive summaries.

17. Section 5.5

Changed to read:

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

- After the first 2 cohorts complete the Study Day 98 evaluation;
- ~~After all cohorts complete~~ **When at least 8 patients in Dose Cohort 4 complete** the Study Day 98 evaluation; and
- After all cohorts complete Study Day 196 evaluation.

~~The interim analyses will be used to help determine the doses and schedule of MEDI-545 for a follow-up Phase 2 study of MEDI-545 in DM and PM.~~

Reason for change: Updated to reflect analyses conducted.

18. Section 10

Added:

[redacted]

Summary of Changes from Version 6.0 to Version 7.0 of the Study Protocol

Version 6.0 of the protocol (dated [redacted]) was amended to Version 7.0 (dated [redacted] The major changes include: 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 second interim analysis (which was to occur after all patients in Dose Cohort 4 completed Day 98) to when a minimum of 8 patients in Dose Cohort 4 complete Study Day 98; clarifying that complete clinical response and remission will not be assessed in this study (as the study duration is not long enough to do so); and providing guidance in Appendix J 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 K.

Reason for addition: Update summary of changes

19. Appendix J

Added:

Appendix J: 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

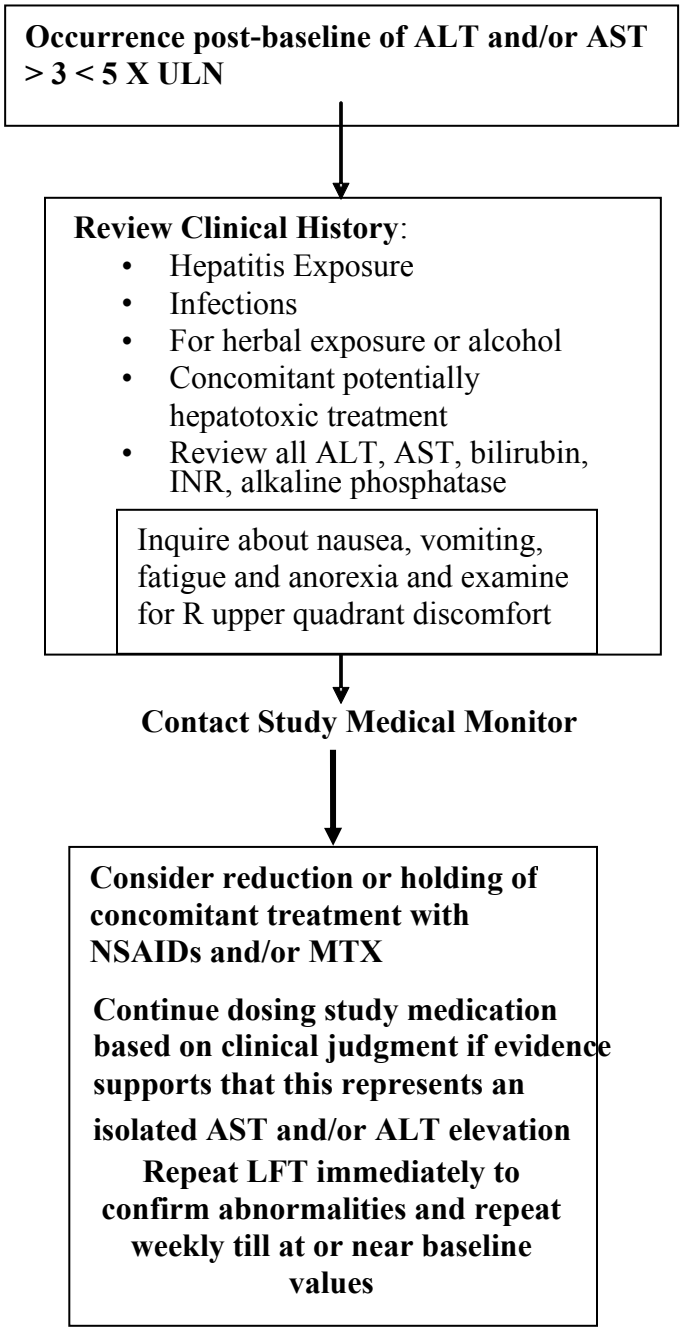
study drug while maximizing safety concerns to minimize the potential for functional liver impairment and damage. There are 2 separate parts to the guidance to detect clinically significant liver injury depending on whether the subject entered the study with normal or mildly elevated (up to 2 × ULN) 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.

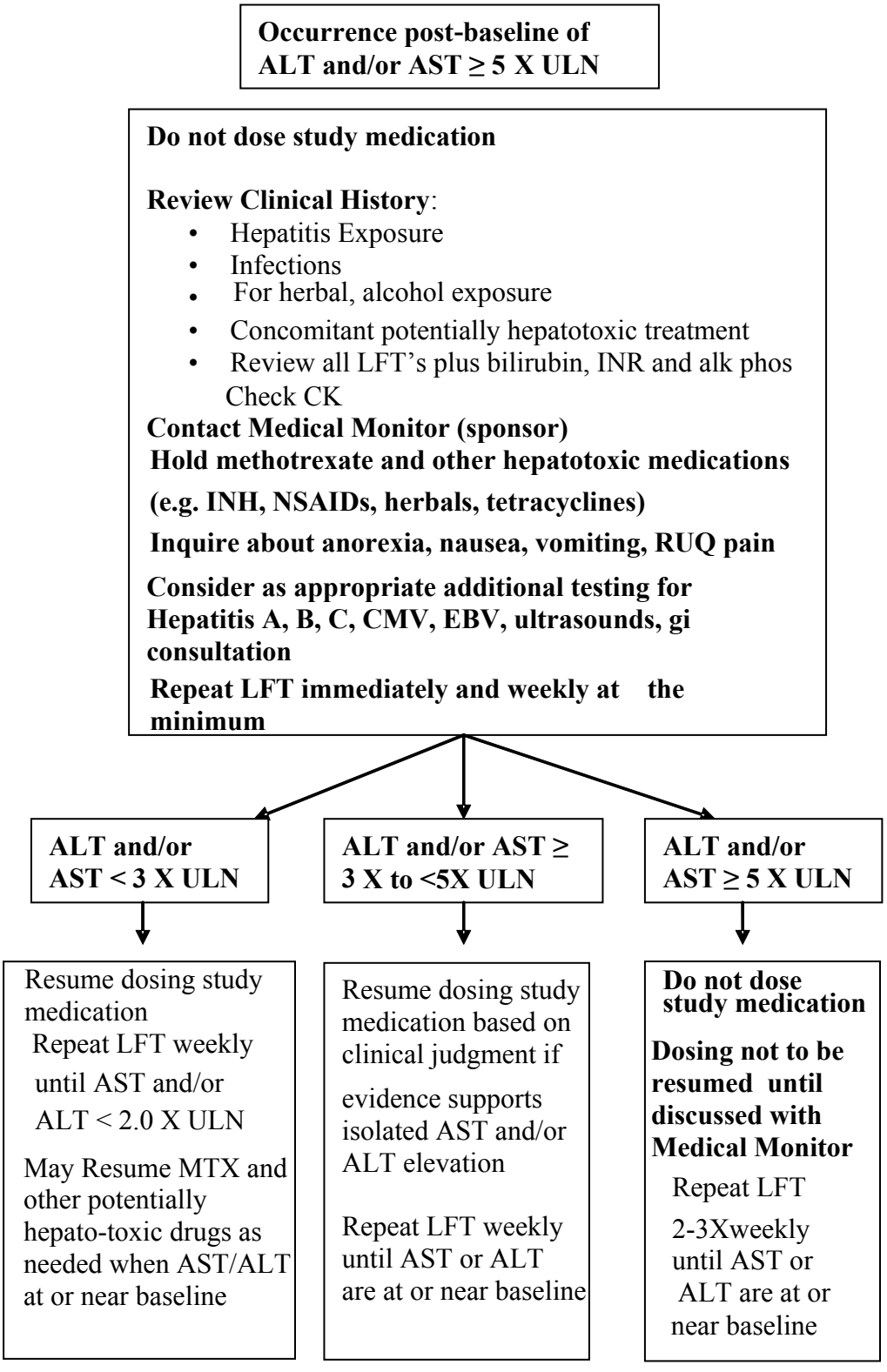
The decision to include subjects in this clinical trial with baseline LFT abnormalities is supported by the FDA draft guidance.

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 151 that develop post-baseline in individuals with ALT or AST ≤2X ULN at baseline

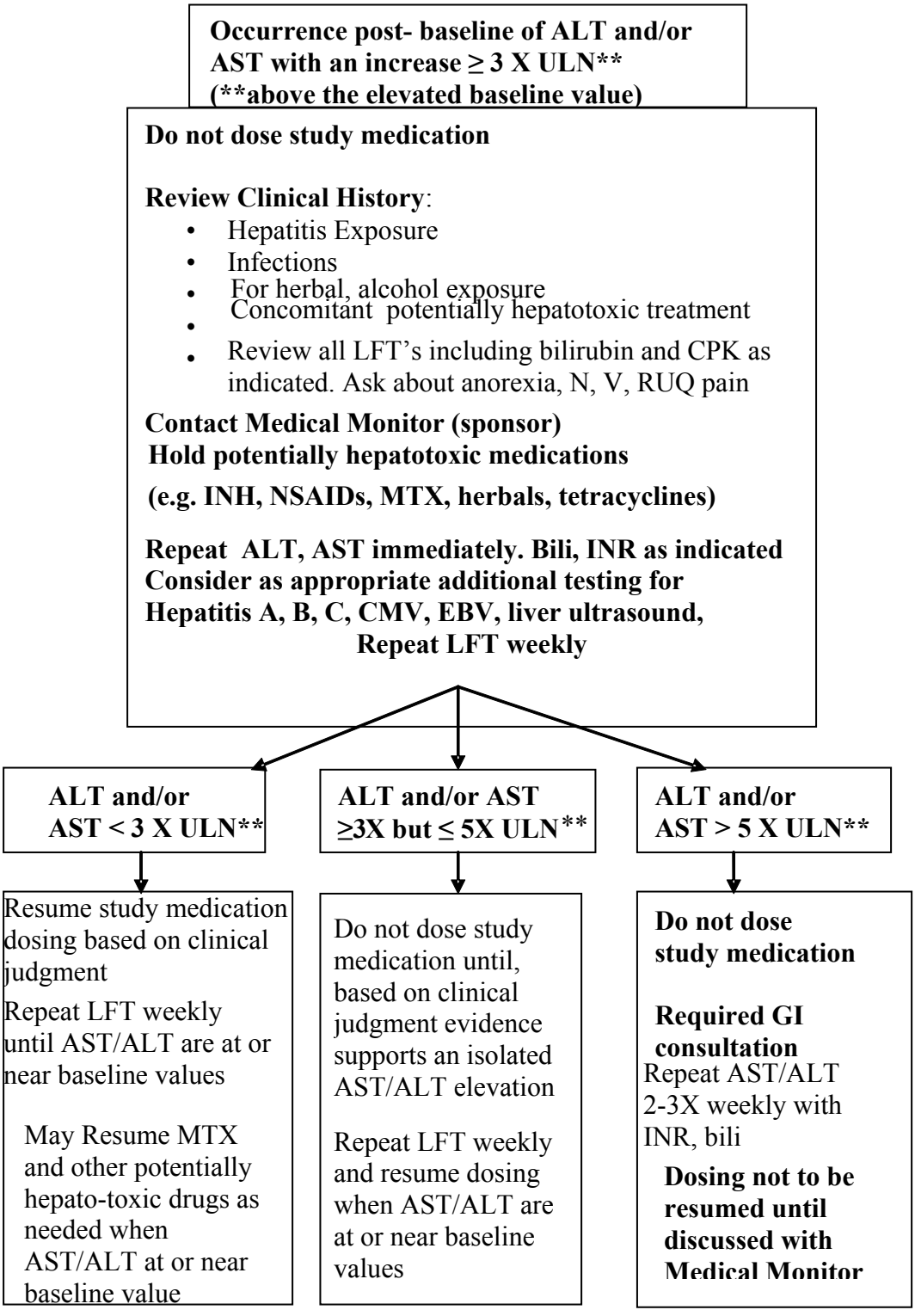


[redacted]



Guidance for abnormal Liver Function Tests during Study 151 that develop post-baseline in individuals with ALT or AST > 2X ULN at baseline

[redacted]



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

[redacted]

ATTACHMENT 1 Toxicity Table

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

[redacted]

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)'

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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