# A Phase 1b Randomized, Double-blind, Placebo-controlled Multiple-ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, Pharmacodynamics, and Clinical Response of MEDI4920 in Subjects with Adult-onset Rheumatoid Arthritis

**Sponsor Protocol Number:** D5100C00002

**Application Number:** IND 128905
EudraCT Number: 2015-005318-30

**Investigational Product:** MEDI4920

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**Contract Research Organization:** ICON

**Protocol History, Date**: Original Protocol, 15Jan2016
Protocol Amendment 1, 05Apr2016
Protocol Amendment 2, 10Aug2016
Protocol Amendment 3, 29Sep2017

# PROTOCOL SYNOPSIS

**TITLE**

A Phase 1b Randomized, Double-blind, Placebo-controlled Multiple-ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, Pharmacodynamics and Clinical Response of MEDI4920 in Subjects with Adult-onset Rheumatoid Arthritis

**HYPOTHESES**

**Primary Hypothesis:** The primary hypothesis is that multiple ascending intravenous (IV) doses up to 1500 mg of MEDI4920 once every 2 weeks (Q2W) over a 12-week period will be safe and well-tolerated in subjects with rheumatoid arthritis (RA) when compared with placebo in combination with methotrexate (MTX) or another conventional disease-modifying anti-rheumatic drug (cDMARD).

**Secondary Hypothesis:** A secondary hypothesis has not been established for this study.

**Exploratory Hypotheses:** The exploratory hypotheses are that CCI [redacted]

**OBJECTIVES**

**Primary Objective:** To assess the safety and tolerability of multiple ascending IV doses of MEDI4920 in subjects with adult-onset RA.

**Secondary Objectives:** To evaluate the pharmacokinetics (PK) and immunogenicity of MEDI4920 in subjects with adult-onset RA.

**Exploratory Objectives:**

1. CCI [redacted]
2. CCI [redacted]
3. CCI [redacted]
4. CCI [redacted]

**STUDY ENDPOINTS**

**Primary Endpoints:**

1. The incidence of adverse events (AEs) and serious adverse events (SAEs).
2. The incidence of treatment-emergent AEs of special interest (AESIs) as follows:
   - Thrombotic and embolic events
   - Hepatic function abnormality (meeting the definition of Hy's Law)
   - Anaphylaxis and serious hypersensitivity reactions
   - Infusion-related reactions
   - Immune complex disease
   - Serious and/or opportunistic infections (including but not limited to reactivation of latent viral infection [varicella zoster, herpes simplex virus, Epstein-Barr virus, cytomegalovirus (CMV)] and tuberculosis)
3. Vital signs, laboratory parameters (including coagulation parameters), electrocardiograms and physical examinations.

**Secondary Endpoints**: The PK profile, PK parameters, and immunogenicity of MEDI4920 will be assessed for each cohort.

**Exploratory Endpoints:**

- CCI [redacted]
- CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

**STUDY DESIGN**

This is a multicenter, randomized, double-blind (investigator, subject, and sponsor will be blinded to treatment assignment), placebo-controlled study to evaluate the safety and tolerability of multiple ascending doses of MEDI4920 in subjects with adult-onset RA (moderate to severe, as defined by DAS28 CRP ≥ 3.2 at screening) with an inadequate response to MTX or other cDMARDs or a biologic anti-tumor necrosis factor alpha agent. The study is planned to be conducted at approximately 15 sites in 2 to 4 countries. A maximum of 54 eligible subjects are planned for this study. Approximately 40 subjects will be randomized in 3 cohorts to receive either 75 mg (Cohort 1), 500 mg (Cohort 2), or 1500 mg (Cohort 3) MEDI4920 or placebo Q2W in combination with MTX or another cDMARD for up to 12 weeks. An additional 14 subjects will be randomized in a 5:2 ratio to an additional cohort (Cohort 4) to better characterize the dose (exposure)-response relationship. The selected dose of MEDI4920 in Cohort 4 is 1000 mg Q2W.

Cohorts 1 to 3 will start sequentially, with escalation from Cohort 1 to Cohort 2 and Cohort 2 to Cohort 3 confirmed by a Dose Escalation Committee (DEC) comprised of MedImmune study team members and the Study Global Chief Investigator, who will assess in a blinded fashion the safety/tolerability data after the last subject in a cohort completes Day 29 (Week 4) of treatment and has AE/safety laboratory data available at that time point. There will be a total of three DEC meetings during the study; the first DEC meeting will only review data from Cohort 1 whereas the second DEC meeting will review cumulative safety data from the first two dose cohorts being tested to date. The third DEC meeting will constitute a thorough evaluation of the cumulative safety and tolerability data for Cohorts 1 and 2 in addition to the data up to Day 85 for Cohort 3. After the last Cohort 3 subject completes the Day 85 (Week 12) assessments, the primary analysis will be conducted to include safety, tolerability, PK, anti-drug antibody (ADA), biomarker, and clinical response. Based on the outcome of this analysis, a fourth cohort will be included to better understand the dose (exposure)-response relationship. Each subject will participate in the study for up to approximately 30 weeks (includes a 6-week screening period, a 12-week treatment period, and a 12-week follow-up period). A screening visit(s) will be performed within 6 weeks (42 days) prior to dosing. All subjects will receive investigational product on the morning of Day 1. An overnight stay on Day -1 prior to administration of investigational product on Day 1 is recommended but not mandatory. If no safety concerns are identified, subjects will be discharged from the study site on Day 2 (end of the inpatient treatment period) after all study procedures have been completed. Subjects in all cohorts will return to the study site Q2W (Days 8, 15, 29, 43, 57, 71, and 85) for investigational product administration and/or specific assessments and blood draws. During the treatment period, assessments of RA parameters as well as evaluations of safety, tolerability, PK, and immunogenicity of MEDI4920 will be performed. Following the final IV infusion of investigational product, subjects will return to the study site for follow-up visits beginning at Week 13 (Day 92) and continuing through Week 24 (Day 169) to evaluate safety, tolerability, PK, and ADA of MEDI4920.

**TARGET SUBJECT POPULATION**

Male or female adults 18-70 years of age, inclusive, with adult-onset RA diagnosed by European League Against Rheumatism /American College of Rheumatology 2010 criteria at least 6 months before screening.

**TREATMENT GROUPS AND REGIMENS**

A maximum of 54 subjects will be randomized to receive either MEDI4920 or placebo as follows: 10 subjects will be randomized in Cohort 1 in a 4:1 ratio to receive 75 mg MEDI4920 (N = 8) or placebo (N = 2) as a single IV dose administered over at least 30 minutes Q2W; 14 subjects will be randomized in Cohort 2 in a 5:2 ratio to receive 500 mg MEDI4920 (N = 10) or placebo (N = 4) as a single IV dose administered over at least 60 minutes Q2W; and 16 subjects will be randomized in Cohort 3 in a 3:1 ratio to receive 1500 mg MEDI4920 (N = 12) or placebo (N = 4) as a single IV dose administered over at least 90 minutes Q2W. An additional 14 subjects will be randomized in Cohort 4 in a 5:2 ratio to receive 1000 mg MEDI4920 (N = 10) or placebo (N = 4) as a single IV dose administered over at least 90 minutes Q2W.

**STATISTICAL ANALYSIS METHODS**

**Sample Size:**

No formal sample size calculations are presented for the evaluation of the primary objective of safety and tolerability of MEDI4920. The sample size calculations are based on the exploratory endpoint CCI [redacted] CCI [redacted] The sample size calculation for Week 12 DAS28 CRP change from baseline is based on combining the data from the cohorts and performing a dose response analysis. Based on the assumption CCI [redacted] CCI [redacted] the sample sizes of 14, 8, 10, 10 and 12 subjects for the placebo, 75, 500, 1000 mg, and 1500 mg dose groups, respectively, will provide approximately 92% power for detecting a statistically significant dose response, using a significance level of 0.10. The power for dose response has been calculated using a multiple comparison procedure with modeling techniques with three candidate models for the dose response (linear, maximum effect attributable to the drug [$E_{max}$], and a Hill-$E_{max}$ model). An overall significance level of 0.10 will be used to test for dose response.

**Statistical Analyses:**

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented. All treatment-emergent AEs will be summarized overall and by MedDRA SOC and PT, by severity, and by relationship to investigational product. In addition, summaries of deaths, SAEs and treatment discontinuations due to AEs will be provided. Treatment-emergent AEs, treatment-emergent SAEs and AESIs with onset after the start of infusion (Day 1) to Day 169/Early Discontinuation Visit inclusive will be summarized by dose. The placebo subjects from each cohort will be combined for the summaries. Other safety parameters, including laboratory assessments and vital signs, will be summarized by dose.

**Interim Analysis:**

The primary analysis will be performed when all subjects in Cohort 3 have completed the Day 85 assessments or have been withdrawn from the study. The primary analysis will include all assessments on the subjects prior to the data cut-off for the primary analysis. MedImmune personnel will be unblinded to the subject treatment assignments from Cohorts 1 to 3 at the primary analysis (Day 85). The data from the primary analysis will not be communicated to personnel at the Contract Research Organization (CRO) or investigational sites or to enrolled subjects, until all subjects in Cohorts 1 to 3 have completed the study and database lock has been achieved. An additional interim analysis will be performed when all subjects in Cohort 4 have completed the Day 85 assessments or have been withdrawn from the study. MedImmune personnel will be unblinded to the subject treatment assignments from Cohort 4 for this interim analysis. Study subjects and personnel at the CRO or investigational sites will remain blinded to Cohort 4 data until all subjects in Cohort 4 have completed the study and database lock has been achieved. The final analysis on the subjects will be performed when all subjects have completed the safety follow-up.

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# LIST OF ABBREVIATIONS

| Abbreviation or Specialized Term | Definition |
|---|---|
| ACPA | anti-cyclic citrullinated peptide antibody |
| ACR | American College of Rheumatology |
| ADA | anti-drug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALP | alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANA | anti-nuclear antibody |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BP | blood pressure |
| CD40L | CD40 ligand |
| CDAI | Clinical Disease Activity Index |
| cDMARD | conventional disease-modifying anti-rheumatic drug |
| CI | confidence interval |
| $C_{max}$ | maximum concentration |
| CMV | cytomegalovirus |
| COPD | chronic obstructive pulmonary disease |
| CRO | Contract Research Organization |
| CRP | C-reactive protein |
| CTLA-4 | cytotoxic T lymphocyte antigen-4 |
| CTPA | computerized tomographic pulmonary angiography |
| DAS28 CRP | Disease Activity Score in 28 joints using C-reactive protein |
| DEC | Dose Escalation Committee |
| DNA | deoxyribonucleic acid |
| DMARD | disease-modifying anti-rheumatic drug |
| DVT | deep vein thrombosis |
| DZP | dapirolizumab pegol |
| EBV | Epstein-Barr virus |
| EDC | electronic data capture |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDV | Early Discontinuation Visit |
| $E_{max}$ | maximum effect attributable to the drug |
| ESR | erythrocyte sedimentation rate |
| FAAN | Food Allergy and Anaphylaxis Network |
| FTIH | first time in human |
| GCP | Good Clinical Practice |
| GH | general health |

| Abbreviation or Specialized Term | Definition |
|---|---|
| GLP | Good Laboratory Practice |
| HbcAb | hepatitis B core antibody |
| HbsAb | hepatitis B surface antibody |
| HbsAg | hepatitis B surface antigen |
| HED | Human Equivalent Dose |
| HSA | human serum albumin |
| HSV | herpes simplex virus |
| HIV | Human Immunodeficiency Virus |
| HL | Hy's Law |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IGRA | interferon-gamma release assay |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin |
| IL | interleukin |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| IV | intravenous |
| IXRS | interactive voice/web response system |
| JAK | Janus kinase |
| KLH | keyhole limpet hemocyanin |
| LFT | liver function test |
| mAb | monoclonal antibody |
| MAD | multiple ascending dose |
| MCP-Mod | multiple comparison procedure with modeling techniques |
| MBDA | multi-biomarker disease activity |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MDGA | Physician's Global Assessment |
| MOA | mechanism of action |
| MTX | methotrexate |
| NIAIDs | National Institute of Allergy and Infectious Diseases |
| NOAEL | no observed adverse effect level |
| NSAID | nonsteroidal anti-inflammatory drug |
| PCR | polymerase chain reaction |
| PD | pharmacodynamics |
| PE | pulmonary embolism |
| PFA | platelet function analyzer |
| PGA | Patient's Global Assessment |
| PK | pharmacokinetics |
| PT | preferred term |
| Q2W | once every 2 weeks |

| Abbreviation or Specialized Term | Definition |
|---|---|
| RA | rheumatoid arthritis |
| RBC | red blood cell |
| RF | rheumatoid factor |
| RNA | ribonucleic acid |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SC | subcutaneous |
| sCD40L | soluble CD40L |
| SID | subject identification |
| SJC | swollen joint count |
| SLE | systemic lupus erythematous |
| SOC | system organ class |
| TAT | thrombin-antithrombin complex |
| TB | Tuberculosis |
| TBL | total bilirubin |
| TDAR | T-cell-dependent antibody response |
| TEAE | treatment-emergent adverse event |
| TESAE | treatment-emergent serious adverse event |
| TJC | tender joint count |
| Tn3 | an engineered form of the third fibronectin type III protein domain from human Tenascin-C |
| TNF | tumor necrosis factor |
| TNFα | tumor necrosis factor alpha |
| ULN | upper limit of normal |
| US FDA | United States Food and Drug Administration |
| VAS | visual analogue scale |
| V/Q | ventilation-perfusion |
| VZ | varicella zoster |
| WBC | white blood cell |
| w/v | weight/volume |

# 1 INTRODUCTION

## 1.1 Disease Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that is associated with significant morbidity and mortality. The disease is characterized by inflammation of the synovial joints that can result in pain, swelling, and joint damage with secondary deformity and progressive disability. Worldwide, the prevalence of RA is estimated to be between 0.6% and 1.1% with variations across geographical regions. The incidence is 2-3 times higher in women than in men with a peak age of onset between 35 and 55 years of age (Symmons, 2002). Uncontrolled active RA causes joint damage, disability, decreased quality of life, comorbidities including cardiovascular disease and osteoporosis, and reduced life expectancy (Wong et al, 2001).

The immunopathology of RA is complex even from relatively early in the clinical course of disease (Tarner et al, 2006; van Baarsen et al, 2013) and B cells are generally accepted to contribute to the pathophysiology of RA. Defective central and peripheral B-cell tolerance checkpoints in RA result in accumulation of autoreactive B cells (Bugatti et al, 2014), and depletion of CD20 positive B cells with rituximab results in clinical improvement in a subset of patients. Approximately 80% of patients with RA have detectable levels of rheumatoid factors (RFs), which are antibodies of any isotype (immunoglobulin [Ig] M, IgG, IgE) against the Fc portion of IgG. The majority of patients with RA also have detectable levels of anti-cyclic citrullinated peptide antibodies (ACPAs). Indeed, the presence of RF or ACPA is included in the American College of Rheumatology (ACR) 2010 diagnostic criteria for RA.

There are 3 main drug classes commonly used in the treatment of RA: 1) nonsteroidal anti-inflammatory drugs (NSAIDs), 2) corticosteroids, which are mainly used as palliative therapy, and 3) disease-modifying anti-rheumatic drugs (DMARDs), used to control disease activity and prevent structural joint damage. Two main classes of DMARDs are available for the treatment of RA: conventional disease-modifying anti-rheumatic drugs (cDMARDs) (such as methotrexate [MTX], sulfasalazine, leflunomide, and hydroxychloroquine) and biologic DMARDs (such as tumor necrosis factor [TNF]-inhibitors). MTX is the most commonly used DMARD for the treatment of moderate and severe RA (Maetzel et al, 1998); however, many patients fail to achieve an adequate or sustained response to MTX alone (Galindo-Rodriguez et al, 1999). To improve efficacy, MTX is being combined with newer biologic agents targeting various components of the immune system, which has induced a step-change in the management and treatment of patients with RA. Such therapies include anti-TNF alpha (TNFα) agents (etanercept, infliximab, adalimumab, certolizumab and golimumab) as well as newer agents targeting different compartments of the immune system,

such as B cells, cytotoxic T-lymphocyte antigen-4 (CTLA-4) (abatacept), and interleukin (IL)-6 receptors (tocilizumab); newer oral compounds such as inhibitors of Janus kinase (JAK; tofacitinib) have also been introduced. These agents are effective at improving the signs and symptoms and at slowing or arresting structural damage in patients with RA (Klareskog et al, 2004; Singh et al, 2009).

Despite the availability of these biological therapeutic agents for the treatment of RA, nearly one third of patients fail to achieve the ACR 20% improvement criteria (Weinblatt et al, 2003), and only a minority of patients achieve clinical remission (Listing et al, 2006). Thus there is a need for new effective treatments to reduce disease activity in patients with RA.

### 1.1.1 Evidence for the CD40 Pathway in RA

Genome-wide association studies have identified a common variant in the CD40 locus that increases the risk of RA (Scheinman, 2013). The CD40 receptor is a member of the TNF family of receptors expressed on the plasma membrane of antigen-stimulated B cells, macrophage, and dendritic cells (Croft et al, 2013). The CD40 receptor functions to provide a co-stimulatory signal for B cells, which have bound antigen. The cognate ligand for CD40 is CD40 ligand (CD40L) (also known as CD154) that is expressed on the plasma membrane of T cells and other cell types, including platelets. Cell contact-dependent interaction between CD40L and CD40 is critical for the development of a comprehensive immune response (Ford et al, 2014). The RA risk allele is a gain-of-function allele that increases the amount of CD40 on the surface of primary human B lymphocyte cells and probably other cell types (Li et al, 2013). The expression of CD40L on CD4+ T helper cells is also increased in patients with active RA compared to those in clinical remission or healthy controls (Berner et al, 2000; Zhang et al, 2013). Taken together, these observations suggest that inhibition of the CD40L/CD40 pathway may be beneficial in RA.

The biology of the CD40/CD40L pathway is not completely understood. Interaction between CD40L and CD40 results in proteolytic cleavage of membrane CD40L that generates a soluble fragment (sCD40L) retaining the ability to bind to CD40 (Alaaeddine et al, 2012). The concentrations of sCD40L are increased in several autoimmune diseases including RA, systemic lupus erythematosus (SLE), and Sjogren's syndrome. The biological significance of this is unknown as sCD40L may simply reflect increased activation of platelet and T cells resulting in release of sCD40L. Others have proposed that sCD40L may have a counter-regulatory immunosuppressive role, at least in a cancer setting (Huang et al, 2012). In addition, CD40L can bind to receptors other than CD40, namely, the integrins αIIbβ3, α5β1,

and αMβ2, and a variety of biological functions for these interactions have been proposed (Alaaeddine et al, 2011).

In previous early clinical studies, the monoclonal anti-CD40L IgG1 antibody, known as BG9588 showed signs of potential efficacy in patients with SLE and immune thrombocytopenic purpura; however, the clinical development of this agent was halted due to clinically significant thromboembolic events (Boumpas et al, 2003; Kuwana 2004). Furthermore, the clinical program of another anti-CD40L monoclonal antibody (mAb), IDEC-131 mAb (which was under evaluation in Phase 1 and 2 trials), was curtailed subsequent to the reporting of a thromboembolic event in Crohn's disease. These mAbs were Fc enabled, and subsequent nonclinical studies identified that platelet activation due to binding of Fc receptor by immune complexes of anti-CD40L and soluble CD40L was the likely mechanism underlying the association between anti-CD40L exposure and thrombosis (Langer et al, 2005; Robles-Carrillo, 2010). Recently, UCB reported data on CDP7657 (Dapirolizumab pegol [DZP]), an anti-CD40L antibody lacking an Fc domain, in non-human primates (Shock et al, 2015) and in healthy volunteers and patients with SLE (Tocoian, et al, 2015; Chamberlain et al, 2015). Single and multiple administrations of DZP over 12 weeks in patients with mild to moderate SLE were well tolerated, and the safety profile supports further development. Exploratory analyses show greater improvement in clinical measures of disease activity in the DZP group vs placebo (Chamberlain et al, 2015).

## 1.2 MEDI4920 Background

MEDI4920 is briefly described below. Refer to the current Investigator's Brochure for details.

MEDI4920 is a CD40L antagonist that comprises two identical Tn3 modules fused to human serum albumin (HSA). Each Tn3 is an engineered form of the third fibronectin type III protein domain from human Tenascin C. Polyglycine linkers join the two Tn3 domains and the second Tn3 domain to the HSA protein. Each Tn3 binds specifically to human CD40L and inhibits its interaction with human CD40.

## 1.3 Summary of Nonclinical Experience

MEDI4920 has been evaluated in several toxicology studies (please refer to Investigator's Brochure for more detailed information). The cynomolgus monkey was selected specifically for use in these studies as MEDI4920 binds to and neutralizes the pharmacological activity of human and cynomolgus monkey CD40L. Human anti-CD40L molecules do not cross-react with murine CD40L.

Several repeat-dose studies (maximum weekly dosing duration of 6 months) and one single dose study were conducted to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of CD40L inhibition by intravenous (IV) and/or subcutaneous (SC) administration of MEDI4920 or its parent molecule.

The no observed adverse effect levels (NOAELs) for repeat-dose studies were the highest doses tested for most of the studies: 150 mg/kg weekly IV or SC and 300 mg/kg weekly IV for the 5-week studies; 250 mg/kg weekly SC for the 6-month study. The NOAEL for the single-dose study was 600 mg/kg IV.

Weekly IV administration of 150 or 300 mg/kg MEDI4920 to sexually mature cynomolgus monkeys for 6 months resulted in early euthanasia of one animal at 150 mg/kg/dose on Day 92 associated with declining clinical condition, adverse clinical pathology changes, and microscopic evidence of inflammatory cell infiltrates in multiple tissues. In addition, one animal dosed at 300 mg/kg/dose had enlarged spleen with nodular and abnormal appearance at scheduled necropsy on Day 192. Microscopically, increased amounts of inflammatory cell infiltrates in multiple organs and tissues were present in this animal and a systemic opportunistic fungal infection was detected; this was considered secondary to the pharmacology of MEDI4920. Therefore, no NOAEL was established for IV dosing in the 6-month study.

There were no MEDI4920-related clinical observations in any of the other animals. In addition, there were no MEDI4920-related changes in body weight, food consumption, ophthalmology, electrocardiology or blood pressure (BP) in any animals. There were no changes in total serum IgM, IgG, IgE, or IgA levels that were considered to be MEDI4920-related.

There were no MEDI4920-related effects on female reproductive endpoints, including menstrual cycling, organ weights, or microscopic pathology. There was no evidence of a MEDI4920-related effect on male reproductive parameters, based on an overall weight of evidence analysis of testicular volume, sperm concentration and motility, sperm morphology, organ weights and histopathology of reproductive and accessory sex organs.

Clinical pathology evaluations, including hematology, clinical chemistry, urinalysis, thrombin-antithrombin complex (TAT), D-dimer, and platelet function analyzer (PFA)-100 collagen/epinephrine closure times were performed on all animals in all studies. There were no MEDI4920-related adverse findings for any of these parameters in the single dose Good Laboratory Practice (GLP) (1468-036), the 1-month GLP (1468-035), the 6-month GLP (20048035), or the non-GLP (1468-027) studies.

Any additional observations noted for hematology, clinical chemistry, or urinalysis parameters in the other studies were of small magnitude and transient in nature or were within the normal range for naive non-human primates.

In all of the repeat-dose studies, observed maximum concentration ($C_{max}$), observed minimum concentration ($C_{trough}$), and area under the concentration-time curve (AUC) increased dose proportionally across the dose range after the first and last dose. Bioavailability with SC dosing ranged between 73% to 83% in the repeat-dose studies. PD sample analysis showed a dose-dependent increase in the levels of sCD40L, consistent with the expected accumulation of sCD40L:MEDI4920 complexes.

Immunologic changes included dose-dependent decreases in CD20+ B-lymphocytes (flow cytometry) and decreases in T-cell-dependent antibody responses (TDARs); (anti-keyhole limpet hemocyanin [KLH] IgG and IgM).

## 1.4 Summary of Clinical Experience

As of 25Aug2015 (cutoff date for D5100C00001 Cohort 6 interim analysis), a total of 46 healthy volunteers have received single IV doses of MEDI4920 over the dose range 3 mg to 1000 mg in Study D5100C00001.

Study D5100C00001 is a Phase 1, randomized, blinded, placebo-controlled, single ascending dose (SAD) study to evaluate the safety and tolerability of single-ascending IV doses of MEDI4920 in healthy adult male subjects and healthy adult female subjects of non-childbearing potential. In addition to assessing safety and tolerability, the study also characterized the PK of MEDI4920, assessed anti-drug antibody (ADA) to MEDI4920, and evaluated the effect of MEDI4920 on TDAR after administration of the KLH antigen. The study was conducted at one site in the United Kingdom. A total of up to 56 subjects were planned for randomization within this study: 3 subjects were randomized in a 2:1 ratio for each of Cohorts 1 and 2 (3 and 10 mg MEDI4920, respectively or placebo) and 10 subjects each randomized in a 4:1 ratio for Cohorts 3 to 7 (30, 100, 300, 1000, and 3000 mg MEDI4920, respectively, or placebo).

When all subjects in Cohort 5 completed Day 43 assessments, a first interim analysis was conducted to evaluate the safety and tolerability of MEDI4920, PK, ADA, and the level of inhibition of the TDAR in Cohorts 1-5. With respect to safety, there were no withdrawals from the study, and one serious adverse event (SAE) of fractured tibia was reported in the placebo arm. Adverse events (AEs) were generally minor and balanced across placebo and MEDI4920 dose groups. One case of herpes zoster reactivation (shingles) was reported in the

30 mg dose group (Grade 2, start date Day 79). There were no deaths, no reports of thromboembolic events, no severe hypersensitivity or severe infection events, and no concerns from the laboratory assessment of platelet function and coagulation. PK parameters ($C_{max}$ and AUC) increased in a dose-proportional fashion, with a half-life of approximately 8 days for the 300 mg IV dose. Between 50% to 100% of subjects in Cohorts 1 to 4 developed ADAs at at least one time point after dosing, whereas only 3 of 8 subjects in Cohort 5 developed ADAs after dosing. The ADA positive subjects had faster clearance and reduced observed MEDI4920 exposure. According to the pre-specified dose escalation criteria, as TDAR inhibition was < 75% vs placebo and no safety concerns were observed, Cohort 6 (1000 mg dose) was initiated. An additional 10 subjects were randomized in a 4:1 ratio to receive either 1000 mg MEDI4920 or placebo.

When all subjects in Cohort 6 completed Day 43 assessments, a second interim analysis was conducted to evaluate the safety and tolerability of MEDI4920, PK, ADA, and the level of inhibition of the TDAR in Cohorts 1-6, in order to evaluate the requirement for Cohort 7 (3000 mg). The safety profile remained consistent with the safety profile observed at the first interim analysis, with no deaths, serious or severe AEs, thromboembolic events, severe hypersensitivity or severe infection events, and no concerns from the laboratory assessment of platelet function and coagulation. No subjects in Cohort 6 (1000 mg) were positive for ADAs up to Day 29, which was the last available ADA time point in Cohort 6 prior to interim assessments.

After the second interim analysis, TDAR inhibition was observed in a dose-dependent manner. A dose response analysis at Day 43 of the dose cohorts up to and including 1000 mg demonstrated a statistically significant linear dose response ($p = 0.003$) with the 1000 mg dose observing a 77% inhibition of the TDAR IgG response compared to placebo (95% confidence intervals [CIs]: 41%, 91%).

## 1.5 Rationale for Conducting the Study

MEDI4920 is being developed for the treatment of B-cell dependent autoimmune diseases.

The current study is designed to characterize the safety, tolerability, PK, biomarkers, immunogenicity, and clinical response of multiple doses of MEDI4920 in subjects with moderate to severe RA.

The results from this study will form the basis for decisions regarding appropriate repeat dosing strategies of MEDI4920 for future studies in subjects with RA and/or other autoimmune conditions.

## 1.6 Potential Risks

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

Based on clinical data from Cohorts 1-6 of the SAD study, there are no identified risks for humans associated with MEDI4920. Potential risks based on the mechanism of action (MOA) of MEDI4920 and mitigation plans included in the protocol are summarized below.

### Anaphylaxis and Serious Hypersensitivity Reactions

No severe or serious hypersensitivity reactions have been observed with MEDI4920 at doses up to 1000 mg in the SAD study.

In the current study, subjects will be excluded from participation if they have had a history of a severe allergic reaction to any component of the investigational product formulation or to any other biologic therapy. The risk of hypersensitivity reactions is considered maximal after the first two IV administrations of MEDI4920 (Days 1 and 15). To monitor for infusion and/or hypersensitivity reactions, subjects will be in a clinical trial facility and closely monitored for 4 hours after the end of the infusion for the first two doses (Days 1 and 15). Doses will be administered by IV infusion over minimum times of 30 minutes for the 75 mg dose, 60 minutes for the 500 mg dose, 90 minutes for the 1000 mg dose, and 90 minutes for the 1500 mg dose. The infusion will be discontinued if there is evidence of infusion reaction and supportive treatment may be instituted. Guidelines for monitoring relevant AEs encompassing hypersensitivity, angioedema and anaphylaxis and for managing acute anaphylactic shock and minor allergic episodes will be in place at investigational sites. Study sites will include facilities and expertise for emergency care/resuscitation, including access to hospital and intensive care unit.

### Serious and/or Opportunistic Infections

No severe or serious infections have been observed in the first time in human (FTIH) SAD study. One case of herpes zoster reactivation was reported in a subject receiving 30 mg MEDI4920.

Weekly IV administration of 150 or 300 mg/kg MEDI4920 to sexually mature cynomolgus monkeys for 6 months resulted in an opportunistic fungal infection in one animal treated with MEDI4920 300 mg/kg IV, and changes suggesting potential systemic infection were observed in another animal treated with MEDI4920 150 mg/kg (see Section 1.3).

Measures taken in the current study to minimize the risk of immunosuppression-related infections include the following:

- During screening, subjects will be excluded from the study if they have had a recent (within 12 months) or active hepatitis A infection; if they test positive or have been treated for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection; if they have evidence of active or untreated latent tuberculosis (TB); if they have a recent history (last 12 months) of recurrent herpes zoster and/or opportunistic infection; and/or if they are taking immunosuppressant medication (see exclusion criteria in Section 4.1.3 and prohibited concomitant medications in Section 4.7.2).
- Subjects will not be allowed to receive live (attenuated) vaccine within the 4 weeks prior to dosing or during the study until the end of follow-up.
- Clinical assessments for signs of infection will be performed at each study visit. Subjects will be given instructions on potential signs of infection and instructed to contact investigator if they have signs or symptoms of an infection. Blood samples for serology and viral polymerase chain reaction (PCR) will be collected at screening and stored to assess new vs reactivation of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) in case an EBV or CMV infection is reported as an AE during the study.

### Unknown Consequences of Exposure in Utero

No embryo-fetal studies have been conducted to date.

This study requires all female subjects of childbearing potential to use at least one highly effective method of contraception from the time of screening up through at least 6 months after the final dose of investigational product. The acceptable methods of contraception are described in Section 4.1.2.

In addition, the investigator must inform the subjects about the risks involved with some of the background medications used in RA and accepted in the current study (eg, MTX or leflunomide) as these agents are known to have potential deleterious effects on conception, pregnancy and fetal health (see Section 4.1.2).

The requirement for adherence with contraceptive guidance in the protocol and screening for pregnancy (serum or urine) will be monitored throughout the duration of the study.

### Thrombotic and Embolic Events

Previous clinical trials with anti-CD40L mAbs that were Fc enabled demonstrated increased incidence of thromboembolic events, and subsequent nonclinical studies identified that platelet activation due to binding of Fc receptor by immune complex of anti-CD40L and

soluble CD40L was the likely mechanism underlying the association between anti-CD40L exposure and thrombosis. MEDI4920 was engineered to lack Fc fragment.

No thromboembolic events have been reported in animal studies and in the human SAD study with MEDI4920.

To minimize the risk of thromboembolic events in the current study, subjects will be excluded from participation if they have a medical history of confirmed venous thromboembolism or arterial thrombosis or if they have significant clinical and molecular risk factors for thromboembolic events or arterial thrombosis. In addition, any subjects with a clinically significant abnormal coagulation panel at screening will be excluded from this study (see Section 4.1.3).

Thromboembolic events will be monitored by AE evaluation and physical examinations performed during the study. If a subject dosed with MEDI4920 experiences a confirmed or suspected thromboembolic event during the evaluation period or follow-up period, the dose escalation will be suspended and the event will be fully evaluated (see Section 3.1.3 for additional details).

#### Immune Complex Disease

The potential risk of immune complex disease is based on the potential risk known to be associated with foreign proteins and mAbs. The occurrence of ADA could result in immune complex disease (with manifestations such as arthralgia, serum-sickness, nephritis, and vasculitis) or altered MEDI4920 levels or activity. Subjects in clinical studies with MEDI4920 will be monitored for the presence of ADA and for clinical manifestations that may be associated with the formation of specific antibodies to MEDI4920.

## 1.7 Research Hypotheses

### 1.7.1 Primary Hypothesis

The primary hypothesis is that multiple ascending IV doses up to 1500 mg of MEDI4920 once every 2 weeks (Q2W) over a 12-week period will be safe and well-tolerated in subjects with RA when compared with placebo in combination with MTX or another cDMARD.

### 1.7.2 Secondary Hypothesis

A secondary hypothesis has not been established for this study.

### 1.7.3 Exploratory Hypotheses

The exploratory hypotheses are that CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted].

# 2 OBJECTIVES AND ENDPOINTS

## 2.1 Objectives

### 2.1.1 Primary Objective

To assess the safety and tolerability of multiple ascending IV doses of MEDI4920 in subjects with adult-onset RA.

### 2.1.2 Secondary Objectives

To evaluate the PK and immunogenicity of MEDI4920 in subjects with adult-onset RA.

### 2.1.3 Exploratory Objectives

1. CCI [redacted]
2. CCI [redacted]
3. CCI [redacted]
4. CCI [redacted]

## 2.2 Study Endpoints

### 2.2.1 Primary Endpoints

1. The incidence of AEs and SAEs.
2. The incidence of treatment-emergent AEs of special interest (AESIs) as follows:
   - Thrombotic and embolic events
   - Hepatic function abnormality (meeting the definition of Hy's Law [HL]; see Section 5.6.2)
   - Anaphylaxis and serious hypersensitivity reactions
   - Infusion-related reactions

- Immune complex disease
- Serious and/or opportunistic infections (including but not limited to reactivation of latent viral infection [varicella zoster (VZ), herpes simplex virus (HSV), EBV, CMV] and TB)

3. Vital signs, laboratory parameters (including coagulation parameters), electrocardiograms (ECGs), and physical examinations.

### 2.2.2 Secondary Endpoints

The PK profile, PK parameters, and immunogenicity of MEDI4920 will be assessed for each cohort

### 2.2.3 Exploratory Endpoints

1. CCI [redacted]
2. CCI [redacted]
3. CCI [redacted]
4. CCI [redacted]
5. CCI [redacted]

# 3 STUDY DESIGN

## 3.1 Description of Study

### 3.1.1 Overview

This is a multicenter, randomized, double-blind (investigator, subject, and sponsor will be blinded to treatment assignment), placebo-controlled study to evaluate the safety and tolerability of multiple ascending doses (MADs) of MEDI4920 in subjects with adult-onset RA (moderate to severe, as defined by DAS28 CRP $\geq$ 3.2 at screening) with an inadequate response to MTX or other cDMARDs or a biologic anti-TNFα agent.

The study is planned to be conducted at approximately 15 sites in 2 to 4 countries. A maximum of 54 eligible subjects are planned for this study. Approximately 40 subjects will be randomized in 3 cohorts to receive either 75 mg (Cohort 1), 500 mg (Cohort 2), or 1500 mg (Cohort 3) MEDI4920, or placebo once Q2W in combination with MTX or another cDMARD for up to 12 weeks.

An additional 14 subjects will be randomized in a 5:2 ratio to an additional cohort (Cohort 4), to better characterize the dose (exposure) - response relationship. The selected dose of MEDI4920 in Cohort 4 is 1000 mg Q2W.

Subjects will undergo a screening period of up to 6 weeks followed by randomization and treatment for 12 weeks. Subjects will be followed for an additional 12 weeks after the treatment period for safety. Each subject will participate in the study for up to approximately 30 weeks (includes a 6-week screening period, a 12-week treatment period, and a 12-week follow-up period).

Subjects will receive an IV dose of MEDI4920 or placebo Q2W for up to 12 weeks as follows:

- Cohort 1: 75 mg MEDI4920 (N = 8) or placebo (N = 2) as a single IV dose administered over at least 30 minutes Q2W
- Cohort 2: 500 mg MEDI4920 (N = 10) or placebo (N = 4) as a single IV dose administered over at least 60 minutes Q2W
- Cohort 3: 1500 mg MEDI4920 (N = 12) or placebo (N = 4) as a single IV dose administered over at least 90 minutes Q2W
- Cohort 4: 1000 mg MEDI4920 (N = 10) or placebo (N = 4) as a single IV dose (administered over at least 90 minutes Q2W )

Subjects will be administered investigational product via IV infusion using an infusion pump.

All subjects will receive a total of 7 doses of investigational product (MEDI4920 or placebo) during the 12-week treatment period. Details about dose escalation can be found in Section 3.1.3.

A screening visit(s) will be performed within 6 weeks (42 days) prior to dosing. All subjects will receive investigational product on the morning of Day 1. An overnight stay on Day -1 prior to administration of investigational product on Day 1 is recommended but not mandatory. If no safety concerns are identified, subjects will be discharged from the study site on Day 2 (end of the inpatient treatment period) after all study procedures have been completed. Subjects in all cohorts will return to the study site Q2W (Days 8, 15, 29, 43, 57, 71, and 85) for investigational product administration and/or specific assessments and blood draws, as indicated in Table 4.2.2-1.

During the treatment period, assessments of RA parameters as well as evaluations of safety, tolerability, PK, and immunogenicity of MEDI4920 will be performed at the time points indicated in Table 4.2.2-1.

Following the final IV infusion of investigational product, subjects will return to the study site for follow-up visits beginning at Week 13 (Day 92) and continuing through Week 24

(Day 169) to evaluate safety, tolerability, PK and ADA of MEDI4920 as indicated in Table 4.2.3-1.

A study flow diagram is presented in Figure 3.1.1-1.

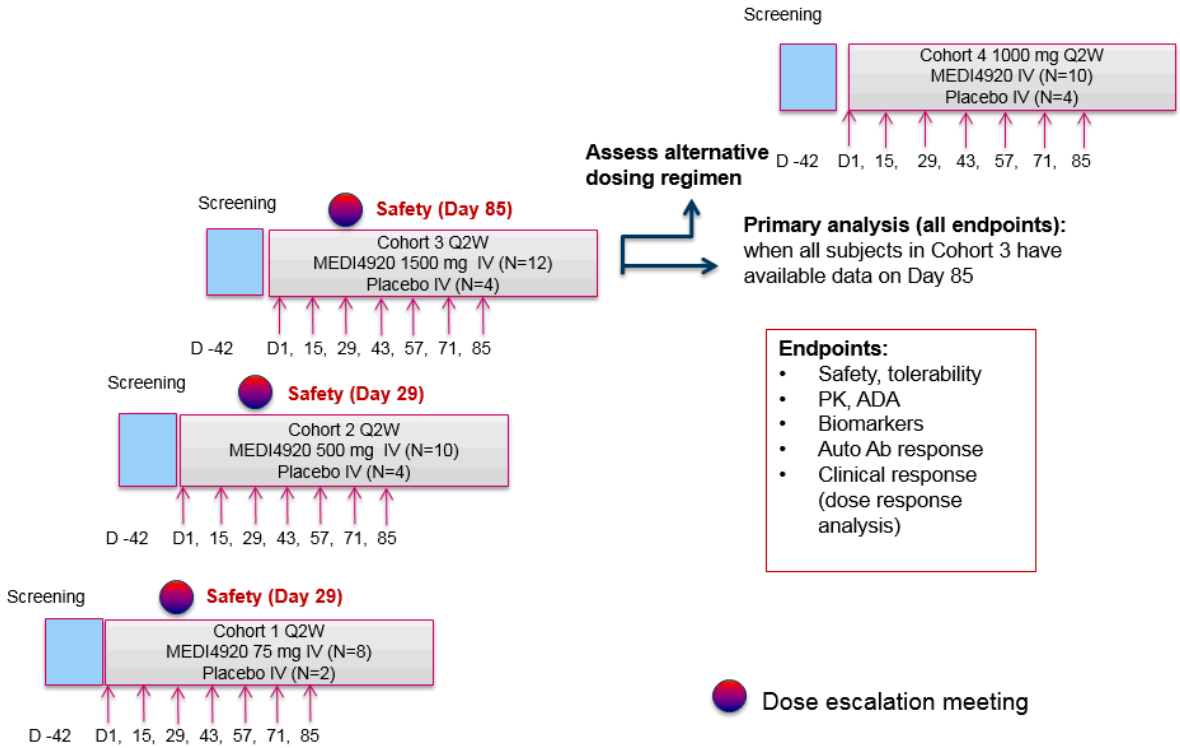


**Figure 3.1.1-1 Study Flow Diagram**

Ab = antibody; ADA = anti-drug antibody; D = day; IV = intravenous; PK = pharmacokinetic; Q2W = once every 2 weeks

The endpoints to be measured in this study are described in Section 2.2.

### 3.1.2 Treatment Regimen

A maximum of 54 subjects will be randomized in a 4:1 ratio (Cohort 1), in a 5:2 ratio (Cohort 2), in a 3:1 ratio (Cohort 3), and in a 5:2 ratio (Cohort 4) to receive either MEDI4920 or placebo as described in Table 3.1.2-1:

**Table 3.1.2-1 Investigational Product Dose and Treatment Regimen**

| Cohort | N (active:placebo) | Dose | Treatment Regimen [a] |
|---|---|---|---|
| 1 | 4:1 | 75 mg | Single IV dose infused over at least 30 minutes on Days 1, 15, 29, 43, 57, 71, and 85 |
| 2 | 5:2 | 500 mg | Single IV dose infused over at least 60 minutes on Days 1, 15, 29, 43, 57, 71, and 85 |
| 3 | 3:1 | 1500 mg | Single IV dose infused over at least 90 minutes on Days 1, 15, 29, 43, 57, 71, and 85 |
| 4 | 5:2 | 1000 mg | Single IV dose infused over at least 90 minutes on Days 1, 15, 29, 43, 57, 71, and 85 |

IV = intravenous; TBD = to be determined.

[a] For Cohorts 1-4, investigational product will be administered via IV infusion using an IV infusion pump.

The timing of administration of investigational product will be staggered within each cohort to allow for review of safety and tolerability data from the first group of subjects before progression to the next group of subjects.

### 3.1.3 Dose Escalation and Cohort Progression

Cohorts 1 to 3 will start sequentially, with escalation from Cohort 1 to Cohort 2 and Cohort 2 to Cohort 3 confirmed by a Dose Escalation Committee (DEC) comprised of MedImmune study team members and the Study Global Chief Investigator, who will assess in a blinded fashion the safety/tolerability data after the last subject in a cohort completes Day 29 (Week 4) of treatment and has AE/safety laboratory data available at that time point. There will be a total of three DEC meetings during the study; the first DEC meeting will only review data from Cohort 1 whereas the second DEC meeting will review cumulative safety data from first two dose cohorts being tested to date. The third DEC meeting will constitute a thorough evaluation of the cumulative safety and tolerability data for Cohorts 1 and 2 in addition to the data up to Day 85 for Cohort 3. While this review will not pertain to a dose escalation, it will contribute to the decision to instigate Cohort 4 (see below).

After the last Cohort 3 subject completes the Day 85 (Week 12) assessments, the primary analysis will be conducted to include safety, tolerability, PK, ADA, biomarker, and clinical response. Based on the outcome of this analysis, a fourth cohort will be included to better understand the dose (exposure)-response relationship.

If one or more of the following criteria are met, dose escalation will be suspended and the event(s) will be fully evaluated:

- A subject dosed with MEDI4920 experiences a confirmed or suspected thromboembolic event during the evaluation period or follow-up period. If the thromboembolic event is initially reported as "suspected", because of the unavailability of sufficient information to support a definitive diagnosis at that time, the DEC will re-assess the event when complete clinical/laboratory information is provided by the study site. A diagnosis algorithm (adapted from Wells and Anderson, 2013; Section 10.5 [Appendix 5]), is recommended to be used for any case of suspected DVT or PE. This includes clinical pre-test probability, D-dimer, and available imaging results. Based on full evaluation of the data as well as the diagnosis algorithm, if a thromboembolic event is ruled out or considered unlikely, dose escalation can be resumed.
- At least 2 subjects dosed with MEDI4920 in a single cohort experience either Grade 3 or higher treatment-emergent AEs (TEAEs) of the same type (excluding rheumatoid joint flares) or any SAE.
- At least 2 subjects dosed with MEDI4920 in a single cohort experience serious infections.
- In addition to the above criteria, the DEC may recommend stopping dose escalation and further evaluation of any significant medical event(s) or confirmed clinically significant laboratory abnormalities (including coagulation tests) that are considered related to investigational product.

If the DEC suspends the dose escalation and subsequently decides to resume dosing at the same or higher doses, approval from the relevant regulatory authorities and Independent Ethics Committees (IECs) will be obtained prior to dosing.

## 3.2 Rationale for Dose, Population, and Endpoints

### 3.2.1 Dose Rationale

The safety, tolerability, and PD effects of single IV doses of 3000 mg of MEDI4920 are currently being evaluated in healthy adult volunteers in the final cohort of study D5100C00001. Data from interim analysis 2 are currently available (see Section 1.4).

To date, there are no dose-limiting toxicities known in humans.

The doses selected in the current study aim to explore the dose-response relationship for the main exploratory efficacy endpoint in RA [redacted] while testing safety/tolerability within a well-defined safety margin predicted based on animal data.

There is no precise relationship between efficacy in autoimmune diseases and PD models (suppression of free sCD40L or inhibition of TDAR to a model neoantigen).

A PK-PD model to describe the relationship between total sCD40L plasma concentration (as a surrogate PD marker of target engagement) and plasma concentrations of MEDI4920 in

healthy subjects from the SAD study has been developed. The free sCD40L suppression after repeated dosing was predicted based on this model. The ability of MEDI4920 to inhibit TDAR has been demonstrated and quantified in non-human primates and also in the FTIH SAD study (D5100C00001). In humans, at single IV dose of 1000 mg (which provides high degrees of target engagement in peripheral blood), TDAR inhibition was shown to be significant; however the dose-response relationship may not have reached a plateau.

The PK-PD model predicts that a dose of 75 mg Q2W should maintain an approximately 95% suppression of free sCD40L throughout the entire dosing interval. The safety margin of this dose is estimated to be approximately 65 fold (method Human Equivalent Dose [HED]), which is calculated using the SC NOAEL of 250 mg/kg weekly demonstrated in the 27-week toxicology study in cynomolgus monkeys. Therefore, a 75 mg dose may provide some level of clinical response for RA patients while maintaining a good safety profile.

The highest dose level in Cohort 3 (1500 mg Q2W) is also driven by the approximately 3-fold safety margin (based on HED). A significant clinical response in RA patients is expected with this dose.

An intermediate dose of 500 mg Q2W was selected as the medium dose for the study; this dose has a safety margin of 10 (based on HED) and is able to inhibit TDAR as shown in the SAD study.

After review of the primary analysis data, which included cumulative safety, PK, and biomarker data through Cohort 3, Day 85, the decision was made to explore a fourth dose (Cohort 4, 1000 mg Q2W), in order to complete the safety analysis as well as the dose-response analysis in the exploratory efficacy endpoint. Based on PK-PD modeling data from Cohorts 1 to 3 combined with clinical judgement, the 1000 mg Q2W dose selected for Cohort 4 is a dose that is expected to result in a clinical response comparable to the 1500 mg Q2W dose (highest dose in the study) but with a larger safety margin.

### 3.2.2 Rationale for Study Population

It is acknowledged that healthy volunteers could also be selected as a study population in a Phase 1 MAD study. However, in the current study, subjects with RA were selected as the study population for the following reasons:

- Opportunity to test MEDI4920 in a disease where B-cell targeted therapy (rituximab) is known to be clinically effective and where nonclinical evidence suggests the CD40L/CD40 pathway is active.

- Potential for providing clinical benefit that can be quantified in a standardized way to subjects with RA after 12 weeks of treatment
- It is important to establish the PK and PD in a patient population with a well-studied autoimmune disease such as RA that is characterized by elevated sCD40L compared to healthy volunteers.
- Concerns about exposing healthy volunteers to known and theoretical risks of AEs related to MEDI4920 over a 12-week treatment period.
- There is no well-defined relationship between the level of TDAR inhibition in healthy volunteers and clinical efficacy in patients with autoimmune conditions; thus no relevant prediction of clinical effectiveness can be provided by assessing TDAR response in a MAD study in healthy volunteers.
- It is important to understand the potentially inhibitory effect of background immunomodulatory therapy given in RA (eg, MTX) on ADAs against MEDI4920.

### 3.2.3 Rationale for Endpoints

This is the first study of MEDI4920 in adult subjects with RA and thus it is appropriate that the safety and tolerability of MADs constitute the primary endpoint. Additionally, the study will assess the PK profile and immunogenicity of MEDI4920 in multiple doses in conjunction with the mechanistic effect of MEDI4920 as secondary endpoints.

CCI [redacted] were chosen as key exploratory endpoints, in order to assess early signals of clinical efficacy with MEDI4920 in RA that might support further studies in the same indication or in different autoimmune conditions. CCI [redacted] and CCI [redacted] have been selected due to their high level of standardization and wide use in clinical trials in RA.

Serum will be collected to measure changes in exploratory biomarkers of disease activity, such as autoantibodies, and biomarkers associated with the CD40L pathway, including biomarkers induced by CD40L signaling. These biomarker measurements will aid in the determination of what biological pathways are impacted by MEDI4920 treatment. The MBDA panel includes adhesion molecules, growth factors, cytokines, matrix metalloproteinases, skeletal proteins, hormones and acute phase proteins. The MBDA panel has been demonstrated to be a sensitive and objective measure of clinical disease activity, with a strong correlation to DAS28 CRP.

# 4 MATERIALS AND METHODS

## 4.1 Subjects

### 4.1.1 Number of Subjects

A maximum of 54 subjects with adult-onset RA (moderate to severe) are planned for this study: 10 subjects will be randomized in a 4:1 ratio in Cohort 1, 14 subjects will be randomized in a 5:2 ratio in Cohort 2, and 16 subjects will be randomized in a 3:1 ratio in Cohort 3. An additional 14 subjects will be randomized in a 5:2 ratio in Cohort 4.

### 4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria. Site staff must contact MedImmune for consultation prior to enrolling, randomizing, or administering investigational product to any subject who deviates from these criteria:

1. Male or female
2. 18-70 years old (inclusively) at the time of informed consent
3. Adult-onset RA diagnosed by European League Against Rheumatism/ACR 2010 criteria (Aletaha et al, 2010). Diagnosis of RA should be established at least 6-months before screening.
4. Subjects must be treated with MTX given orally, SC or intramuscular at a dose of 7.5-25 mg/week for at least 12 weeks and the dose must have been stable for at least 6 weeks prior to screening. The following exception is permitted:
   - MTX-intolerant subjects may enter the study if they are on cDMARDs for at least 12 weeks and the dose has been stable for at least 6 weeks prior to screening. Combination of two or more cDMARDs is allowed if recommended by national guidelines and/or standard medical practice.
5. Subjects who may have been treated with anti-TNFα biologic agents that were stopped for any reason (lack of efficacy, safety/tolerability issues or lack of access to drug) at least 8 weeks before randomization are eligible.
6. Subjects treated with an agent with a MOA other than anti-TNF (eg, anti-IL-6, CTLA-4 or anti-IL-1) are only eligible if at least 3 months or 5 half-lives of the drug (whichever is shorter) have passed between the last dose and the randomization visit.
7. DAS28 CRP of $\geq 3.2$ at screening.
8. At least 4 tender and 4 swollen joints assessed at screening and confirmed at randomization out of the 28 joints assessed for DAS28.
9. Positive for serum RF and/or ACPA at screening, according to the central laboratory's definition of positivity.
10. Age-specific vaccinations, as based on local expert recommendations and local standard medical practice, administered at least 4 weeks prior to randomization.

11. Written informed consent and any locally required authorization (eg, data privacy) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
12. Willing and able to comply with the protocol, complete study assessments, and complete the study period.
13. Females of childbearing potential who are or might become sexually active with a nonsterilized male partner during the duration of study must use at least one highly effective method of contraception from screening, and must agree to continue using such precautions at least 6 months after the final dose of investigational product. It is strongly recommended for the male partner of a female subject to also use a male condom plus spermicide throughout this period. Cessation of contraception after this point should be discussed with a responsible physician.
    - Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause).
    - A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 4.1.2-1.
14. Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a condom with spermicide from Day 1 through to the end of the study.

In relationship with inclusion criteria 13 and 14, since some of the background medications used in RA and accepted in the current study (eg, MTX or leflunomide) are known to have potential deleterious effects on conception, pregnancy and fetal health, the investigator must inform the subjects about these risks and should manage every case of planned conception or pregnancy according to the local medical practice standards.

**Table 4.1.2-1 Highly Effective Methods of Contraception for Females of Childbearing Potential**

| Physical Methods | Hormonal Methods |
|---|---|
| • Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS) [a]<br>• Bilateral tubal occlusion<br>• Vasectomized partner [b]<br>• Sexual abstinence [c] | Combined (estrogen and progestogen containing hormonal contraception)<br>• Oral (combined pill)<br>• Injectable<br>• Transdermal (patch)<br>Progestogen-only hormonal contraception associated with inhibition of ovulation [d]<br>• Injectable<br>• Implantable<br>• Intravaginal |

[a] This is also considered a hormonal method.
[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.
[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (minipill) is not accepted as a highly effective method.

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

### 4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study. Site staff must contact MedImmune for consultation prior to enrolling, randomizing, or administering investigational product to any subject who deviates from these criteria:

1. A history of, or current inflammatory joint disease other than RA (eg, gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, or Lyme disease) or other systemic autoimmune disorder (eg, SLE, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease, or other overlapping syndrome). Subjects with polymyalgia rheumatica will be excluded from the study.
2. Subjects with a medical history of confirmed venous thromboembolism or arterial thrombosis.
3. Subjects with risk factors for venous thromboembolism or arterial thrombosis (eg, immobilization or major surgery within 12 weeks before screening), prothrombotic status (including but not limited to congenital or inherited deficiency of antithrombin III, protein C, protein S, or confirmed diagnosis of antiphospholipid syndrome).
4. Subjects with clinically significant abnormal coagulation panel at screening (including but not limited to multiple and significant shifts in prothrombin time ratio, activated partial thromboplastin time (D-dimer, etc). In case of doubts in assessing coagulation abnormalities as being clinically significant, the investigator may contact and discuss with the study medical monitor.

5. RA functional class IV, presence of severe systemic comorbidities (extensive vasculitis, pericarditis, amyloidosis, lymphoma), hemochromatosis, IgG4-related diseases, auto-inflammatory syndromes including Still's and Felty's syndrome.
6. Active or recent history (within the last 10 years) of malignancies (except for non-melanoma skin cancers and in situ cervical carcinoma, treated and considered cured).
7. Pregnancy or lactation.
8. Subjects with recent (within 12 months) or active hepatitis A infection as evidenced by clinical history and/or positive test for anti-hepatitis A antibodies.
9. Subjects who have a positive test for, or have been treated for hepatitis B, hepatitis C, or HIV infection. Regarding hepatitis B, any of the following would exclude the subject from the study:
    - Subjects positive for hepatitis B surface antigen (HbsAg)
    - Subjects with hepatitis B virus deoxyribonucleic acid (DNA) levels > 200 copies/mL (quantified by real-time polymerase chain reaction) in case the subject is positive for hepatitis B surface antibody (HbsAb) but negative for HbsAg.
    - Positive for hepatitis B core antibody (HbcAb)
10. Evidence or history of active or untreated latent TB:
    - Signs or symptoms suggestive of active TB upon medical history or physical examination
    - Positive diagnostic TB test during screening (defined as a positive interferon-gamma release assay [IGRA] test for TB at screening).
    - Subjects with an indeterminate IGRA should undergo a repeat test, and if still indeterminate, must be excluded.
11. More than one episode of herpes zoster and/or opportunistic infection in the last 12 months.
12. Known history of severe allergy or reaction to any component of the investigational product formulation or to any other biologic therapy.
13. Any severe cardiovascular, respiratory, endocrine, gastro-intestinal, hematological, neurological, psychiatric, or systemic disorder that could impact the evaluation of safety and efficacy assessments or affect the subject's ability to participate in the study or the subject's safety.
14. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results. This includes important and extensive joint pain and swelling not due to RA (eg, severe polyarticular osteoarthritis involving small joints in hands and feet). Those medical conditions that are only limited to a small number of joints such as localized osteoarthritis (eg, knee, hip, and spine) can be included in the study.
15. Receipt of live (attenuated) vaccine within the 4 weeks before screening or during the study.
16. Last administration of licensed or experimental biologic agents used for treatment of RA targeting any other mechanism other than direct anti-TNF blockade, (eg, CTLA-4 and anti-IL-6) ≤ 3 months before randomization; last administration of new oral compounds

targeting any other mechanisms (eg, JAK inhibitors) for treating RA ≤ 3 months before randomization.

17. Previous treatment with any biologic cell-depleting therapy (eg, rituximab) for RA or anti-CD40/CD40L agents.
18. Concurrent treatment with any biologic or nonbiologic DMARDs excluding stable background MTX or other cDMARDs including stable sulfasalazine, leflunomide, hydroxychloroquine, azathioprine, cyclosporine, or D-penicillamine.
19. Injectable corticosteroids (including intraarticular) or treatment with > 10 mg/day dose oral prednisone or equivalent within 4 weeks prior to randomization. Concomitant treatment with oral corticosteroids ≤ 10 mg/day prednisone or equivalent is permitted provided that the dose is stable for ≥ 4 weeks prior to randomization and remains stable for the duration of the treatment period. Inhaled or topical corticosteroids given for asthma, chronic obstructive pulmonary disease (COPD) or dermatological conditions are allowed provided doses are stable between screening and Day 85 visit.
20. At screening blood tests, any of the following:
    - Aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) > 2 × ULN
    - Alkaline phosphatase (ALP) > 2 × ULN
    - Total bilirubin (TBL) > 2 × ULN
    - Hemoglobin < 75 g/L
    - Neutrophils < $1.5 \times 10^9$/L
    - Platelets < $100 \times 10^9$/L

21. History of alcohol or drug abuse within 2 years prior to randomization.

Subjects may be re-screened only once if they do not meet the eligibility criteria related to disease activity or previous RA medication wash-out. Subjects not fulfilling any of the other eligibility criteria cannot be re-screened.

### 4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice/web response system [IXRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure.

### 4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments), at any time without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the investigator. All AEs will be followed up. If a subject withdraws consent from further participation in the study, then no further study visits or data collection should take place.

### 4.1.6 Discontinuation of Investigational Product

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

- Withdrawal of consent from the study
- Withdrawal of consent from further treatment with investigational product
- Lost to follow-up
- AE or significant laboratory abnormality that, in the opinion of the investigator and/or the sponsor, warrants discontinuation of further dosing
- Pregnancy or a decision to become pregnant (see Section 5.6.3)
- Subjects who require biologic DMARD therapy other than MEDI4920
- Hepatic function abnormality defined as any increase in ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than 2 × ULN related to MEDI4920:
- Anaphylaxis or a serious hypersensitivity reaction.
- Any life-threatening or serious infection or opportunistic infection. Subjects with a diagnosis of serious and/or opportunistic infections including but not limited to reactivation of TB, hepatitis B, or hepatitis C will not receive any further investigational product.
- Any confirmed or suspected serious or severe thromboembolic event
- AEs of malignancy

Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn from further study participation (Section 4.1.5), or the subject is lost to follow-up.

### 4.1.7 Replacement of Subjects

Only subjects who are randomized but do not receive investigational product (MEDI4920 or placebo) may be replaced to maintain the stipulated cohort sizes. This would include subjects who are randomized and then withdraw consent before receipt of investigational product.

### 4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

#### Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

#### Samples Obtained for Genetic or Future Research

Samples obtained for genetic or future research will be labeled with a sample identification number. If the subject withdraws consent for participating in the genetic or future research, the sponsor will locate the subject's sample and destroy it.

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

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

## 4.2 Schedule of Study Procedures

### 4.2.1 Enrollment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at the screening visit. Assessments should be performed in the order shown in the table.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last. The timing of the first 2 assessments should be such that it allows the blood draw (eg, serum chemistry) to occur at the proper nominal time.

**Table 4.2.1-1 Schedule of Screening Procedures**

| **Study Period** | **Screening** |
|---|---|
| **Visit Number** | **V1** |
| **Procedure / Study Day** | **Day -42 to Day -1** |
| Written informed consent | X |
| IXRS assignment of SID number | X |
| Medical history | X |
| Verify eligibility criteria | X |
| **Safety assessments** | |
| Assessment of AEs/SAEs | X |
| Assessment of concomitant medications | X |
| Complete physical examination (includes weight) | X |
| Height | X |
| 12-lead ECG [a] | X |
| Vital signs [b] | X |
| TB test [c] | X |
| **Blood collection for:** | |
| Serum chemistry | X |
| Hematology | X |
| Coagulation parameters: | |
| Screening for deficiency of protein C, protein S, AT3, and APL antibodies | X |
| Baseline coagulation panel | X |
| Autoantibody panel (RF, RF isotypes, ACPA, ANA, anti-Ro, anti-La [serum]) | X |
| Exploratory biomarkers (serum) | X |
| RNA PAXgene (whole blood) | X |
| Acute-phase reactants (CRP, ESR[d]) | X |

### Table 4.2.1-1 Schedule of Screening Procedures

| Study Period | Screening |
|---|---|
| **Visit Number** | **V1** |
| **Procedure / Study Day** | **Day -42 to Day -1** |
| Virology: hepatitis A, B, C; HIV-1, HIV-2, CMV, EBV | X |
| Serum β-hCG (females of childbearing potential only) | X |
| **Urine collection for:** | |
| Urinalysis | X |
| **Rheumatoid assessments** | |
| TJC/SJC: 28 joints count | X |
| VAS Patient's Global Assessment of disease activity | X |
| Physician's Global Assessment | X |

AE = adverse event; ACPA = anti-cyclic citrullinated peptide antibody; ANA = antinuclear antibody; APL = antiphospholipid; AT = anti-thrombin; β-hCG = beta-human chorionic gonadotropin; CMV = cytomegalovirus; CRP = C-reactive protein; EBV = Epstein-Barr virus; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; IXRS = interactive voice/web response system; RF = rheumatoid factor; RNA = ribonucleic acid; SAE = serious adverse event; SID = subject identification; TB = tuberculosis; TJC = tender joint count; SJC = swollen joint count; V = visit; VAS = visual analogue scale.

[a] The screening ECG will be obtained in triplicate (all 3 within a 5-minute time period, at least 1 minute apart).

[b] Vital sign measurements include body temperature, blood pressure, heart [pulse] rate, and respiratory rate.

[c] TB screening will be performed according to the local medical standards. If the local standard requires a chest X-ray it must be from within the last 6 months prior to screening and source documents must be available. QuantiFERON®-TB Gold test at screening will be mandatory for all subjects and will constitute an exclusion criterion per se.

[d] ESR will be analyzed at the local laboratories.

## 4.2.2 Treatment Period

Table 4.2.2-1 shows all procedures to be conducted during the treatment period (Part A through Day 85 [Week 12]).

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, blood draws should occur last. The timing of the first two assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the proper nominal time. All laboratory sample collections and assessments on dosing day must be performed at predose, unless specified otherwise.

## Table 4.2.2-1 Schedule of Treatment Period Study Procedures

| Study Period | Treatment Period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9** | **V10** |
| **Procedure / Study Day** | **Day 1 ± 1 Day** | **Day 2 ± 1 Days** | **Day 8 ± 1 Day** | **Day 15 ± 1 Day** | **Day 29 ± 1 Day** | **Day 43 ± 1 Day** | **Day 57 ± 1 Day** | **Day 71 ± 1 Day** | **Day 85 ± 1 Day** |
| **Randomization** | | | | | | | | | |
| Verify eligibility criteria | X | | | | | | | | |
| IXRS randomization call | X | | | | | | | | |
| **Safety assessments** | | | | | | | | | |
| Assessment of AEs/SAEs | X | X | X | X | X | X | X | X | X |
| Assessment of concomitant medications | X | X | X | X | X | X | X | X | X |
| Complete physical examination (includes weight) | X | | | | | | | | |
| Abbreviated physical examination [a] | | | X | X | X | X | X | X | X |
| 12-lead ECG | X | | | | | | | | X |
| Vital signs [b] | X | X | X | X | X | X | X | X | X |
| **Blood collection for:** | | | | | | | | | |
| Serum chemistry | X | | X | X | X | | X | | X |
| Hematology | X | | X | X | X | | X | | X |
| Coagulation panel | X | | X | X | X | | X | | X |
| Autoantibody panel (RF, RF isotypes, ACPA, ANA, anti-Ro, anti-La [serum]) | X | | | | X | | X | | X |
| Exploratory biomarkers (serum) | X | | X | X | X | | X | | X |
| RNA PAXgene (whole blood) | X | | | X | X | | X | | X |
| Acute-phase reactants (CRP, ESR[c]) | X | | | X | X | | X | | X |
| CD4+ counts | X | | X | X | | X | X | X | X |
| Flow cytometry (whole blood) | X | | | | X | | X | | X |
| Vectra® DA (MBDA) (serum) | X | | X | X | X | | X | | X |
| Total CD40L (plasma) | X | | X | X | X | | X | | X |
| PK (plasma) | X [d] | X | X | X [e] | X [e] | | X [e] | | X [e] |
| ADA (plasma) [f] | X | | | | X | | X | | X |
| Anti-PAD4 antibody (serum) | X | | | | X | | X | | X |
| **Urine collection for:** | | | | | | | | | |
| Urinalysis | X | | X | | | X | X | X | X |

## Table 4.2.2-1 Schedule of Treatment Period Study Procedures

| Study Period | Treatment Period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9** | **V10** |
| **Procedure / Study Day** | **Day 1 ± 1 Day** | **Day 2 ± 1 Days** | **Day 8 ± 1 Day** | **Day 15 ± 1 Day** | **Day 29 ± 1 Day** | **Day 43 ± 1 Day** | **Day 57 ± 1 Day** | **Day 71 ± 1 Day** | **Day 85 ± 1 Day** |
| Urine β-hCG (women of childbearing potential only) | X | | | X | X | X | X | X | X |
| **Rheumatoid assessments** | | | | | | | | | |
| TJC/SJC: 28 joints count | X | | | X | X | | X | | X |
| VAS Patient assessment of disease activity | X | | | X | X | | X | | X |
| Physician's global assessment | X | | | X | X | | X | | X |
| **Investigational product administration** | **X** | | | **X** | **X** | **X** | **X** | **X** | **X** |

ADA = anti-drug antibody; AE = adverse event; ACPA = anti-cyclic citrullinated peptide antibody; ANA = antinuclear antibody; Anti-PAD4 = antibody against isoform 4 of peptidyl arginine deiminase; β-hCG = beta-human chorionic gonadotropin; CRP = C-reactive protein; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; IXRS = interactive voice/web response system; MBDA = multi-biomarker disease activity; PK = pharmacokinetic; RF = rheumatoid factor; RNA = ribonucleic acid; SAE = serious adverse event; CD40L = CD40 ligand; TJC = tender joint count; SJC = swollen joint count; V = visit; VAS = visual analogue scale.

Note: An overnight stay prior to administration of investigational product on Day 1 is recommended but not mandatory. An overnight stay post-investigational product administration on Day 1 is mandatory.

Note: All laboratory sample collections and assessments on dosing day must be performed at predose, unless specified otherwise.

Note: RA assessments on dosing day should be performed at predose.

[a] Abbreviated physical examination includes cardiovascular, respiratory and nervous system examinations.

[b] Vital sign measurements include body temperature, blood pressure, heart [pulse] rate, and respiratory rate. On the first two dosing days (Day 1 and Day 15), vital signs will be measured within 30 minutes prior to the start of infusion, every 30 minutes (± 5 minutes) during the infusion, at the end of the infusion (+ 5 minutes), then at 1 hour, 2 hours and 4 hours after the end of infusion (± 10 minutes). On subsequent dosing days, vital signs will be measured within 30 minutes prior to the start of infusion, every 30 minutes (± 5 minutes), and at the end of the infusion (+ 5 minutes).

[c] ESR will be analyzed at the local laboratories.

[d] Blood sample for PK on Day 1 collected post-dose only (at the end of infusion).

[e] Blood samples for PK on Days 15, 29, 57 and 85 collected pre- and post-dose (at the end of infusion).

[f] Blood samples for ADA collected at predose only.

### 4.2.3 Follow-up Period

Table 4.2.3-1 shows all procedures to be conducted during the follow-up period. Assessments should be performed in the order shown in the table.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, blood draws should occur last. The timing of the first two assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the proper nominal time.

**Table 4.2.3-1 Schedule of Follow-up Procedures**

| Study Period | Follow-up Period | | | | |
|---|---|---|---|---|---|
| | FU 1 | FU 2 | FU 3 | FU4 | FU5 |
| Visit Number | V11 | V12 | V13 | V14 | V15 |
| Procedure / Study Day | Day 92 ± 3 Days | Day 99 ± 3 Days | Day 113 ± 3 Days | Day 141 ± 3 Days | Day 169 ± 3 Days /EDV |
| **Safety assessments** | | | | | |
| Assessment of AEs/SAEs | X | X | X | X | X |
| Assessment of concomitant medications | X | X | X | X | X |
| Complete physical examination (includes weight) | | | | | X |
| Abbreviated physical examination [a] | X | X | X | X | |
| 12-lead ECG | | | | | X |
| Vital signs [b] | X | X | X | X | X |
| **Blood collection for:** | | | | | |
| Serum chemistry | X | X | X | X | X |
| Hematology | X | X | X | X | X |
| Coagulation panel | X | X | X | X | X |
| Autoantibody panel (RF, RF isotypes, ACPA, ANA, anti-Ro, anti-La [serum]) | | | | | X |
| Exploratory biomarkers (serum) | | | X | | X |
| RNA PAXgene (whole blood) | | | | | X |
| Acute-phase reactants (CRP, ESR[c]) | | | X | X | X |
| CD4+ counts | | X | X | | X |
| Flow cytometry (whole blood) | | | X | | X |
| Vectra DA (MBDA) (serum) | | | X | | X |
| Total CD40L (plasma) | | | X | | X |
| PK (plasma) | X | X | X | X | X |
| ADA (plasma) | | | | X | X |
| **Urine collection for:** | | | | | |
| Urinalysis | | X | X | X | X |
| Urine β-hCG (women of childbearing potential only) | | X | X | X | X |

**Table 4.2.3-1 Schedule of Follow-up Procedures**

| Study Period | Follow-up Period | | | | |
|---|---|---|---|---|---|
| | FU 1 | FU 2 | FU 3 | FU4 | FU5 |
| Visit Number | V11 | V12 | V13 | V14 | V15 |
| Procedure / Study Day | Day 92 ± 3 Days | Day 99 ± 3 Days | Day 113 ± 3 Days | Day 141 ± 3 Days | Day 169 ± 3 Days /EDV |
| **Rheumatoid assessments** | | | | | |
| TJC/SJC: 28 joints count | | | X | X | X |
| VAS Patient's assessment of disease activity | | | X | X | X |
| Physician's global assessment | | | X | X | X |

AE = adverse event; ACPA = anti-cyclic citrullinated peptide antibody; ANA = antinuclear antibody; β-hCG = beta-human chorionic gonadotropin; CRP = C-reactive protein; ECG = electrocardiogram; EDV = Early Discontinuation Visit; ESR = erythrocyte sedimentation rate; FU = follow-up; MBDA = multi-biomarker disease activity; PK = pharmacokinetic; RF = rheumatoid factor; RNA = ribonucleic acid; SAE = serious adverse event; CD40L = CD40 ligand; TJC = tender joint count; SJC = swollen joint count; V = visit; VAS = visual analogue scale.

[a] Abbreviated physical examination will include cardiovascular, respiratory and nervous system examinations.

[b] Vital sign measurements include body temperature, blood pressure, heart [pulse] rate, and respiratory rate.

[c] ESR will be analyzed at the local laboratories.

## 4.3 Description of Study Procedures

### 4.3.1 Medical History, Physical Examination, Electrocardiogram, Weight, Height, and Vital Signs

#### 4.3.1.1 Medical History

A complete medical history will be obtained at screening and will include past and current medical conditions such as cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, drug and surgical history, and/or any other diseases or disorders.

#### 4.3.1.2 Physical Examination, Height, and Weight

Complete physical examinations (including weight) and abbreviated physical examinations will be performed by a licensed healthcare provider (ie, physician, physician's assistant, or licensed nurse practitioner). Complete physical examinations will include assessment of weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Abbreviated physical examinations will include assessment of cardiovascular, respiratory, and nervous systems. Each clinically significant abnormal finding will be recorded in the electronic case report

form (eCRF). Physical examinations will be performed at study visits specified in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1. Height will be measured at screening only.

#### 4.3.1.3 Vital Signs

Vital signs (body temperature, BP, heart [pulse] rate, and respiratory rate) will be obtained at the visits specified in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1.

On the first two dosing days (Day 1 and Day 15), vital signs will be measured within 30 minutes prior to the start of infusion, every 30 minutes (± 5 minutes) during the infusion, at the end of the infusion (+ 5 minutes), then at 1 hour, 2 hours and 4 hours after the end of infusion (± 10 minutes). On subsequent dosing days, vital signs will be measured within 30 minutes prior to the start of infusion, every 30 minutes (± 5 minutes), and at the end of the infusion (+ 5 minutes).

#### 4.3.1.4 Electrocardiogram

Twelve-lead ECG recordings will be evaluated at screening and at the visits specified in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1.

At screening, the ECG will be performed in triplicate (all 3 within a 5-minute time period, at least 1 minute apart) and the mean value of the triplicate measurement will be recorded as the baseline value. ECGs taken at all other times (ie, during the treatment period) will be single assessments.

All ECG recordings will be made with the subject in a supine position having rested in this position for at least 5 minutes before the start of the ECG.

All ECGs will be recorded at a speed of 25 mm/seconds with amplitude recording of 10 mm/mV. At least 3 full complexes must be recorded. A multi-channel ECG machine should be used (equals 3 leads recorded simultaneously) and there must be amplitude index calibration for each lead.

Electronic software will be used to assess the following parameters: pulse rate, QRS, QT, and QTc time intervals. All ECGs must be reviewed by the principal investigator or a qualified designee before the subject is permitted to leave the clinic. The occurrence of de- or re-polarization disorders, arrhythmic disorders or other abnormalities will be assessed and obvious changes in ECG parameters from baseline will be assessed by the principal investigator for clinical significance.

### 4.3.2 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study. The Laboratory Manual pertains to samples that will be sent to a licensed central laboratory (ie, samples for clinical laboratory safety tests, PK, immunogenicity, and biomarker analysis).

Clinical laboratory safety tests include serum chemistry, hematology, coagulation, urinalysis, serum pregnancy tests, and other safety tests (as outlined below). Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed (see Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1).

#### Serum Chemistry

- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Bicarbonate
- AST
- ALT
- Cholesterol
- IgA, IgG, IgE, IgM, total Ig
- Erythrocyte sedimentation rate (ESR)
- ALP
- TBL (if result is > 1.5 ULN, indirect and direct bilirubin will be measured)
- Creatinine
- Blood urea nitrogen
- Glucose
- Albumin
- Total protein
- Uric acid
- Triglycerides

**Note for serum chemistry:** Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

#### Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Platelet count
- Hemoglobin

### Coagulation

- International normalized ratio
- Prothrombin time
- Partial thromboplastin time
- D-dimer
- Fibrinogen
- TAT

### Urinalysis

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

### Pregnancy Test (females of childbearing potential only)

- Urine β-hCG
- Serum β-hCG (performed at screening only)

### Other Safety Tests

- Hepatitis A antibody (IgM), HbsAg, HbsAb; HbcAb, hepatitis C antibody, hepatitis B virus DNA copy number (assessed at screening only)
- HIV-1 antibody, HIV-2 antibody (assessed at screening only), sample for collection and retention for CMV and EBV (at screening only)
- Protein S, Protein C, anti-thrombin 3, antiphospholipid antibodies (assessed at screening only)
- TB test (eg, QuantiFERON-TB Gold Test) as per local standard of care guidelines (assessed at screening only)
- Autoantibody panel: RF, RF isotypes (IgA, IgG, IgM), ACPA, anti-nuclear antibody (ANA), anti-Ro, anti-La
- Acute-phase reactants: C-reactive protein (CRP) and ESR

### 4.3.3 Pharmacokinetic Evaluation and Methods

Plasma samples to determine the concentration of MEDI4920 will be collected at the visits specified in Table 4.2.2-1 and Table 4.2.3-1. MEDI4920 plasma concentrations will be measured by MedImmune using a validated immunoassay.

### 4.3.4 Immunogenicity Evaluation and Methods

Plasma samples will be collected for the assessment of ADA against MEDI4920 at the visits specified in Table 4.2.2-1 and Table 4.2.3-1. Samples will be measured for the presence of ADA by MedImmune using a validated immunoassay. Sample may be used for further

characterization of the ADA response, including possible assessment of neutralizing antibody.

### 4.3.5 Biomarker Evaluation and Methods

#### 4.3.5.1 Flow Cytometry

Blood samples will be collected for the assessment of changes in the number, activation status and frequency of major leukocyte populations, including B lymphocytes, T lymphocytes, and natural killer cells using flow cytometry according to the schedule of events as outlined in Table 4.2.2-1 and Table 4.2.3-1.

A CD40L blockade is expected to reduce the frequency of certain B-cell and plasmablast/plasma cell populations and may indirectly also reduce the frequency of T cells and other immune cell populations.

#### 4.3.5.2 Autoantibody Panel

Serum will be collected to assess the presence of ACPA, RF, RF isotypes, ANA, anti-Ro, and anti-La according to the schedule of events as outlined in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1.

#### 4.3.5.3 Exploratory Serum Biomarkers

Serum will be collected to measure changes in exploratory biomarkers of disease activity, autoantibodies associated with RA such as CCI [redacted] CCI [redacted] CCI [redacted], according to the schedule of events as outlined in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1.

These biomarker measurements will aid in determining what biological pathways are impacted by MEDI4920 treatment.

#### 4.3.5.4 Total CD40L Levels

Plasma samples will be collected for the measurement of total CD40L levels (free and bound) as a measure of target engagement by MedImmune using a qualified immunoassay method according to the schedule of events as outlined in Table 4.2.2-1 and Table 4.2.3-1.

#### 4.3.5.5 Blood Transcriptome

Blood RNA will be used to measure the expression levels of genes associated with disease activity, specific cell types and signaling including the CD40L-CD40 pathway. These

biomarker measurements will aid in the determination of what biological pathways are impacted by MEDI4920 treatment.

A blood sample will be collected using the PAXgene Blood RNA System for the collection, transport, and storage of blood and stabilization of intracellular RNA in a closed tube and subsequent isolation and purification of intracellular RNA from whole blood for microarray analysis and quantitative PCR. RNA PAXgene blood samples will be collected according to the schedule of events as outlined in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1.

#### 4.3.5.6 MBDA Test

A commercially available and validated biomarker panel (Vectra DA) measures 12 biomarkers and combines them into a single score to assess the key mechanisms and pathways that drive RA disease activity. The biomarker panel includes adhesion molecules, growth factors, cytokines, matrix metalloproteinases, skeletal proteins, hormones and acute phase proteins. The MBDA biomarker panel has been demonstrated to be a sensitive objective measure of clinical disease activity, with a strong correlation to DAS28 CRP. Changes in MBDA score are also an objective measure of changes in disease activity, showing a significant correlation to changes in DAS28 CRP. Serum samples will be collected for the Vectra DA (MBDA) biomarker panel according to the schedule of events as outlined in Table 4.2.2-1 and Table 4.2.3-1.

### 4.3.6 Disease Evaluation and Methods

The RA assessments should be performed prior to the treatment infusion if on a dosing day.

#### 4.3.6.1 Tender and Swollen Joint Counts

The tender joint count (TJC) and swollen joint count (SJC) assess the following 28 joints for tenderness and swelling: the 8 proximal interphalangeal joints of the fingers, the interphalangeal joints of the thumbs (n = 2), the 10 metacarpophalangeal joints plus the wrists (n = 2), elbows (n = 2), shoulders (n = 2), and knees (n = 2) (Prevoo et al, 1995).

The TJC and SJC will be assessed by a qualified, independent, blinded Joint Counts Assessor. This person will be responsible for completing the TJC and SJC without access to any other study-related outcomes. The TJC and SJC will be performed according to the schedule of events as outlined in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1.

#### 4.3.6.2 Patient's Global Assessment of Disease Activity

The Patient's Global Assessment (PGA) of disease activity is a measure of the patient's general health on a 100 mm visual analogue scale (VAS) from 0 mm = best to 100 mm = worst and will be performed according to the schedule of events as outlined in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1.

#### 4.3.6.3 Physician Global Assessment of Disease Activity

The Physician's Global Assessment (MDGA) of disease activity is a 100 mm VAS that asks the investigator to rate their subject's current disease activity on a scale of 0 mm (none) to 100 mm (extremely active). The MDGA will be performed according to the schedule of events as outlined in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1.

#### 4.3.6.4 Acute-phase Reactants

Blood samples for acute-phase reactants, CRP and ESR, will be collected according to the schedule of events as outlined in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1. Both CRP and ESR are strong correlates of disease activity in RA.

**Disease Activity Score in 28 Joints Using C-reactive Protein**

The DAS28 CRP considers 28 of the 68 TJC and 28 of the 66 SJC, general health (GH; PGA [0-100 mm VAS]), plus levels of an acute-phase reactant (CRP [mg/L]). CRP levels are more sensitive to short-term changes in disease activity and more specific to inflammatory conditions, whereas ESR is less specific and can be influenced by a number of unrelated factors, such as age, gender, red blood cell count, or plasma proteins.

DAS28 CRP values will be calculated as follows (Wells et al, 2009):

*DAS28 CRP = 0.56 × square root (sqrt) (TJC28) + 0.28 × sqrt(SJC28) + 0.014 × GH + 0.36 × ln(CRP+1) + 0.96*

**Clinical Disease Activity Index**

The CDAI is a composite index (without acute-phase reactant) for assessing disease activity and is defined as the sum of the TJC (using 28 joints), the SJC (using 28 joints), the PGA (0-100 mm VAS), and the MDGA (0-100 mm VAS). The CDAI has a range from 0 mm to 76 mm. The greatest advantage associated with CDAI is its potential to be employed in evaluation of patients with RA consistently with close frequency and independently of any calculating device; therefore, it can essentially be used everywhere and anytime for disease activity assessment in RA patients.

### 4.3.7 Estimate of Volume of Blood to Be Collected

The estimated volume of blood to be collected from each subject at each visit (and across all visits) from screening through Day 169/Early Discontinuation Visit (EDV) is presented in Table 4.3.7-1. If repeats of any blood tests are required, the volume of blood collection will increase accordingly.

**Table 4.3.7-1 Estimate of Blood Volume to Be Collected**

| Visit Day | Estimated Blood Volume (mL) |
|---|---|
| Day -42 to Day -1 (Screening) | 65.9 |
| Day 1 | 59.5 |
| Day 2 | 9 |
| Day 8 | 35.5 |
| Day 15 | 48.5 |
| Day 29 | 58 |
| Day 43 | 10 |
| Day 57 | 59 |
| Day 71 | 10 |
| Day 85 | 59 |
| Day 92 | 18.8 |
| Day 99 | 21.5 |
| Day 113 | 46.5 |
| Day 141 | 18.8 |
| Day 169/EDV | 52 |
| **Total** | 572 |

EDV = Early Discontinuation Visit.

## 4.4 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or permanently terminate this study at any time. The reasons for temporarily suspending or permanently terminating the study may include but are not limited to the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
2. Subject enrollment is unsatisfactory
3. Non-compliance that might significantly jeopardize the validity or integrity of the study
4. Sponsor decision to terminate development of the investigational product for this indication

If MedImmune determines that temporary suspension or permanent termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

## 4.5 Investigational Products

### 4.5.1 Identity of Investigational Products

MedImmune will provide the investigator(s) with investigational product (Table 4.5.1-1) using designated distribution centers.

**Table 4.5.1-1 Identification of Investigational Products**

| Investigational Product | Manufacturer | Concentration and Formulation as Supplied |
|---|---|---|
| MEDI4920 (250 mg/vial) | MedImmune, LLC | 20 mL lyophilized vial with a nominal 250 mg of MEDI4920 at a post-reconstitution concentration of 50 mg/mL, containing 10 mM sodium monobasic/dibasic phosphate, 250 mM sucrose and 0.02% (w/v) polysorbate 80, pH 7.4 |
| Placebo | Provided by the site | 0.9% saline for injection |

(w/v) = (weight/volume)

MEDI4920 will be supplied by MedImmune to the site in containers with identical appearances in coded, open-label kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton is labeled with a unique number range that corresponds to the labeled

number series of the containers within the carton. Placebo will be prefilled IV saline bags sourced by each site.

#### 4.5.1.1 Investigational Product Handling

The investigational product manager will select the MEDI4920 vials assigned by the IXRS to prepare the subject's dose. For subjects assigned to placebo, the sites should use prefilled IV saline bags only.

Do not remove MEDI4920 from 2°C to 8°C (36°F to 46°F) storage until all procedures for subject dosing have been completed. When preparing a dose for administration, immediately remove the vials from the carton and replace the carton in 2°C to 8°C (36°F to 46°F) storage.

The investigational product manager/unblinded study personnel must ensure that only the unblinded team members have access to the areas of the pharmacy where the investigational product is being prepared.

#### 4.5.1.2 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. MEDI4920 is supplied as a sterile lyophilized drug product with post-reconstitution concentration of 50 mg/mL.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section for further instructions (Section 4.5.1.9).

#### 4.5.1.3 Dose Preparation Steps

No incompatibilities between MEDI4920 and plastics passing compatibility tests (ie, polyethylene bags; polyethylene and polyvinyl chloride infusion lines; polypropylene and polycarbonate syringes for IV infusion using IV infusion pump) have been observed. MEDI4920 does not contain preservatives and any unused portions must be discarded. Preparation of investigational product and IV bags is to be performed aseptically. Total in-use storage time from reconstitution of investigational product/needle puncture of the investigational product vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If storage time exceeds these limits, a new dose must be prepared from new vials.

Each vial of investigational product must be reconstituted with 5.0 mL of sterile water for injection to achieve 5.5 mL (5 mL nominal) of 50 mg/mL MEDI4920.

#### 4.5.1.4 Reconstitution Procedure

Slowly add 5.0 mL of sterile water for injection by tilting the vial to one side such that the liquid stream is directed along the vial wall and not directly onto the lyophilized cake. Gently swirl the solution and repeat this procedure until all solids are dissolved. DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL. Visually inspect the solution to ensure that the entire content of the lyophilized cake is completely reconstituted. The reconstituted solution should appear clear to opalescent. A thin layer of bubbles on the surface of the liquid is normal.

#### 4.5.1.5 Preparation of Intravenous Dose

**For Subjects Randomized to the MEDI4920 Group:**

Preparation of MEDI4920 doses for IV infusion with an IV infusion pump:

The dose preparation steps are as follows:

1. For each of the IV doses (ie, 75, 500, 1000, and 1500 mg), the volume of 0.9% saline (weight/volume [w/v]) equivalent to volume of MEDI4920 is removed first and then the required volume of MEDI4920 will be added to a prefilled IV bag (Table 4.5.1.5-1). Syringes used to prepare the IV bag must be polycarbonate or polypropylene.
2. A vial should be used only one time to prepare a single dose. The required volume of MEDI4920 (Table 4.5.1.5-1) will be obtained by pooling the contents of as many MEDI4920 vials as necessary (ie, 1 vial for the 75 mg dose, 2 vials for the 500 mg dose, 4 vials for the 1000 mg dose, and 6 vials for the 1500 mg dose) with an appropriately sized syringe. For ease of preparation, a 1.5-inch 20-gauge withdrawal needle should be used. Use a new needle for withdrawing investigational product from each vial.
3. Gently mix the contents of the IV bag. The admixture should then be inspected to ensure the solution is clear.

**Table 4.5.1.5-1 MEDI4920 Dose Preparation for IV Infusion with an IV Infusion Pump**

| Dose (mg) | Prefilled IV Bag Size (mL) | Volume of Saline Removed from IV Bag (mL) | MEDI4920 Dose Volume Added to IV Bag (mL) |
|---|---|---|---|
| 75 | 50 | 1.5 | 1.5 |
| 500 | 100 | 10 | 10 |
| 1000 | 250 | 20 | 20 |
| 1500 | 250 | 30 | 30 |

IV = intravenous; FTIH = first time in human; SAD = single ascending dose.

Note: The maximum concentration of reconstituted investigational product solution will not exceed that used in the FTIH SAD study.

**For Subjects Randomized to the Placebo Group:**

Preparation of placebo for IV infusion with an IV infusion pump:

For each of the doses, the prefilled IV saline bag size to be used is listed in Table 4.5.1.5-2. No additional IV bag preparation is required.

**Table 4.5.1.5-2 Placebo Dose Preparation for IV Infusion with an IV Infusion Pump**

| Dose (mg) | Prefilled IV Bag Size (mL) |
|---|---|
| 75 | 50 |
| 500 | 100 |
| 1000 | 250 |
| 1500 | 250 |

IV = intravenous

During preparation of the investigational product infusion, the capacity of the tubing should be calculated in order to adjust the volume of investigational product solution needed to prime the IV tubing. This step is necessary because the same volume of saline will be needed at completion of the infusion to flush the IV tubing in order to deliver the complete volume of investigational product solution. Because the IV tubing contains investigational product solution, the flush must be infused using the same infusion rate as that used for the investigational product solution in the infusion bag.

For example, if the IV tubing capacity is 15 mL, the IV tubing should be primed with 15 mL of investigational product solution from the infusion bag before initiating the infusion. Once the infusion bag is empty, the IV tubing should be flushed with at least 15 mL of 0.9% saline (w/v) via the infusion pump at the same rate as dosing.

The start time of the infusion will be the time when infusion of the investigational product solution from the infusion bag (with IV tubing primed with investigational product solution) is started. The stop time of the infusion will be the time when the IV tubing has been flushed with a volume of 0.9% normal saline equivalent to IV tubing capacity (eg, 15 mL for the example above) to administer the residual investigational product solution.

### 4.5.1.6 Intravenous Administration

All Cohorts (1-4) will be administered investigational product via IV infusion using an IV infusion pump.

Each subject in each cohort must receive the entire volume of investigational product solution in the IV bag. Table 4.5.1.6-1 provides the duration of infusion and flow rate by dose level. Investigational product must be infused through a low-protein binding 0.2- or 0.22-µm in-line filter using an IV infusion pump.

**Table 4.5.1.6-1 Intravenous Administration of Investigational Product**

| Cohort | Dose (mg) | Total Volume in IV Bag (mL) | Minimum Administration Time (min) | Flow Rate at Minimum Time (mL/min) |
|---|---|---|---|---|
| 1 | 75 | 50 (IV bag) | 30 | 1.7 mL/min |
| 2 | 500 | 100 (IV bag) | 60 | 1.7 mL/min |
| 3 | 1500 | 250 (IV bag) | 90 | 2.8 mL/min |
| 4 | 1000 | 250 (IV bag) | 90 | 2.8 mL/min |

IV = intravenous; min = minute; TBD = to be determined

### 4.5.1.7 Treatment Administration

The first day of dosing is considered Day 1.

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

- Female subjects must have a negative urine pregnancy test prior to receiving MEDI4920 or placebo.
- A physician must be present at the site or immediately available to respond to emergencies during administration of investigational product. Fully functional resuscitation facilities should be available.
- Investigational product will be administered as a single IV infusion as described in Table 4.5.1.6-1.

### 4.5.1.8 Monitoring of Dose Administration

Vital signs (BP, heart [pulse] rate, respiratory rate, and body temperature) will be obtained as outlined in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1). In addition, if signs and symptoms indicative of an infusion reaction occur, the infusion will be stopped or slowed according to the judgment of the investigator.

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

#### 4.5.1.9 Reporting Product Complaints

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

MedImmune contact information for reporting product complaints:

Email: PPD

Phone: PPD
PPD PPD

Fax: PPD

Mail: MedImmune
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

### 4.5.2 Additional Study Medications

#### 4.5.2.1 Background Medications for RA

All permitted background medications from initiation of screening through to the end of the study must be recorded in the source records and include the specific indication for use as well as the dose, start and stop dates, frequency, and route of administration.

**MTX and Other cDMARDs**

All subjects (except patients with intolerance to MTX or having been switched to another cDMARD after MTX failure) must be on MTX (7.5 to 25 mg/week) administered the same route (oral or injectable), for at least 12 weeks and at a stable dose for at least 6 weeks prior to screening. Subjects must continue with the same dose and route of administration for MTX during the 12-week treatment period (Days 1 to 85). Any dose changes in background MTX should be discussed and agreed with the medical monitor. Changes in MTX dose are permitted for safety/tolerability reasons (which must be clearly documented) or, after Week 12 for control of disease activity.

To minimize MTX toxicity, it is recommended that subjects receive 5.0 mg/week folic acid during the study as a single or divided dose.

It is recommended that MTX is withheld if liver function tests (LFTs), particularly ALT or AST enzymes, are increased to > 3 × ULN and MTX dose should be reduced by 2.5 mg/week if LFT enzymes are increased between 2 and 3 × ULN. After normalization of the LFT, MTX can be reinitiated and/or titrated up to the dose used prior to modulation. In case of newly occurred blood cytopenias (WBC < $3 \times 10^9$/L, neutrophil count < $2 \times 10^9$/L, platelet count < $150 \times 10^9$/L) MTX should be withheld until blood cell counts recover.

Protocol-permitted alternative cDMARDs (for subjects with documented MTX intolerance or if subjects have been treated with this DMARD after a previous MTX failure) are leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, D-penicillamine, and cyclosporine. These must be given at the doses specified by the local RA treatment guidelines and the local Summary of Product Characteristics. Subjects should be treated with the alternative cDMARD for at least 12 weeks and at a stable dose for at least 6 weeks prior to screening. Subjects must continue with the same dose and route of administration during the 12-week treatment period (Days 1 to 85). Changes in dose are permitted for safety/tolerability reasons (which must be clearly documented) or, after Week 12 for control of disease activity.

### Corticosteroids

Corticosteroids should be maintained at a stable oral dose (< 10 mg equivalent prednisone/day) for the duration of the study through to the end of the 12-week treatment period unless changes are needed for safety reasons. Any change in background oral corticosteroids, or addition of injectable corticosteroids, is prohibited from 4 weeks prior to Day 1 up to Week 12 (Day 85), unless used for the treatment of a non-RA AE. It is strongly recommended to avoid changes in corticosteroids dosage within 4 weeks prior to the Week 12 (Day 85) visit to avoid confounding the evaluation of efficacy. After Week 12, a change in oral corticosteroid dose and/or addition of injectable corticosteroids for control of disease activity is permitted. A maximum of 2 intra-articular injections of corticosteroids (up to 40 mg of triamcinolone or equivalent) can be allowed as required to control severe/refractory mono/oligoarthritis during the treatment period (no more than 4 joints allowed to be treated). Treated joint(s) will need to be excluded from the joint counts until 12 weeks post-injection. Intra-articular steroid injections are not allowed within 4 weeks prior to the Day 85(Week 12) visit to avoid confounding the evaluation of efficacy. Inhaled

or topical corticosteroids given for asthma, COPD, or dermatological conditions are allowed provided doses are stable between screening and Day 85 visit.

#### Analgesics/NSAIDs

Analgesics and NSAIDs given primarily for RA signs and symptoms should be maintained at a stable dose for the duration of the study through to the end of the 12-week treatment period (Day 85) unless changes are needed for safety/tolerability reasons or inadequate response after the Week 12 visit. Subjects should refrain from taking the usual morning dose of analgesics on visit days until after all clinical assessments have been completed.

### 4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local languages, as required.

### 4.5.4 Storage

Investigational product is to be stored at 2 to 8°C (36 to 46°F).

### 4.5.5 Treatment Compliance

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

### 4.5.6 Accountability

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

## 4.6 Treatment Assignment and Blinding

### 4.6.1 Methods for Assigning Treatment Groups

An IXRS will be used for randomization to a treatment group and assignment of investigational product kit numbers if assigned to an active treatment arm. A subject is considered randomized into the study when the investigator notifies the IXRS that the subject

meets eligibility criteria and the IXRS provides the assignment of treatment group and allocates active treatment if assigned to the active treatment arm.

Subjects will be randomized in a 4:1 ratio (Cohort 1), in a 5:2 ratio (Cohort 2), in a 3:1 ratio (Cohort 3), and in a 5:2 ratio (Cohort 4) to receive either MEDI4920 or placebo respectively as described in Table 3.1.2-1.

Investigational product (MEDI4920 or placebo) must be administered the same day the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

### 4.6.2 Methods for Ensuring Blinding

This is a double-blind study in which MEDI4920 and the saline placebo are not identical in appearance. As such, neither the subject/legal representative nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (ICH E9) (see Section 4.6.4 for unblinding related to interim analysis). For maintaining the blinding of the principal investigator, site staff, sponsor, Contract Research Organization (CRO) or staff, a local unblinded pharmacy staff member will be nominated by each site and will have the responsibility of allocating, dispensing and preparing the investigational product in order to maintain the study blind. In addition, a separate unblinded monitor will be used for the oversight of investigational product management. If treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified *immediately*.

### 4.6.3 Methods for Unblinding

#### 4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

### 4.6.4 Unblinding for Interim Analysis Purposes

The primary analysis will be performed when all subjects in Cohort 3 have completed the Day 85 assessments or have been withdrawn from the study. The primary analysis will include all assessments on the subjects prior to the data cut-off for the primary analysis.

MedImmune personnel will be unblinded to the subject treatment assignments from Cohorts 1 to 3 at the primary analysis (Day 85). The data from the primary analysis will not be communicated to personnel at the CRO or investigational sites or to enrolled subjects, until all subjects in Cohorts 1 to 3 have completed the study and database lock has been achieved.

MedImmune personnel will be unblinded for Cohort 4, and the data will be analyzed when all subjects in Cohort 4 have completed the Day 85 assessments or have been withdrawn from the study. Study subjects and personnel at the CRO or investigational sites will remain blinded to Cohort 4 data until all subjects in Cohort 4 have completed the study and database lock has been achieved.

The final analysis on the subjects will be performed when all subjects have completed the safety follow-up.

## 4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including over-the-counter products (and any herbal supplements), taken during the study will be recorded in the eCRF.

### 4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “excluded” as listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

### 4.7.2 Prohibited Concomitant Medications

Subjects must refrain from alcohol consumption for 48 hours prior to all visits.

Subjects must refrain from strenuous exercise for approximately 48 hours before each study day where safety samples will be taken, and Day 169/EDV. Physical therapy including cold/hot applications, electrical stimulation, and hydrotherapy, applied specifically for RA, is not permitted between Days 1 and 85.

The introduction of the following medications is not permitted from initiation of screening through to the end of the study. The sponsor must be notified if any of the following medications are given to a subject during the study (with the exception of stable doses of DMARDs permitted prior to screening/randomization as applicable):

1. Investigational drug therapy other than MEDI4920
2. Biologic DMARD therapies (such as anti-TNF, recombinant IL-1 receptor antagonist, anti-IL-6, CTLA-4 Ig, B-cell depleting therapies, etc) or JAK inhibitors.
3. Mycophenolate mofetil, cyclophosphamide, and other alkylating agents
4. Live (attenuated) vaccine. Immunization with any live or live attenuated vaccine (ie, measles, mumps, rubella and polio vaccine, Bacillus Calmette-Guerin, typhoid, yellow fever, cold adapted live influenza strain vaccine, or any other vaccines not yet licensed but belonging to this category) is specifically excluded during the treatment period (ACIP, 2011).
5. Immunoabsorption columns, total lymphatic irradiation, plasmapheresis and IV immunoglobulin therapy

After Day 85, the dose of background cDMARDs and corticosteroids may be adjusted or a new additional cDMARD may be added to an existing one (except for combining MTX and leflunomide) if it is clinically indicated to improve disease management.

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

## 4.8 Statistical Evaluation

### 4.8.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan.

The intent-to-treat (ITT) population is defined as all subjects who are randomized and receive any amount of investigational product. Subjects will be analyzed by the randomized

treatment group. All efficacy and biomarker analyses will be performed on the ITT population unless otherwise specified.

The as-treated population is defined as all subjects who are randomized and treated with investigational product. Subjects will be analyzed by the treatment received. All safety analyses will be performed on the As-Treated population unless otherwise specified.

### 4.8.2 Sample Size and Power Calculations

No formal sample size calculations are presented for the evaluation of the primary objective of safety and tolerability of MEDI4920. The sample size calculations are based on the exploratory endpoint CCI [redacted] CCI [redacted].

The sample size calculation for the change from baseline in DAS28 CRP at Week 12 is based on combining the data from the cohorts and performing a dose response analysis. Based on the assumption CCI [redacted] CCI [redacted] the sample sizes of 14, 8, 10, 10 and 12 subjects for the placebo, 75, 500, 1000 and 1500 mg dose groups, respectively, will provide approximately 92% power for detecting a statistically significant dose response, using a significance level of 0.10.

The power for dose response has been calculated using a multiple comparison procedure with modeling techniques (MCP-Mod; Bretz et al, 2005), with three candidate models for the dose response (linear, maximum effect attributable to the drug [$E_{max}$], and a Hill-$E_{max}$ model). An overall significance level of 0.10 will be used to test for dose response.

### 4.8.3 Exploratory Efficacy Analyses

CCI [redacted]

#### 4.8.3.1 CCI [redacted]

CCI [redacted]

CCI

#### 4.8.3.2 CCI

CCI

#### 4.8.3.3 CCI

CCI

### 4.8.4 Safety

#### 4.8.4.1 Analysis of Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented. All TEAEs will be summarized overall and by MedDRA SOC and PT, and by severity and relationship to investigational product. In addition, summaries of deaths, SAEs and treatment discontinuations due to AEs will be provided.

TEAEs, treatment-emergent SAEs (TESAEs) and AESIs with onset after the start of infusion (Day 1) to Day 169/EDV inclusive will be summarized by dose. The placebo subjects from each cohort will be combined for the summaries.

Other safety parameters, including laboratory assessments and vital signs, will be summarized by dose.

#### 4.8.4.2 Analysis of Clinical Laboratory Parameters

Laboratory parameters will be assessed at baseline as well as throughout the study. Frequencies of abnormal laboratory measurements will be presented for each laboratory parameter. Also, laboratory parameters will be assessed by presenting tables containing information related to laboratory shifts from baseline relative to the normal range, as well as descriptively over time.

#### 4.8.4.3 Other Safety and Tolerability Endpoints

Other safety parameters, including vital signs and ECGs, will be summarized by dose and time point.

### 4.8.5 Analysis of Immunogenicity/Pharmacokinetics

The number and percentage of subjects who develop detectable ADA will be summarized by dose. The impact of ADA on PK and the association with AEs and SAEs will be assessed. Plasma MEDI4920 concentration data at each time point will be tabulated by dose cohort together with descriptive statistics. Individual and mean plasma concentration-time profiles of MEDI4920 by dose cohort will be generated. Non-compartmental PK data analysis will be performed and descriptive statistics for PK parameters will be provided.

### 4.8.6 Interim Analysis

The primary analysis will be performed when all subjects in Cohort 3 have completed the Day 85 assessments or have been withdrawn from the study. The primary analysis will include all assessments on the subjects prior to the data cut-off for the primary analysis.

MedImmune personnel will be unblinded to the subject treatment assignments from Cohorts 1 to 3 at the primary analysis (Day 85). The data from the primary analysis will not be communicated to personnel at the CRO or investigational sites or to enrolled subjects, until all subjects in Cohorts 1 to 3 have completed the study and database lock has been achieved.

An additional interim analysis will be performed when all subjects in the Cohort 4 have completed the Day 85 assessments or have been withdrawn from the study. MedImmune personnel will be unblinded to the subject treatment assignments from Cohort 4 for this interim analysis. Study subjects and personnel at the CRO or investigational sites will remain blinded to Cohort 4 data until all subjects in Cohort 4 have completed the study and database lock has been achieved.

The final analysis on the subjects will be performed when all subjects have completed the safety follow-up.

# 5 ASSESSMENT OF SAFETY

## 5.1 Definition of Adverse Events

The ICH Guideline for GCP E6(R1) defines an AE as:

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

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

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

Elective treatment or surgery, or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical

event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

## 5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

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

## 5.3 Definition of Adverse Events of Special Interest

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

The following AESIs will be particularly monitored in this study (see the Safety Handling Plan for instructions and timing on completing any additional information required for specific types of events related to the categories noted below):

- Thrombotic and embolic events
- Hepatic function abnormality (meeting the definition of HL as described in Section 5.6.2).
- Anaphylaxis and serious hypersensitivity reactions
- Immune complex disease

- Infusion-related reactions
- Serious and/or opportunistic infections (including but not limited to reactivation of latent viral infection [VZ/HSV/, EBV/CMV] and TB)

## 5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor (see Section 5.5). See Section 5.2 for the definition of SAEs and Section 10.2 for guidelines for assessment of severity and relationship. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

Infusion of biological products is commonly associated with infusion-related reactions. Anaphylaxis and infusion-related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion-related reactions are commonly observed during or shortly after the first time exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion-related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to MEDI4920, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the investigator's convenience and to facilitate consistency in judgments a copy of the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Section 10.3.

### 5.4.1 Time Period for Collection of Adverse Events

AEs will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period (Day 169).

### 5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF.

MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

## 5.5 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs during the course of the study, the investigator or other site personnel will inform the appropriate sponsor representative(s) within 1 day; ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all the necessary information is provided to the sponsor patient safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel will inform sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day; ie, immediately but no later than 24 hours of when he or she becomes aware of it.

Once the investigator or other site personnel indicates an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to inform the designated sponsor representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports the SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

## 5.6 Other Events Requiring Immediate Reporting

### 5.6.1 Overdose

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

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose with a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel informs appropriate sponsor representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.5. For other overdoses, reporting must occur within 30 days.

### 5.6.2 Hepatic Function Abnormality

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as AESIs. Refer to Section 10.4 for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 5.6.3 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor.

#### 5.6.3.1 Maternal Exposure

If a subject becomes pregnant during the course of the study, the investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 day; ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site within 1 or 5 calendar

days for SAEs (see Section 5.5) and within 30 days for all other pregnancies. The same timelines apply when the outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

# 6 STUDY AND DATA MANAGEMENT

## 6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

## 6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that investigational product accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

### 6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

### 6.2.2 Study Agreements

The principal investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. If there is any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the principal investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

### 6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

## 6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through the last protocol-specified visit/assessment (including telephone contact), regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.1.5 and Section 4.1.6).

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

## 6.4 Data Management

Data management will be performed by the MedImmune Data Management staff according to the Data Management Plan.

A Web Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

### 6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the principal investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the Clinical Study Protocol, and the principal investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third-party vendor.

## 7 ETHICAL AND REGULATORY REQUIREMENTS

### 7.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

### 7.2 Subject Data Protection

The Informed Consent Form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals

might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune medical monitor or an investigator might know a subject's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

## 7.3 Ethics and Regulatory Review

An IRB/IEC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to MedImmune before enrollment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

MedImmune should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

MedImmune will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide regulatory authorities, the IRB/IEC, and principal investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

Each principal investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. MedImmune will provide this information to the principal investigator so that he/she can meet these reporting requirements.

## 7.4 Informed Consent

The principal investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each subject is notified that he/she is free to discontinue from the study at any time.
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information is provided.
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the investigator's study file.
- Ensure a copy of the signed ICF is given to the subject.
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC.

## 7.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the principal investigator and MedImmune.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each principal investigator(s). For distribution to the IRB/IEC see Section 7.3.

If a protocol amendment requires a change to a site's ICF, MedImmune and the site's IRB/IEC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

## 7.6 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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# 9 CHANGES TO THE PROTOCOL

All changes described below have been incorporated into the current version of the protocol.

## Protocol Amendment 3, 29Sep2017

In the original protocol (dated 15Jan2016), 3 dose levels of MEDI4920 (75 mg [Cohort 1], 500 mg [Cohort 2], or 1500 mg [Cohort 3]) or placebo were planned to be administered Q2W in combination with MTX or another cDMARD for up to 12 weeks. An option to include a fourth dose cohort (dose not to exceed 1500 mg Q2W) was also included in the original protocol, if required, to further characterize the dose-response relationship.

After review of the primary analysis data, which included cumulative safety, PK, and biomarker data through Cohort 3, Day 85, the decision was made to explore a fourth dose (Cohort 4, selected to be 1000 mg Q2W) to better characterize the dose-response relationship. The changes in this protocol amendment are a result of the addition of this fourth cohort and are outlined below:

1. Protocol Synopsis: Updated wording in the Study Design, Treatment Groups and Regimen, Statistical Analysis Methods sections of the synopsis to include the addition of Cohort 4
2. Section 1.6 (Potential Risks); Section 3.1.1 (Overview); Section 3.1.3 (Dose Escalation and Cohort Progression); Section 4.1.1 (Number of Subjects): Modified the language to reflect the addition of fourth dose cohort (1000 mg Q2W).
3. Figure 3.1.1-1 (Study Flow Diagram): Modified the study design diagram to include the fourth dose cohort (1000 mg Q2W).
4. Section 3.1.2 (Treatment Regimen): Added the treatment regimen for Cohort 4 including the dose (1000 mg), and duration of the IV infusion (90 minutes on Days 1, 15, 29, 43, 57, 71, and 85).
5. Section 3.2.1 (Dose Rationale): Added additional language to explain that the rationale for the selection of the 1000 mg Q2W dose for Cohort 4 was based on PK-PD modeling data from Cohorts 1 to 3 as well as clinical judgement and that the dose is expected to result in a clinical response comparable to the highest dose in the study (1500 mg Q2W) but with a larger safety margin.
6. Section 4.5.1.5 (Preparation of Intravenous Dose); Section 4.5.1.6 (Intravenous Administration): Updated the IV dose preparation and administration language to include the 1000 mg dose and the appropriate volume and duration of the IV infusion in Cohort 4.
7. Section 4.6.4 (Unblinding for Interim Analysis Purposes); Section 4.8.6 (Interim Analysis): Updated the language to reflect the addition of the fourth cohort.

8. Section 4.8.2 (Sample Size and Power Calculations): Updated the language to reflect the addition of the fourth cohort and the resultant change in the power calculations from 80% to 92%.

## Protocol Amendment 2, 10Aug2016

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

1. Protocol Synopsis; Section 3.1.1 (Overview): Updated wording to reflect the current number of countries planned for this study; revised wording to clarify that while an overnight stay prior to administration of investigational product on Day 1 is recommended, it is not mandatory. This revision was made to allow sites the flexibility to perform all pre-dose study procedures on the same day as the day of investigational product administration if absolutely necessary.
2. Section 4.1.2 (Inclusion Criteria): Modified Inclusion Criterion #4 to allow a combination of cDMARDs if recommended by national guidelines and/or standard medical practice instead of just a single cDMARD as outlined in the original protocol; modified Inclusion Criterion #9 to remove the specific numerical thresholds for the detection of RF-IgM and ACPA2 positivity that were included in the original protocol and instead include a generic statement about serum RF and ACPA positivity to accommodate the different ranges of detection that may be exhibited by the assays used by the central laboratory.
3. Section 4.1.3 (Exclusion Criteria): Corrected a typographical error in Exclusion Criterion #10 by changing “intermediate” to “indeterminate”. Because MEDI4920 is a CD40L antagonist, Exclusion Criterion #17 was updated to specify that subjects who had undergone previous treatment with anti-CD40/CD40L agents will also be excluded from participation in the study.
4. Table 4.2.1-1 (Schedule of Screening Procedures), Table 4.2.2-1 (Schedule of Treatment Period Study Procedures), and Table 4.2.3-1 (Schedule of Follow-up Procedures): Added a footnote to specify that ESR will be analyzed at the local laboratories.
5. Table 4.2.2-1: Added a note to specify that an overnight stay prior to administration of investigational product on Day 1 is recommended but not mandatory whereas an overnight stay post-investigational product administration on Day 1 is mandatory.
6. Section 4.3.2 (Clinical Laboratory Tests): Corrected a typographical error by changing the abbreviation for total bilirubin from “TLB” to “TBL”.
7. Section 4.5.1.5 (Preparation of Intravenous Dose): Added sub-headings to clearly differentiate between the MEDI4920 and placebo dose preparation steps; relocated the following sentence “A vial should be used only one time to prepare a single dose” to the MEDI4920 sub-section for clarification as no vials are used for the placebo treatment.

## Protocol Amendment 1, 05Apr2016

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

1. Protocol Synopsis, Section 2.2.1 (Primary Endpoints): Revised wording for AESIs to be consistent with the standard potential risks language used in other clinical programs in MedImmune/AstraZeneca and in other MEDI4920 regulatory documents; added additional language for serious and/or opportunistic infections to clarify that the evaluations are not limited to just VZ, HSV, EBV, EMV, and TB. These changes will not affect the actual endpoints that are planned to be evaluated in the study or the safety monitoring of these events.
2. Section 1.6 (Potential Risks): Revised wording pertaining to the potential risks associated with MEDI4920 for consistency with the aforementioned changes in the AESI language; based on recommendations from the United States Food and Drug Administration (US FDA), the language pertaining to thromboembolic events was modified by adding the phrase "or suspected" such that dose escalation will be suspended even in the case of a suspected thromboembolic event, until additional data allow an informed diagnosis of the event to be made.
3. Section 3.1.1 (Overview); Section 6.2 (Monitoring of the Study): Changed the term "study drug" to "investigational product" for consistency with wording in the protocol.
4. Section 3.1.3 (Dose Escalation and Cohort Progression): Based on recommendations from the US FDA, the language in the first dose escalation criterion was modified such that dose escalation would be suspended even in the case of a suspected thromboembolic event; additional language regarding the use of a diagnosis algorithm for determining a likely thromboembolic event was added to the first criterion; modified the second dose escalation criterion such that dose escalation would be suspended if 2 subjects (instead of 3) dosed with MEDI4920 in a single cohort experiences either a Grade 3 or higher TEAE of the same type or any SAE.
5. Section 4.1.6 (Discontinuation of Investigational Product): Revised the language pertaining to anaphylaxis/serious hypersensitivity reactions, serious/opportunistic infections, and thromboembolic events for consistency with the aforementioned changes.
6. Section 4.2.2 (Treatment Period); Table 4.2.2-1: Modified wording in the text and table note to clarify that all laboratory sample collections and assessments on dosing day "must" (instead of "should") be performed at predose, unless specified otherwise.
7. Section 5.3 (Definition of Adverse Events of Special Interest): Clarified statement regarding follow-up for AESIs: indicated that clinical monitoring of AESIs will be performed under the instructions of the "Safety Handling Plan", instead of "Medical Monitoring Plan" and that AESIs will not be reported in detail in the eCRF, as stated in the original protocol; revised wording for AESIs to harmonize it with standard language used in other clinical programs in MedImmune/AstraZeneca and for consistency with the changes mentioned above.
8. Section 8 (References): Based on the changes in the amendment per recommendations from the US FDA, an additional reference was added to support the algorithm for diagnosing a DVT/PE event.
9. Appendix 4; Section 10.4.2.3: (Identification of Potential Hy's Law Cases); Section 10.4.4 (Review and Assessment of Potential Hy's Law Cases): Removed the laboratory eCRF as one of the types of documents in which laboratory data are entered as it was included in error, and replaced it with the correct document, "Medical Monitoring Plan".

10. Appendix 5; Section 10.5 (Diagnosis of a Potential Thromboembolic Event): Based on the changes in the amendment per recommendations from the US FDA, an additional Appendix was added to describe in detail the algorithm that will be used to determine the likelihood of a DVT/PE event.

# 10 APPENDICES

## 10.1 Appendix 1 - Signatures

## Sponsor Signature(s)

A Phase 1b Randomized, Double-blind, Placebo-controlled Multiple-ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, Pharmacodynamics, and Clinical Response of MEDI4920 in Subjects with Adult-onset Rheumatoid Arthritis

I agree to the terms of this protocol.

Signature and date: electronic signature appended

Jorn Drappa, MD, Ph.D., PPD, Clinical Development

PPD

One MedImmune Way, Gaithersburg, MD, 20878, USA

Telephone number: PPD

## Signature of Principal Investigator

A Phase 1b Randomized, Double-blind, Placebo-controlled Multiple-ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, Pharmacodynamics, and Clinical Response of MEDI4920 in Subjects with Adult-onset Rheumatoid Arthritis

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

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

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available)_____

## 10.2 Appendix 2 - Additional Safety Guidance

### Further Guidance on the Definition of a Serious Adverse Event

### Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from an AE as it occurred or it is suspected that use or continued use of the investigational product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

### Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

### Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

### Assessment of Severity

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

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

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

## Assessment of Relationship

### Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational product.

- Did the subject actually receive the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology) or products of the same pharmacological class, OR could the AE be anticipated from its pharmacological properties? Is this event frequently observed in the study population regardless of treatment?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? MedImmune would not normally recommend or support a re-challenge.
- Laboratory tests. Did a specific laboratory investigation (if performed) confirm the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

If available information describing the event and the circumstances is insufficient to make a definitive assessment of causal association the nature of AE, and likelihood of this event occurring in the study population should be taken into account (eg, events not typically seen in the study population are more likely to lack an alternative explanation).

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any de-challenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism? Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as "no reasonable possibility".

## Relationship to Protocol Procedures

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

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

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

## 10.3 Appendix 3 - National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

NIAIDs and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   c. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

## 10.4 Appendix 4 - Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

### 10.4.1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report cases of HL. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential HL (PHL) criteria at any point during the study.

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational product.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

### 10.4.2 Definitions

#### 10.4.2.1 Potential Hy's Law

AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN at any point during the study following the start of investigational product irrespective of an increase in ALP.

#### 10.4.2.2 Hy's Law

AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

#### 10.4.2.3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to sponsor study representative).

The investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the investigator will:

- Notify the sponsor study representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Notify the sponsor study representative
- Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits

### 10.4.3 Follow-up

#### 10.4.3.1 Potential Hy's Law Criteria Not Met

If the subject does not meet PHL criteria the investigator will:

- Inform the study representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the study protocol.

#### 10.4.3.2 Potential Hy's Law Criteria Met

If the subject does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment
- Notify the sponsor study representative who will then inform the study team

The medical monitor contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor. This includes deciding which tests available in the HL laboratory kit should be used.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

### 10.4.4 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the medical monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the investigational product. The medical monitor and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is not an AE, record the alternative explanation according to the Medical Monitoring Plan
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the sponsor's standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Report an SAE (report term 'Hy's Law') according to sponsor's standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

### 10.4.5 Actions Required When Potential Hy's Law Criteria Are Met Before and After Starting Study Treatment

This section is applicable to subjects with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met the investigator will:

- Determine if there has been a significant change in the subjects' condition compared with the last visit where PHL criteria were met
  - If there is no significant change no action is required
  - If there is a significant change, notify the study representative, who will inform the central study team, then follow the subsequent process described in Section 10.4.3.2

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

### 10.4.6 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment and has already met PHL criteria at a previous on-study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection, or liver disease, or did the subject meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 10.4.5?

If No: Follow the process described in 10.4.3.1

If Yes: Determine if there has been a significant change in the subject's condition compared with when PHL criteria were previously met:

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 10.4.3.2

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of

whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

### 10.4.7 References

The United States Food and Drug Administration Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

## 10.5 Appendix 5 – Diagnosis of a Potential Thromboembolic Event

### 10.5.1 Clinical Probability Score of Deep Vein Thrombosis - Wells Criteria

| DVT: Wells | |
|---|---|
| **Variable** | **Points** |
| Active cancer (treatment ongoing or within previous 6 mo or palliative) | 1 |
| Paralysis, paresis, or recent plaster immobilization of the lower extremities | 1 |
| Recently bedridden for more than 3 d or major surgery within 4 wk | 1 |
| Localized tenderness along distribution of the deep venous system | 1 |
| Entire leg swollen | 1 |
| Calf swelling by more than 3 cm compared with asymptomatic leg (measured 10 cm below tibial tuberosity) | 1 |
| Pitting edema (greater in the symptomatic leg) | 1 |
| Collateral superficial veins (nonvaricose) | 1 |
| Past history of DVT | 1 |
| Alternative diagnosis as likely or greater than that of DVT | −2 |

d = days; DVT = deep vein thrombosis; mo = months; wk = weeks
Score ≤ 1 = DVT is clinically unlikely; Score ≥ 2 = DVT is clinically likely

#### Algorithm for Suspected Deep Vein Thrombosis

In every case of a clinically suspected deep vein thrombosis (DVT), the clinical probability score must be calculated using by the aforementioned Wells criteria and a D-dimer test must be performed.

- If clinical probability shows “DVT unlikely” (ie, score ≤ 1), and D-dimer value is ≤ ULN, DVT is excluded.
- If clinical probability shows “DVT unlikely” (ie, score ≤ 1), and D-dimer value is > ULN, compression ultrasound will be performed.
  - If ultrasound shows no abnormal changes, DVT is excluded.
  - If ultrasound shows abnormal changes, compatible with thrombosis, DVT is confirmed.
  - If ultrasound is unavailable/equivocal and D-dimer is only increased at the time of event, DVT is considered “likely”.
- If clinical probability shows “DVT likely” (ie, score ≥ 2), compression ultrasound will be performed irrespective the D-dimer value.
  - If ultrasound shows no abnormal changes, ultrasound should be repeated within 7 days; if ultrasound again shows no abnormal changes, DVT is excluded.

- If ultrasound shows abnormal changes compatible with thrombosis, DVT is confirmed.
- If ultrasound is unavailable or equivocal, DVT is considered "likely".

- Each situation that cannot be adjudicated using the algorithm above will be considered as "DVT likely" and dose escalation will be suspended.

### 10.5.2 Clinical Probability Score of Pulmonary Embolism - Wells Criteria

**PE: Wells**

| Variable | Points |
|---|---|
| Signs or symptoms of DVT | 3 |
| Alternative diagnosis is less likely than PE | 3 |
| Heart rate > 100 bpm | 1.5 |
| Immobilization/surgery in previous 4 wk | 1.5 |
| Prior history of DVT or PE | 1.5 |
| Hemoptysis | 1 |
| Active cancer | 1 |

bpm = beats per minute; DVT = deep vein thrombosis; PE = pulmonary embolism; wk = week
Score ≤ 4 = PE is clinically unlikely; Score ≥ 4 = PE is clinically likely

### Algorithm for Suspected Pulmonary Embolism:

In every case of suspected pulmonary embolism (PE), clinical probability score must be calculated using by the aforementioned Wells criteria and a D-dimer test must be performed.

- If clinical probability shows "PE unlikely" (ie, score ≤ 4), and D-Dimer value is ≤ ULN, PE is excluded.
- If clinical probability shows "PE likely" (ie, score ≥ 4) or D-dimer value is > ULN, chest X-Ray will be performed.
  - If chest X-ray is normal, a ventilation-perfusion (V/Q) scan will be performed.
  - If chest X-Ray is abnormal, computerized tomographic pulmonary angiography (CTPA) will be considered.
  - If V/Q scan or CTPA are not available or equivocal, PE is considered "likely" unless clinical probability shows "PE unlikely" and D-dimer is > ULN at previous time points during the study, including at baseline.
- Each situation that cannot be adjudicated using the algorithm above will be considered as "PE likely" and dose escalation will be suspended.

Adapted from Wells P and Anderson D. The diagnosis and treatment of venous thromboembolism. Hematology Am Soc Hematol Educ Program. 2013;2013:457-63.

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|---|---|
| **Document Name:** | protocol-d5100c00002-amendment-3-clean |
| **Document Title:** | protocol-d5100c00002-amendment-3-clean |
| **Document ID:** | Doc ID-003702578 |
| **Version Label:** | 1.0<br>Approved<br>CURRENT<br>LATEST |

| **Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)** | **Signed By** | **Meaning of Signature** |
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| 02-Oct-2017 08:56 GMT+0100 | PPD | Biostatistics Approval |
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| 02-Oct-2017 20:16 GMT+0100 | PPD | Nonclinical Scientist Approval |
| 05-Oct-2017 17:57 GMT+0100 | Jorn Drappa | Clinical Development Approval |
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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.