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CLINICAL STUDY PROTOCOL

A prospective, open-label, single center abatacept in IgG4-Related Disease 10-patient proof-of-concept study

BMS Protocol No.:	IM101-744
Trial Registration Number/EUDRACT No.:	
NCT03669861	
Test Product:	Abatacept
Indication:	IgG4-Related Disease
Sponsor:	Massachusetts General Hospital
Development Phase:	Phase 2
Principal Investigator:	John H. Stone, MD, MPH
	JHStone@mgh.harvard.edu
Date of the Protocol:	October 28, 2018
Version of the Protocol:	3.1

PROTOCOL SYNOPSIS

Protocol Title:	A prospective, open-label, single center abatacept in IgG4-Related Disease 10-patient proof-of-concept study
Protocol Short	Abatacept in IgG4-Related Disease: A 10-patient proof-of-concept study
Study Number:	BMS Protocol No.: IM101-744
Investigational	Abatacept
Development	Phase 2
Indication	IgG4-Related Disease (IgG4-RD)
Sponsor:	Massachusetts General Hospital
Coordinating Investigator:	Dr. John H. Stone, Harvard, Massachusetts General Hospital
Study Center(s):	Single Center: Massachusetts General Hospital
Study Objectives:	**Primary Objective** • To assess the effect of weekly subcutaneous (SC) administration of abatacept on complete remission of IgG4-RD **Secondary Objectives** • To assess the effect of abatacept on disease response at 4, 12 and 24 weeks and complete remission at 36 weeks • To assess the effect of abatacept on time to disease remission (IgG4-RD RI = 0), remission rates, number of disease flares per subject over time • To assess the effect of abatacept on physician global assessment (PGA), Symptom Severity Index, and cumulative corticosteroid doses • To assess the effect of abatacept on serum immunoglobulin levels, IgG4 subclass concentrations, IgE levels, eosinophils, and serum C3 and C4 levels at 4, 12, 24 and 36 weeks **Exploratory Objectives** To assess the effect of abatacept on CD4+ T cells and B cell subsets, specifically: - CD4+ cytotoxic T lymphocytes - CD8+ cytotoxic T lymphocytes - CD4+ T follicular helper cells - CD4+ peripheral helper T cells - Plasmablasts - Activated B cells

Study Design:	This is a Phase 2, single center, proof of concept clinical trial in subjects with active IgG4-RD. Approximately 10 subjects with active IgG4-RD will be enrolled into this study. Subjects will receive weekly subcutaneous doses of abatacept (125mg) for 24 doses. Subjects who are on prednisone at baseline will begin an investigator-directed corticosteroid taper designed to discontinue prednisone not later than 8 weeks after the baseline visit.
Investigational Medicinal Product(s); IMP, Dose and Route of	Dose and route of administration: abatacept (125mg) will be given by SC injection every 7 days for up to 24 doses (24 weeks).
Reference	None
Number of Subjects Planned:	Approximately 10 subjects with active IgG4-RD
Diagnosis and Main Criteria for Inclusion:	Male and female subjects age 18 or older who fulfill the ACR/EULAR 2018 Classification Criteria for IgG4-RD with a minimum IgG4-RD Responder Index score of 2
Study Duration:	After screening and enrollment, eligible subjects will receive an initial subcutaneous dose of abatacept (125mg) followed by weekly subcutaneous doses of abatacept (125mg) for a total of up to 24 doses (24 weeks). If subjects are on prednisone at baseline, they will begin an investigator-directed corticosteroid taper designed to discontinue prednisone not later than 8 weeks after the baseline visit. Subjects will be followed on study for 12 weeks following the last dose for a total study period of up to 36 weeks.
Inclusion Criteria:	Subjects who meet the following criteria will be considered eligible to participate in the clinical study if they: 1. Are male or female 18 years of age or older 2. Meet the ACR/EULAR 2018 Classification Criteria for IgG4-RD (see appendix G) 3. Have active disease based on an IgG4-RD RI ≥2 at screening with disease manifestation in at least one organ system excluding lymph nodes at screening 4. May or may not have received prior IgG4-RD therapy 5. Must be willing to taper off any systemic corticosteroid therapy within 8 weeks of first dose of trial drug. 6. Must be able and willing to discontinue any immunosuppressive agent at screening (e.g. methotrexate, mycophenolate mofetil, 6-mercaptopurine, tacrolimus, cyclophosphamide or azathioprine). 7. No history of severe allergic reactions to monoclonal antibodies. 8. Are able and willing to complete the entire study per the study schedule. 9. Are willing to forego other forms of experimental treatment during the study. 10. can provide written informed consent.

Exclusion Criteria:	Subjects who meet one or more of the following criteria will not be considered eligible to participate in the clinical study: 1. History or evidence of a clinically unstable/uncontrolled disorder, condition or disease (including but not limited to cardiopulmonary, oncologic, renal, hepatic, metabolic, hematologic or psychiatric) other than IgG4-RD that, in the opinion of the Investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures or completion. 2. Malignancy within 5 years (except successfully treated in situ cervical cancer, resected squamous cell or basal cell carcinoma of the skin, or prostate cancer with no recurrence ≥3 years following prostatectomy). 3. Liver disease: Acute or chronic non-IgG4-related liver disease deemed sufficiently severe to impair their ability to participate in the trial. 4. Uncontrolled disease: evidence of another uncontrolled condition, including drug and alcohol abuse, which could interfere with participation in the trial according to the protocol. 5. Presence of recurrent or chronic infections, defined as ≥3 infections requiring antimicrobials over the past 6 months prior to screening. 6. Active infection requiring hospitalization or treatment with parenteral antimicrobials within the 30 days prior to randomization. 7. Prior use of rituximab (or other B cell depleting agents) within 6 months of enrollment unless B cells have been demonstrated to have repopulated. 8. Use of any investigational agent within 5 half-lives of the agent (or 6 months if the half-life is unknown) prior to enrollment. 9. White blood cell count < 2.5 x 103/µL. 10. Absolute neutrophil count (ANC) < 1.0 x 103/µL. 11. IgG4-related renal disease with serum creatinine >2.0 mg/dL. 12. Hemoglobin < 10 g/dL. 13. Platelet count < 75 x 109/L. 14. Known positive result for HIV I or II antibody, hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody. 15. Has received live vaccines within 4 weeks' ok enrollment. 16. Inability to communicate reliably with the investigator. 17. Patient is pregnant or breast feeding or planning to become pregnant while enrolled in the study, up to EOS visit. 18. Positive pregnancy test at screening or during the study. 19. Subjects of childbearing potential who do not agree to use medically acceptable methods of contraception. 20. Known or suspected sensitivity to mammalian cell-derived products or any components of the study drug. 21. History of alcohol and/or substance abuse within 12 months prior to screening. 22. Unable or unwilling to partake in follow-up assessments or required protocol procedures.

Study Procedures:	After obtaining informed consent, all screening procedures and tests establishing eligibility will be performed on the initial screening visit. Subjects determined to be eligible at screening will receive an initial subcutaneous dose of abatacept (125mg), which will be continued weekly for a total of up to 24 doses (24 weeks). Steroid therapy must be tapered off and discontinued over 8-week period (taper must be completed no later than week 8). Should patients be deemed to have worsening disease or failing therapy at 4 weeks then a trial of steroids can be considered. Subjects will return on weeks 1, 2, 4, 8, 12, 16, 20, and 24 while on treatment for their injections, and for the scheduled safety and disease response assessments. Subjects will be allowed to self-administer their injections at home. The full treatment period is 24 doses given weekly for 24 weeks. Subjects who are not able to be tapered off corticosteroids or who require reinstitution of corticosteroid therapy at any time during the study will be counted as treatment failures but may continue study. Should the IgG4-RD responder index fail to improve by 8 weeks or who develop new organ INVOLVEMENT by week 4 will be deemed a treatment failure, patient's will be deemed treatment failure and can begin corticosteroid or alternative immunosuppressive therapy at the Investigator's discretion. Those who require rituximab or who require addition of other oral immunosuppressive will be counted as treatment failures and will terminate the study. All subjects completing the treatment period will have follow up visits off protocolized treatment at 28 and 36 weeks. All AE(s) (including serious AEs and deaths) and use of concomitant medication information will be collected throughout the study from screening through study termination. Subjects developing treatment-emergent AEs or clinically significant safety lab abnormalities will be followed until resolution or until stabilization of the AEs/abnormalities.
Criteria for Evaluation:	**Disease Activity:** The following disease activity parameters will be recorded at scheduled intervals throughout the study: • IgG4-RD RI score • Physician Global Assessment of Disease Activity (Visual Activity Score) • Symptom Severity Index • Glucocorticoid Toxicity Index

Safety:

The following safety parameters will be recorded at regular intervals during the study:

- Adverse events
- Physical examinations
- Vital signs (supine blood pressure [BP], heart rate [HR], oral body temperature, respiratory rate [RR])
- Clinical laboratory testing (clinical chemistry, hematology, serum immunoglobulins, serum IgG4 subclasses, complements, and urinalysis)
- Concomitant medications

Serologic Indicators of Response:

- Immunoglobulin levels
- IgG4 subclasses
- IgE
- Eosinophil levels
- C3 and C4 levels

Correlative Studies:

Additional mechanistic studies will be conducted through the MGH NIH-funded Autoimmunity Center of Excellence for IgG4-RD, which has established translational collaborations between the MGH Clinic and the Ragon Institute of Harvard, MGH, and MIT (the laboratory of Dr. Shiv Pillai).

Briefly, peripheral blood mononuclear cells (PBMCs) and plasma will be isolated and frozen from each subject at weeks 0, 1, 4, 12 and 24 corresponding with clinical blood draws. PBMCs and plasma will be stored in liquid nitrogen for preservation. The following experiments will be carried out in batches of 10 patient time points per experiment:

1. Flow cytometric quantification of plasmablasts, activated B cells, terminally differentiated CD4+ cytotoxic T cells (CD4+CTLs), terminally differentiated CD8+ cytotoxic T cells (CD8+CTLs), activated follicular helper T (TFH) cells and peripheral helper T (TPH) cells. Terminal differentiation will be defined by the loss of CD28 surface expression and gain of CD57 surface expression within the respective effector (CD45RA-CCR7-) T cell population. These cell populations will be assessed at weeks 0, 1, 4, 12 and 24 to determine the treatment effect on the absolute numbers and proportions of these cell types.
2. Quantified cell populations will be analyzed for correlation with one another, disease activity, plasma IgG4 levels and clinical responsiveness to abatacept.
3. From 5 of the enrolled subjects with known expansions of the respective cell type and clinical responsiveness to abatacept, terminally differentiated CD4+CTLs, terminally differentiated CD8+CTLs and activated B cells will be sorted by FACS at weeks 0, 12 and 24. RNA will be isolated to undergo RT-PCR amplification of the TCR-β/IgH, respectively. Next-Generation Sequencing will be used to define the diversity of the TCR/BCR repertoire longitudinally to ascertain how abatacept may impact clonality.

Endpoints:	Primary: - Complete remission at 36 weeks. Complete remission is defined as an IgG4-RD Responder Index Score of 0 and a prednisone dose of 0 mg/day beyond week 4 and no flare since beginning treatment. Secondary: - Disease response at 4, 12, 24, and 36 weeks. Disease response will be defined at 6 months as: 1) improvement of ≥ 1 point in the IgG4-RD RI score over baseline; 2) no glucocorticoid use following the week 4 visit; 3) no disease flares, as assessed by the IgG4-RD RI. Disease flare will be defined as recurrence of disease activity or demonstration of a disease exacerbation such that additional therapy beyond the trial protocol is indicated. Such additional therapy may include glucocorticoids or alternative immunosuppressive agents. - Complete remission at 36 weeks. - Time to disease remission (IgG4-RD RI = 0) - Remission rates - Number of disease flares per subject over time - Cumulative corticosteroid doses and Glucocorticoid Toxicity Index - Physician Global Assessment (PGA). A PGA consisting of a 10-centimeter visual analog scale is collected at each patient visit. Only active disease (as opposed to damage) is considered in the scoring of the PGA. - Symptom Severity Index - Serum immunoglobulin levels, IgG4 subclass concentrations, IgE levels, eosinophils, and serum C3 and C4 levels. Secondary Safety: - Safety: Incidence of adverse events - Safety: Incidence of corticosteroid-related adverse events - Composite of vital signs assessment as a measure of safety - Composite of clinical laboratory tests assessment as a measure of safety
Statistical Methods:	**Analysis Populations** • The primary analysis will be an intention-to-treat analysis in which the proportion of subjects achieving the primary outcome is assessed. **Primary efficacy analysis:** The primary analysis will be based on the proportion of subjects achieving the primary outcome.

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3 INTRODUCTION AND STUDY BACKGROUND

3.1 Abatacept

Abatacept is a selective costimulation modulator that consists of a fusion protein of human IgG1 and the extracellular domain of CTLA4, which inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This blocks the ability of antigen presenting cells to deliver the co-stimulatory signal needed to activate T cells. It is currently indicated for use in adult rheumatoid arthritis, juvenile idiopathic arthritis. It is not currently indicated for use in IgG4-RD.

3.2 IgG4-Related Disease

IgG4-RD is a chronic fibro-inflammatory condition that can affect virtually every organ system including the pancreas, biliary tract, salivary and lacrimal glands, orbits, lungs, kidneys, meninges, pituitary gland, prostate and thyroid among others. It may also involve the retroperitoneum. This multi-organ immune-mediated condition was previously regarded as a group of isolated single organ diseases but has recently been recognized as a unifying entity linked by common histopathological and immunohistochemical features. The histopathological features include a dense lymphoplasmacytic infiltrate consisting of T cells and IgG4+ plasma cells, storiform fibrosis and obliterative phlebitis. Immunoperoxidase staining of affected tissues generally demonstrates a ratio of ≥40% IgG4/IgG+ plasma cells (Deshpande et al. 2012). Serum IgG4 concentrations are elevated in at least 50-60% of cases before the initiation of treatment (Wallace et al. 2015).

The frequency of IgG4-RD is unknown in most countries other than Japan, where it is thought to affect at least 8000 individuals (Uchida et al. 2012). However, because this disease has only been recognized and described in the last 10 years, recognition of the disease is growing in other parts of the world, including the US and Europe. IgG4-RD appears to have a modest predilection for affecting men more often than women and tends to afflict middle-aged to elderly individuals. Although IgG4-RD can affect a single organ at presentation, it is not uncommon for patients to present with or develop multi-organ disease. As the disease progresses, additional organs develop lesions and the cellular inflammation characterizing early disease moves toward a more fibrotic stage, causing major tissue damage, dysfunction and ultimately organ failure.

It is unclear whether IgG4 itself is involved in the pathogenesis of the disease. T cells comprise the major inflammatory cell in this disease. In fact, two CD4+ T cells are believed to play crucial roles in this condition: 1) A CD4+ cytotoxic T lymphocyte bearing SLAMF7 on its surface, secreting profibrotic cytokines IL-1B and TGF-B1 and IFN-gamma, as well as cytotoxic molecules such as perforin and granzyme B. 2) A CD4+ T follicular helper cell, known to drive the class switch within lymph nodes and extra-nodal germinal centers (Mattoo et al. 2016)

Additionally, several B cell subsets have recently been described by flow cytometry to be elevated in the peripheral blood of IgG4-RD patients. Circulating IgG4+ plasmablasts (CD19lowCD38+CD20-CD27+) have been shown to be elevated in active disease as compared to individuals with other diseases and normal controls, even in IgG4-RD patients with normal IgG4 serum levels. Total plasmablasts can therefore be utilized as a diagnostic feature of IgG4-RD (Wallace et al. 2014, Mattoo et al. 2014).

This study will enroll male and female subjects age 18 or older who fulfill the ACR/EULAR 2018 Classification Criteria for IgG4-RD with a minimum IgG4-RD Responder Index score of 2 Subjects are not required to have failed prior therapy for their disease to be eligible for this study.

3.3 Current Treatment of IgG4-RD and Rationale for the Clinical Study

IgG4-RD is currently incurable. The goals of treatment are to reduce inflammation and swelling in the organs, prevent or reverse (if possible) fibrosis and increase glandular secretion. Aggressive treatment is warranted to prevent organ failure when vital organs are involved. For example, cholangitis due to IgG4-RD can lead to hepatic failure, IgG4-related (type 2) autoimmune pancreatitis can lead to failure of either or both the endocrine and exocrine pancreas, and IgG4-related aortitis can lead to aneurysms and/or aortic dissection. At the present time, glucocorticoids at daily doses of 0.6 mg/kg daily for 2 to **4 8** weeks followed by tapering to low doses (or discontinuing altogether) over 3-6 months is the first line of therapy. Although this approach is effective initially in most patients, the relapse rate upon tapering or discontinuation is high (Khosroshahi et al. 2015). In addition, the long term use of glucocorticoids in older populations such as that affected by IgG4-RD can lead to many untoward side effects such as osteoporosis, high blood pressure and diabetes. Immunosuppressive medications such as azathioprine, mycophenolate mofetil and methotrexate have been used as glucocorticoid-sparing agents, with no clear indication of efficacy (Stone et al. 2012, Yamamoto et al. 2014, Khosroshahi et al. 2015). A high disease response rate has been observed in one small open-label trial with rituximab, utilizing an IgG4- RD Responder Index (RI) as a measure of disease response (Khosroshahi et al. 2010, Carruthers et al. 2015). More recently, a single case report from Japan has described dramatic efficacy in a patient with multi-organ IgG4-RD whose symptoms and signs of disease were refractory to B cell depletion with rituximab (Yamamoto et al. 2016). A strategy targeting CD4+ T cells may indeed be successful in controlling IgG4-RD. We seek to confirm this hypothesis in a prospective, single center, open-label, 10-patient proof-of-concept study. Subjects will receive weekly subcutaneous doses of abatacept (125mg) for 25 doses.

3.4 Dose Rationale

The dose abatacept 125mg subcutaneously weekly is currently approved for use in adult rheumatoid arthritis, juvenile idiopathic arthritis

3.5 Potential Risks

Based on experience in human studies to date and class effects of immunomodulating medications, subjects receiving SC abatacept may be at risk for adverse events.

The following adverse effects are based on abatacept administered intravenously in patients with active RA in placebo-controlled studies (1955 patients with ORENCIA, 989 with placebo). The subcutaneous data is based on a randomized, double-blind, double-dummy, non-inferiority study that compared the efficacy and safety of abatacept administered subcutaneously (SC) and intravenously (IV) in 1457 subjects with rheumatoid arthritis being treated with background methotrexate. In patient's receiving intravenous abatacept for active RA in placebo-controlled trials, the most common adverse events reported in greater than ten percent of patients were headache, upper respiratory infection, nasopharyngitis and nausea. Adverse events that occurred in at least 3% of patients and at least 1% more frequently in abatacept-treated patients than placebo-treated patients were headache, nasopharyngitis,

dizziness, cough, back pain, hypertension, dyspepsia, urinary tract infection, rash, and pain in extremity. The most serious adverse events were infection and malignancy.

I. Infections

Infections were reported in 54% of patients receiving abatacept and 48% of those receiving placebo. The most common infections were upper respiratory, nasopharyngitis, sinusitis, urinary tract infection, influenza, and bronchitis. Other infections reported in fewer than 5% of patients were rhinitis, herpes simplex, and pneumonia. The most common serious infections reported were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis.

II. Malignancies

In placebo-controlled portions of clinical trials, the frequency of malignancies are similar in the two groups with 1.3% in those receiving abatacept and 1.1% on placebo. However, more cases of lung cancer were observed in abatacept-treated patients (4, 0.2%) than placebo-treated patients (0). In the cumulative abatacept clinical trials (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the National Cancer Institute's Surveillance, Epidemiology, and End Results Database. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers.

III. Hypersensitivity Reactions

Anaphylaxis was observed in patients dosed with ORENCIA administered intravenously in controlled and open-label clinical trials, and the occurrence was rare (<0.1%). Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea that occurred within 24 hours of ORENCIA infusion, were uncommon (<1%).

IV. Adverse Reactions in Patients with COPD

COPD patients treated with ORENCIA developed adverse events more frequently than those treated with placebo (97% vs 88%, respectively). Respiratory disorders occurred more frequently in ORENCIA-treated patients compared to placebo-treated patients (43% vs 24%, respectively) including COPD exacerbation, cough, rhonchi, and dyspnea. A greater percentage of ORENCIA-treated patients developed a serious adverse event compared to placebo-treated patients (27% vs 6%), including COPD exacerbation (3 of 37 patients [8%]) and pneumonia (1 of 37 patients [3%]).

V. Injection Site Reactions in Adult RA Patients Treated with Subcutaneous Orencia

The overall frequency of injection site reactions was 2.6% (19/736) and 2.5% (18/721) for the subcutaneous abatacept group and the intravenous abatacept group (subcutaneous placebo), respectively. All these injection site reactions (including hematoma, pruritus, and erythema) were mild (83%) to moderate (17%) in severity, and none necessitated drug discontinuation.

VI. Immunogenicity in Adult RA Patients Treated with Subcutaneous ORENCIA

The overall immunogenicity frequency to abatacept was 1.1% (8/725) and 2.3% (16/710) for the subcutaneous and intravenous groups, respectively. There was no correlation of immunogenicity with effects on pharmacokinetics, safety, or efficacy.

VII. Immunogenicity and Safety of Subcutaneous ORENCIA Administration as Monotherapy without an Intravenous Loading Dose

In a study that was conducted to determine the effect of monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an intravenous load in 100 RA patients, who had not previously received abatacept or other CTLA4Ig, who received either subcutaneous ORENCIA plus methotrexate (n=51) or subcutaneous ORENCIA monotherapy (n=49). No patients in either group developed anti-product antibodies after 4 months of treatment. The safety observed in this study was consistent with that observed in the other subcutaneous studies.

VIII. Immunogenicity and Safety of Subcutaneous ORENCIA upon Withdrawal (Three Months) and Restart of Treatment

In a study conducted to investigate the effect of withdrawal (three months) and restart of ORENCIA subcutaneous treatment on immunogenicity in RA patients treated concomitantly with methotrexate, one hundred sixty-seven patients were enrolled in the first 3-month treatment period and responders (n=120) were randomized to either subcutaneous ORENCIA or placebo for the second 3-month period (withdrawal period). Patients from this period then received open-label ORENCIA treatment in the final 3-month period of the study (period 3). At the end of the withdrawal period, 0/38 patients who continued to receive subcutaneous ORENCIA developed anti-product antibodies compared to 7/73 (9.6%) of patients who had subcutaneous ORENCIA withdrawn during this period. Half of the patients receiving subcutaneous placebo during the withdrawal period received a single intravenous infusion of ORENCIA at the start of period 3 and half received intravenous placebo. At the end of period 3, when all patients again received subcutaneous ORENCIA, the immunogenicity rates were 1/38 (2.6%) in the group receiving subcutaneous ORENCIA throughout, and 2/73 (2.7%) in the group that had received placebo during the withdrawal period. Upon reinitiating therapy, there were no injection reactions and no differences in response to therapy in patients who were withdrawn from subcutaneous therapy for up to 3 months relative to those who remained on subcutaneous therapy, whether therapy was reintroduced with or without an intravenous loading dose. The safety observed in this study was consistent with that observed in the other studies.

3.6 Conclusion and Ethical Considerations

The design of the proposed trial contains measures appropriate to the mitigation of risk factors for AEs. Furthermore, frequent safety monitoring is an inherent part of the protocol. In summary, the benefits and risk assessment for the application of abatacept appears favorable and supportive for initiation of the proposed clinical trial.

This study will be performed in the following manner:

- **In accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), WHO and any local directives.**
- **In compliance with the protocol.**

- **The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.**
- **With personnel who are qualified by education, training, and experience to perform their respective tasks and that the study will not use the services of study personnel for whom sanctions have been invoked or where there has been scientific misconduct or fraud**
- **With signed, dated Informed Consent from each of the participants**
- **Investigators/Sponsors must ensure that subjects--or, in those situations where consent cannot be given by subjects, their legally acceptable representatives--are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. The approved informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.**
- **Include relevant safety information regarding dose/schedule of IP and any other drugs/procedures**
- **BMS and health authority to have direct access to study records BMS will provide the study drug and funding for this study.**

4 STUDY OBJECTIVES

4.1 Primary Objectives

- To evaluate the effect of weekly subcutaneous (SC) administration of abatacept on complete remission of IgG4-RD at 24 weeks

4.2 Secondary Objectives

- To evaluate the effect of abatacept on disease response at 4, 12 and 24 weeks and complete remission at 36 weeks
- To evaluate the effect of abatacept on time to disease remission (IgG4-RD RI = 0), remission rates, number of disease flares per subject over time
- To evaluate the effect of abatacept on physician global assessment (PGA), Symptom Severity Index, and cumulative corticosteroid doses
- To evaluate the effect of abatacept on serum immunoglobulin levels, IgG4 subclass concentrations, IgE levels, eosinophils, and serum C3 and C4 levels at 4, 12, 24 and 36 weeks

4.3 Exploratory Objectives

To evaluate the effect of abatacept on CD4+ T cells and B cell subsets, specifically:

- CD4+ cytotoxic T lymphocytes

- CD8+ cytotoxic T lymphocytes

- CD4+ T follicular helper cells

- CD4+ peripheral helper T cells

- Plasmablasts

- Activated B cells

5 INVESTIGATIONAL PLAN

Overall Study Design and Plan

Description

This is a Phase 2, prospective, open-label, single center clinical trial in subjects with active IgG4-RD. Approximately 10 subjects with active IgG4-RD will be enrolled. After screening and enrollment, eligible subjects will receive an initial subcutaneous dose of abatacept (125mg) followed by weekly subcutaneous doses of abatacept (125mg) for a total of up to 24 doses (24 weeks). Subjects will be followed on study for 12 weeks following the last dose for a total study period of up to 36 weeks.

After obtaining informed consent, all screening procedures and tests establishing eligibility will be performed on the initial screening visit. Subjects determined to be eligible at screening will receive an initial subcutaneous dose of abatacept (125mg), which will be continued weekly for a total of up to 24 doses (24 weeks). Steroid therapy must be tapered off and discontinued over a 4 week period (taper must be completed no later than week 4). Should patients be deemed to have worsening disease or failing therapy at 4 weeks then a trial of steroids can be considered.

Subjects will return on weeks 1, 2, 4, 8, 12, 16, 20, and 24 while on treatment for their injections, and for the scheduled safety and disease response assessments. Subjects will be allowed to self-administer their injections at home. The full treatment period is 24 doses given weekly for 24 weeks. Subjects who are not able to be tapered off corticosteroids or who require reinstitution of corticosteroid therapy at any time during the study will be counted as treatment failures but may continue on study. Should the IgG4-RD responder index fail to improve by 8 weeks or who develop new organ involvement by week 4 will be deemed a treatment failure, patient's will be deemed treatment failure and can begin corticosteroid or alternative immunosuppressive therapy at the Investigator's discretion. Those who require rituximab or who require addition of other oral immunosuppressive will be counted as treatment failures and will terminate the study.

All subjects completing the treatment period will have follow up visits off protocolized treatment at 28 and 36 weeks. All AE(s) (including serious AEs and deaths) and use of concomitant medication information will be collected throughout the study from screening through study termination. Subjects developing treatment-emergent AEs or clinically significant safety lab abnormalities will be followed until resolution or until stabilization of the AEs/abnormalities.

Signs and symptoms of IgG4-RD activity will be measured periodically throughout the study using a modification of the IgG4-RD RI (Carruthers et al. 2012, Wallace et al. 2016). The IgG4-RD RI is based on the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (Stone et al. 2001) utilized for the evaluation and licensure of rituximab in ANCA-associated vasculitis (Stone et al. 2010). The IgG4-RD RI is an instrument designed to detect change in disease activity and identify improvements and worsening in the same or

different organ systems and has been used in prior clinical trials to monitor IgG4-RD disease activity (Khosroshahi et al. 2010, Carruthers et al. 2015, Stone et al. 2016).

Assessments will include AE assessment, physical examination, vital signs, clinical laboratory testing (clinical chemistry, hematology, serum immunoglobulins, serum IgG4 subclasses, complements, and urinalysis) and concomitant medications. Additional serologic indicators of response will include immunoglobulin levels, IgG4 subclasses, IgE, Eosinophil levels, C3 and C4 levels.

Additional mechanistic studies will be conducted through the MGH NIH-funded Autoimmunity Center of Excellence for IgG4-RD, which has established translational collaborations between the MGH Clinic and the Ragon Institute of Harvard, MGH, and MIT (the laboratory of Dr. Shiv Pillai).

Briefly, peripheral blood mononuclear cells (PBMCs) and plasma will be isolated and frozen from each subject at weeks 0, 1, 4, 12 and 24 corresponding with clinical blood draws. PBMCs and plasma will be stored in liquid nitrogen for preservation. The following experiments will be carried out in batches of 10 patient time points per experiment:

1. Flow cytometric quantification of plasmablasts, activated B cells, terminally differentiated CD4+ cytotoxic T cells (CD4+CTLs), terminally differentiated CD8+ cytotoxic T cells (CD8+CTLs), activated follicular helper T (TFH) cells and peripheral helper T (TPH) cells. Terminal differentiation will be defined by the loss of CD28 surface expression and gain of CD57 surface expression within the respective effector (CD45RA-CCR7-) T cell population. These cell populations will be assessed at weeks 0, 1, 4, 12 and 24 to determine the treatment effect on the absolute numbers and proportions of these cell types.
2. Quantified cell populations will be analyzed for correlation with one another, disease activity, plasma IgG4 levels and clinical responsiveness to abatacept.
3. From 5 of the enrolled subjects with known expansions of the respective cell type and clinical responsiveness to abatacept, terminally differentiated CD4+CTLs, terminally differentiated CD8+CTLs and activated B cells will be sorted by FACS at weeks 0, 12 and 24. RNA will be isolated to undergo RT-PCR amplification of the TCR-β/IgH, respectively. Next-Generation Sequencing will be used to define the diversity of the TCR/BCR repertoire longitudinally to ascertain how abatacept may impact clonality.

5.1 Schedule of Assessments

The schedule of assessments is presented in table format in the study synopsis

Study Phase	Screening	Treatment														
VISIT NUMBER	1	2			3				4				5			
WEEK	0	1[1]	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed consent	X	X														
Study drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug Instruction		X														
Medical history[2]	X[2]	X[2]			X[2]				X[2]				X[2]			
Physical examination[3]	X[3]	X[3]			X[3]				X[3]				X[3]			
Adverse Event		X			X				X				X			
Record concomitant medications[4]	X	X			X				X				X			
Vital signs[5]	X	X			X				X				X			
CBC w/ differential, platelet count	X	X			X				X				X			
Comprehensive Metabolic Panel (CMP)	X	X			X				X				X			
Urinalysis and Urine protein/creatinine	X	X														
Urine Pregnancy test[7]	X	X			X				X				X			
HBsAg, HBcAb, HCV**Not required if collected 6 months prior to screening	X															
Serum immunoglobulin levels (IgM, IgE, IgG)	X	X														
Serum IgG subclasses	X	X			X				X				X			
C3 and C4	X															
Mechanistic samples	X	X			X								X			
Fasting lipid profile	X	X			X				X				X			
CT chest, abdomen, pelvis[8]	X															
IgG4-RD RI	X	X			X				X				X			
Physician Global Activity VAS	X	X			X				X				X			
Symptom Severity Index	X	X			X				X				X			
Glucocorticoid Toxicity Index	X	X			X				X				X			
SF-36 Health Survey	X	X			X				X				X			

Study Phase											
VISIT NUMBER	**6**				**7**				**8**	**9**	**10/EO**
WEE	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**28**	**36**
Informed consent											
Study drug administration	X	X	X	X	X	X	X	X	X		
Medical history[2]	X				X[2]				X	X[2]	X[2]
Physical examination[3]	X				X[3]				X	X[3]	X[3]
Adverse Event assessment[4]	X				X				X	X	X
Record concomitant medications[4]	X				X				X	X	X
Vital signs[5]	X				X				X	X	X
CBC w/ differential, platelet	X				X				X	X	X
Chemistry Panel	X				X				X	X	X
Urinalysis and Urine protein/creatinine											X
Urine Pregnancy test[7]	X				X				X	X	X
HBsAg, HBcAb, HCV[8]											
Serum immunoglobulin levels (IgM, IgE, IgG)									X		X
IgG subclasses	X				X				X		X
C3 and C4											X
Fasting lipid profile	**X**				**X**				**X**		**X**
Mechanistic samples									X		
IgG4-RD RI	X				X				X		X
Physician Global Activity VAS	X				X				X		X
Symptom Severity Index	X				X				X		X
Glucocorticoid Toxicity Index	X				X				X		X
SF-36 Health Survey	X				X				X		X

[1]The Screening visit (Visit 1) and the Treatment Week 1 (Visit 2) visit could potentially be on the same day

2 Includes prior history and treatment of IgG4-RD

3 Complete physical examinations will be performed at Screening, on Day 1 (could potentially be the same visit) and at EOS. Abbreviated, symptom directed PE will be performed at all other visits. Include height at screening only and weight at visits 1, 2, 4, 8, 12, 16, 20, 24, 28, and EOS.

4 Adverse events and concomitant medications to be collected by site personnel via phone or email.

5 Supine blood pressure and heart rate, body temperature, respiratory rate. Vital sign assessments will be made immediately prior to injection.

6 Urinalysis and urine protein/creatinine ratios, at screening or baseline and EOS, and at each study visit if renal involvement

7 Pregnancy test only for women of child-bearing potential (urine)

7 If the patient has a documented negative result within 60 days before the first dose of abatacept, this item may be omitted

8 All patients will need to have a screening CT chest, abdomen and pelvis with head and/or orbits if there is head and neck or extraocular muscle involvement. If abnormal, it will be repeated at approximately 6 months or earlier based on disease activity.

*Not required if collected 6 months prior to screening visit

5.2 Study Assessments

Screening Visit

The following procedures will be performed:

1. Obtain written informed consent after consent presentation
2. Obtain Medical history
   a) Including demographics
   b) Including history of IgG4-RD
3. Physical examination
4. Record concomitant medication
5. Vital signs including; BP, P, R, T, weight, and height.
   a. Weight will be measured with outerwear and shoes removed
   b. Height will be measured with shoes removed (screening visit only)
   c. Blood pressure and pulse rate obtained after the subject has been supine $\geq$ 5 minutes
6. Adverse Event monitoring (from time of study drug administration)
7. Laboratory tests:
   a. CBC with cell differential and platelets
   b. Chemistry panel
   c. Urinalysis and urine protein/creatinine ratio
   d. Urine pregnancy test (only for woman of child bearing age)
   e. Hepatitis B and C tests (not required if collected 30 days prior to screening visit)
   f. Serum Immunoglobulin levels (IgM, IgE, IgG)
   g. Serum IgG4 subclasses
   h. Complement levels
   i. Fasting lipid profile
   j. Mechanistic samples will be collected from subject at weeks 0, 1, 4, 12 and 24 studies)
8. Imaging tests: CT chest, abdomen, pelvis
9. Physician reported outcomes
   a. IgG4 Responder Index (IgG4-RD RI)
   b. Physician Global Activity VAS
10. Patient reported outcomes
    a. Symptom Severity Index
    b. Glucocorticoid Toxicity Index
    c. SF-36 Health Survey
    d. Patient Global Activity VAS

Baseline Visit: Visit 2 (week 1)

The screening (visit 1) and baseline visit (visit 2) could potentially be combined and completed on the same day

The following procedures will be performed:

1. Verify eligibility criteria.
2. Review general medical and IgG4 history
3. Brief physical examination
4. Record concomitant medication
5. Vital signs including; BP, P, R, T, weight, and height.

a. Weight will be measured with outerwear and shoes removed
b. Blood pressure and pulse rate obtained after the subject has been supine ≥ 5 minutes

6. Adverse Event monitoring
7. Laboratory tests:
   a. CBC with cell differential and platelets
   b. Chemistry panel
   c. Urinalysis and urine protein/creatinine ratio
   d. Urine pregnancy test (only for woman of child bearing age)
   e. Serum Immunoglobulin levels (IgM, IgE, IgG)
   f. Serum IgG4 subclasses
   g. Fasting lipid profile
   h. Mechanistic samples will be collected from subject at weeks 0, 1, 4, 12 and 24 studies)
8. Patient-reported outcomes:
   a. Symptom Severity Index
   b. Glucocorticoid Toxicity Index
   c. SF-36 Health Survey
   d. Patient Global Activity VAS
9. Physician-reported outcomes
   a. Glucocorticoid Toxicity Index
   b. Physician global activity VAS
   c. IgG4-RD RI
10. Study drug administration and teaching
11. Study medication dispense

Visit 3 (week 4)-visit 10 (week 36)

Patients will have visits at Weeks 4, 8, 12, and then every 4 weeks per the schedule of assessments shown in Table 1

1. Brief physical exam including vital signs (Full physical exam at EOS)
2. Assessment of signs and symptoms of IgG4-RD
3. Concomitant Medications review
4. Adverse Events Assessments
5. Assessment of signs and symptoms of IgG4-RD activity
6. Abatacept administration (baseline, w4, w12, w20, w28, w36, w44)
7. Laboratory tests (to be drawn before study product administration). See schedule of events.
   i. Mechanistic samples will be collected from subject at weeks 0, 1, 4, 12 and 24 studies)
8. Patient-reported outcomes (per schedule of events, table 1)
9. Physician reported outcomes (per schedule of events, table 1)
10. Study medication accountability and dispense

Safety follow up visit (if needed)

During the safety follow up the following procedures will be completed

1. Vital signs and Physical exam
2. Concomitant Medications review

3. Adverse Events Assessments
4. Assessment of signs and symptoms of IgG4-RD

5.3 Discussion of Study Design

No therapies for IgG4-RD have been approved by regulatory authorities and thus there are no established study designs for this disease indication. This study design is consistent with the focus of this trial on proof-of-concept and mechanistic studies and will be suitable to achieve this goal based on the strict primary outcome criteria. There is no control group in this proof of concept study. The design will be able to assess whether abatacept can have an effect on disease response as has been shown in a prior case report as discussed above. The design of this trial is appropriate to our current understanding of the potential role of abatacept in IgG4-RD, which is presently too limited to justify a randomized trial. Should patients fail to respond to the study drug abatacept or should they develop end-organ manifestations, they will be able to obtain standard of care glucocorticoid treatment.

A washout period is built into the study protocol. Exclusion criteria include the prior use of rituximab (or other B cell depleting agents) within 6 months of enrollment unless B cells have been demonstrated to have repopulated or the use of any investigational agent within 5 half-lives of the agent (or 6 months if the half-life is unknown) prior to enrollment. This should be sufficient in identifying any adverse effects due to the investigational product abatacept. However, patient's may have been on glucocorticoids during trial entry, but must be willing to taper off of glucocorticoids within ~~4~~ **8** weeks of beginning abatacept. This is necessary in order to sufficiently recruit patients for the study.

The investigational medication abatacept is dosed weekly by subcutaneous route which is consistent with its pharmacokinetic and pharmacodynamic profile. It is approved for the treatment of rheumatoid arthritis at this dosing interval. These medications may be continued indefinitely for control of the disease and any effect should be seen within 24 weeks of treatment.

5.4 Early Termination of the Study

If the Investigator or the Sponsor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. The clinical study may be terminated at the Sponsor's discretion also in the absence of such a finding.
Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study;
- Failure to enroll subjects at the required rate;
- A decision of the Sponsor to suspend or discontinue development of the IMP.

Should the study be terminated, and/or the site closed for whatever reason, all documentation pertaining to the study and IMP must be returned to the Sponsor. Any actions required for assessing or maintaining study subject safety will continue as required, despite termination of the study by the Sponsor.

End-of-Study is defined as completion of the End-of-Study Visit on Week 36.

5.5 Selection of Study Population

Male and female subjects who meet the ACR/EULAR 2018 Classification Criteria for IgG4-RD AND active disease (defined by IgG4-RD RI ≥2 at screening with disease manifestation in at least one organ system excluding lymph nodes at screening). Subjects are not required to have failed prior therapy for their disease to be eligible for this study.

Inclusion Criteria

Subjects who meet the following criteria will be considered eligible to participate in the clinical study if they:

2. Are male or female 18 years of age or older
3. Meet the ACR/EULAR 2018 Classification Criteria for IgG4-RD (see appendix)
4. Have active disease based on an IgG4-RD RI ≥2 at screening with disease manifestation in at least one organ system excluding lymph nodes at screening
5. May or may not have received prior IgG4-RD therapy
6. Must be willing to taper off any systemic corticosteroid therapy within 4 **8** weeks of first dose of trial drug.
7. Must be able and willing to discontinue any immunosuppressive agent at screening (e.g. methotrexate, mycophenolate mofetil, 6-mercaptopurine, tacrolimus, cyclophosphamide or azathioprine).
8. No history of severe allergic reactions to monoclonal antibodies.
9. Are able and willing to complete the entire study according to the study schedule.
10. Are willing to forego other forms of experimental treatment during the study.
11. Are able to provide written informed consent.

Exclusion Criteria

Subjects who meet one or more of the following criteria will not be considered eligible to participate in the clinical study:

1. History or evidence of a clinically unstable/uncontrolled disorder, condition or disease (including but not limited to cardiopulmonary, oncologic, renal, hepatic, metabolic, hematologic or psychiatric) other than IgG4-RD that, in the opinion of the Investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures or completion.
2. Malignancy within 5 years (except successfully treated in situ cervical cancer, resected squamous cell or basal cell carcinoma of the skin, or prostate cancer with no recurrence ≥3 years following prostatectomy).
3. Liver disease: Acute or chronic non-IgG4-related liver disease deemed sufficiently severe to impair their ability to participate in the trial.
4. Uncontrolled disease: evidence of another uncontrolled condition, including drug and alcohol abuse, which could interfere with participation in the trial according to the protocol.
5. Presence of recurrent or chronic infections, defined as ≥3 infections requiring antimicrobials over the past 6 months prior to screening.

6. Active infection requiring hospitalization or treatment with parenteral antimicrobials within the 30 days prior to randomization.
7. Prior use of rituximab (or other B cell depleting agents) within 6 months of enrollment unless B cells have been demonstrated to have repopulated.
8. Use of any investigational agent within 5 half-lives of the agent (or 6 months if the half- life is unknown) prior to enrollment.
9. White blood cell count $< 2.5 \times 10^3/\mu L$.
10. Absolute neutrophil count (ANC) $< 1.0 \times 10^3/\mu L$.
11. IgG4-related renal disease with serum creatinine >2.0 mg/dL.
12. Hemoglobin < 10 g/dL.
13. Platelet count $< 75 \times 10^9/L$.
14. Known positive result for HIV I or II antibody, hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody.
15. Has received live vaccines within 4 weeks ok enrollment.
16. Inability to communicate reliably with the investigator.
17. Patient is pregnant or breast feeding, or planning to become pregnant while enrolled in the study, up to EOS visit.
18. Positive pregnancy test at screening or during the study.
19. Subjects of childbearing potential who do not agree to use medically acceptable methods of contraception.
20. Known or suspected sensitivity to mammalian cell-derived products or any components of the study drug.
21. History of alcohol and/or substance abuse within 12 months prior to screening.
22. Unable or unwilling to partake in follow-up assessments or required protocol procedures.

5.6 Withdrawal of Subjects

Subjects are encouraged to complete all study evaluations. However, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any subject withdraws from the study prematurely. All subjects who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. At the time that a subject withdraws prematurely for any reason, all assessments as listed for the EOS visit should be performed. If a subject withdraws prematurely after dosing, all data to be collected prior to discharge from the clinical site will be collected at the time of premature discontinuation or at the scheduled end-of-study visit. Subject participation may be terminated prior to completing the study and the reason recorded as follows:

1. Adverse event
2. Protocol violation

3. Loss to Follow-up
4. Subject withdrew consent
5. Investigator withdrew subject to give rescue therapy other than steroids
6. Other

A comprehensive effort must be made to determine the reason(s) why a subject fails to return for the necessary visits or is discontinued from the study. If the subject is unreachable by telephone, a registered letter, at minimum, should be sent to the subject requesting him/her to contact the study site.

Subjects withdrawn due to AEs considered to have a possible relationship to study drug will not be replaced. Subjects withdrawn for a non-drug related reason will be replaced if deemed necessary by the Sponsor. The decision regarding the replacement of subjects will be documented.

If a subject withdraws prematurely, all assessments as listed for the EOS visit should be performed and recorded on an unscheduled visit eCRF page. In addition, the subject should be scheduled for a follow-up visit 4 weeks from the time of the last injection of study drug, at which time all assessments as listed for the EOS visit should be performed.

5.7 Other Subject Restrictions

Subjects must have signed and dated an IRB/IEC-approved written informed consent form in accordance with regulatory and institutional guidelines before the performance of any protocol-related procedures. Prisoners or subjects who are compulsory detained will not be eligible to participate.

5.8 Stopping Criteria for the Clinical Study

Participation for any individual subject will be stopped if the subject experiences a possibly drug-related SAE or a possibly drug-related significant non-serious AE, which in the opinion of the PI or Sponsor's medical representative, warrants discontinuation of the subject in the study in the interest of that subject's well-being. Discontinuation of the subject from the study will be discussed with the Sponsor.

The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's medical representative will review individual safety information as it becomes available throughout the study.

An IDMC will be used to evaluate interim safety and efficacy results and to determine if the trial should be stopped early. All unblinded analyses for IDMC review will be prepared by an independent Data Coordinating Center (IDCC). Members of the IDMC will be external to the Sponsor's study team and will follow a charter that outlines their roles and responsibilities. Prior to the planned interim analyses of the primary endpoint, the IDMC will meet approximately twice annually to review safety.

6.TREATMENT OF SUBJECTS

6.1 Identity of Study Treatment(s)

ORENCIA (abatacept) is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of abatacept is 92 kilodaltons.

ORENCIA solution for subcutaneous administration is supplied as a sterile, preservative-free, clear, colorless to pale-yellow solution with a pH of 6.8 to 7.4. Each single dose of subcutaneous injection provides 125 mg abatacept, dibasic sodium phosphate anhydrous (0.838 mg), monobasic sodium phosphate monohydrate (0.286 mg), poloxamer 188 (8 mg), sucrose (170 mg), and quantity sufficient to 1 mL with water for injection. Unlike the intravenous formulation, ORENCIA solution for subcutaneous administration contains no maltose.

Active substance: abatacept

Tested indication: IgG4-RD

Strength: 125.0 mg/syringe

Dosage form: prefilled glass syringe

Route of administration: SC injection

The dosing and schedule are supported by Phase I or later research.

6.2 Administration of Study Treatment(s)

All subjects will receive abatacept.

6.3 Treatment Protocol

•Abatacept (Orencia): One 125 mg/mL single-dose prefilled glass syringe will be administered by subcutaneous (SC) injection weekly by the patients or caregivers. Patients and caregivers will be trained on how to administer the medication by the study investigators or a designated study staff member during baseline and week 1 visits. Abatacept interruptions or withdrawals will be as per the current U.S. product insert (See Attached Package Insert).

•Prednisone taper: Subjects who are on prednisone at baseline will begin an investigator-directed corticosteroid taper designed to discontinue prednisone not later than 8 weeks after the baseline visit.

6.4 Study Treatment Packaging and Labelling

ORENCIA (abatacept) injection solution for subcutaneous administration is supplied either as a single-dose disposable prefilled glass syringe with UltraSafe Passive needle guard with flange extenders or as a single-dose disposable prefilled glass syringe with flange extender. The Type I glass syringe has a coated stopper and fixed stainless-steel needle (5 bevel, 29- gauge thin wall, ½-inch needle) covered with a rigid needle shield. The prefilled syringe provides 125 mg

of abatacept in 1 mL and is provided in the following packages:

- NDC 0003-2188-11: pack of 4 syringes with a passive needle safety guard
- NDC 0003-2188-31: pack of 4 syringes without a passive needle safety guard

6.5 Storage

ORENCIA solution supplied in a prefilled syringe should be refrigerated at 2C to 8 C (36F to 46F). The medications should not be used beyond the expiration date on the prefilled syringe.

It should be protected from light by storing in the original package until time of use. The prefilled syringe should not be allowed to freeze.

The Investigator/Institution is responsible for the following.

- Investigational product is to be stored in a secure area according to local regulations and stored under the appropriate environmental conditions (temperature, light, and humidity). If marketed product is used, it should be stored in accordance with the package insert, Summary of Product Characteristics (SmPC), United States prescribing information (US PI), or similar guidance.
- The investigational product will be dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations
- Current disposition record of IP (supplied by BMS) is to be maintained at each study site where study drug is inventoried and dispensed
- Procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures

6.6 Subject Compliance

Dosing will be performed by trained, qualified personnel designated by the PI. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures.

6.7 Study Treatment Accountability, Handling, and Disposal

The Investigator or designee is responsible for maintaining accurate accountability records of the IMPs throughout the clinical study. The drug accountability log includes information such as amount dispensed and amount returned to the pharmacy (if any).

All dispensing and accountability records will be available for Sponsor review after database lock. The site pharmacist (or designee under the direction of the pharmacist) will dispense IMP for each subject according to the protocol and pharmacy manual, if applicable.

After receiving Sponsor approval in writing, the site is responsible for either returning all unused or partially used IMP to the Sponsor or designated third party or for the destruction of the IMP according to locally compliant procedures.

6.8 Concomitant Therapy

Previous/Concomitant Medication

Concurrent administration of a TNF antagonist with abatacept has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF

antagonists alone. Concurrent therapy with abatacept and TNF antagonists is not recommended.

Disallowed previous or concomitant medications:

- Prior use of rituximab (or other B cell depleting agents) within 6 months of enrollment unless B cells have been demonstrated to have repopulated.
- Use of any investigational agent within 5 half-lives of the agent (or 6 months if the half-life is unknown) prior to enrollment
- Received live vaccines within 4 weeks of enrollment.

From Abatacept Package Insert (section 5.1): Concomitant Use with TNF Antagonists

- In controlled clinical trials in patients with adult RA, patients receiving concomitant ORENCIA and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively) [see Adverse Reactions (6.1) from package insert]. These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of ORENCIA with TNF antagonist; therefore, concurrent therapy with ORENCIA and a TNF antagonist is not recommended. While transitioning from TNF antagonist therapy to ORENCIA therapy, patients should be monitored for signs of infection.
    - Enbrel (etanercept)
    - Kineret (anakinra)
    - Cimzia (certolizumab pegol)
    - Humira (adalimumab)
    - Rituxan (rituximab)
    - Actemra (tocilizumab)
    - Remicade (infliximab)
    - Simpon (golimumab)
- Details of all prior and concomitant medication must be recorded at study entry (i.e., at the first visit) including prior treatment for IgG4-RD, prior IgG4-RD clinical trial participation and prior monoclonal antibody use. All therapies (prescription or over-the-counter medications, including vitamins and herbal supplements) different from the study drug must be recorded. Any medicinal product, prescribed or OTC, including herbal and other non-traditional remedies, is considered a concomitant medication. Any changes in concomitant medication must be recorded at each visit. If the change influences the subject's eligibility to continue in the study, the Sponsor must be informed. Concomitant medication use may be warranted for the treatment of AEs. In the interest of subject safety and acceptable standards of medical care the Investigator will be permitted to prescribe treatment(s) at his/her discretion. All treatments must be recorded in the subjects' case report form (CRF); medication, dose, treatment duration and indication.
- The information collected for each concomitant medication includes, at a minimum, start date, end date or ongoing, dose and unit, frequency, route of administration and indication.

6.9 Contraception

- Women of childbearing potential must have a negative pregnancy test during screening and at baseline (Day 1) and must use 1 highly effective method of birth control during the study and for 3 months following the last dose of abatacept. Highly effective methods of birth control include hormonal birth control, intrauterine devices (IUDs), or any barrier methods (sponges, female condoms) used by the woman in addition to contraception used by their male partner such as a vasectomy or a condom supplemented with spermicide.
- Women of non-childbearing potential must have a documented reason (i.e., postmenopausal by history with no menses for one year and confirmed by FSH [using local reference ranges], OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy).
- Male subjects of childbearing potential must be willing to practice a highly effective method of birth control for the duration of the study and continuing for 3 months after the last dose of abatacept. Highly effective methods of birth control include a vasectomy or a condom in combination with barrier methods, hormonal birth control or IUD used by the woman.

6.10 Treatment Compliance

Patients will be asked to maintain diaries to record medication taken at home. These diaries will be reviewed by the coordinators at each visit to assess compliance.

7. ASSESSMENT OF EFFICACY

7.1 Efficacy Variables

Efficacy will be measured by the ability of abatacept to sustain the disease improvement. Disease activity will be followed using the following assessments to be recorded by study investigators:

- IgG4-RD RI will be the primary efficacy variable
- The following assessments will also be obtained:
- Physician Global Assessment of Disease Activity (Visual Activity Score)
- Subject's Global Disease Activity VAS
- Symptom Severity Index
- Glucocorticoid Toxicity Index
- SF-36 Health Survey

7.2 Efficacy Assessments

The following efficacy assessments will be performed according to the time points defined in the Schedule of Assessments (Table 1).

- **IgG4-RD Responder Index**

Disease activity will be measured per schedule of assessments. For determination of the IgG4-RD responder index as described in the schedules of assessments (IgG4-RD RI), the following criteria will be used (modified after Carruthers et al. 2012): Organ site, symptomatic, urgent disease (as per IgG4-RD RI) over the previous 28 days.

The original IgG4-RD RI has been modified to include the full spectrum of organs affected

most frequently by IgG4-RD and to eliminate serum IgG4 concentrations as part of the instrument. In addition, an assessment of damage caused by IgG4-RD in each affected organ is included. A sample assessment form is included in Appendix.

- **Physician Global Disease Activity VAS**

The physician's overall assessment of the subject's current disease activity will be recorded on a 100 mm linear horizontal VAS, where the left hand extreme of the line is considered "Very Good" (symptom free and no IgG4-RD symptoms) and the right-hand extreme is considered "Very Bad" (maximum IgG4-RD activity).

Details on the efficacy assessments can be found in Appendix.

- **Subject's Global Disease Activity VAS**

The subject's overall assessment of the subject's current disease activity will be recorded on a 100 mm linear horizontal VAS, where the left hand extreme of the line is considered "Very Good" (symptom free and no IgG4-RD symptoms) and the right hand extreme is considered "Very Bad" (maximum IgG4-RD activity).

- **Symptom Severity Index**

The Symptom Severity Index is a novel instrument for assessing patient-reported disease severity. It has not yet been validated in a longitudinal study of patients with IgG4-RD but is based on similar instruments used in other conditions like diabetes mellitus, hypertension, and benign prostate hypertrophy. The instrument queries patients on symptoms that can be associated with different manifestations of IgG4-RD. For each organ, the patient scores the severity of his/her symptoms and a total score is then derived. In addition to helping assess the efficacy of treatment, data collected through the use of this instrument in this trial will be used to assess the validity of the instrument.

- **Glucocorticoid Toxicity Index**

The glucocorticoid toxicity index is a comprehensive assessment of the change in glucocorticoid toxicity over times. It factors in a number of variables including body mass index, glucose tolerance, blood pressure, lipids, bone density, steroid myopathy, skin toxicity, neuropsychiatric toxicity, infection, and endocrine (adrenal insufficiency), gastrointestinal, musculoskeletal, and ocular toxicities.

- **36-Item Short Form Health Survey**

The SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. It has been used in many diseases to assess the subject's perspective of the effect that the disease plays in their activities of daily life. These measures rely upon patient self-reporting and are now widely utilized

7.3 POST- STUDY ACCESS & ADVERSE EVENT REPORTING INFORMATION FOR INTERVENTIONAL PROTOCOLS

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If the BMS safety address is not included in the protocol document (eg, multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) will be used to report SAEs to BMS.

  - The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
  - The MedWatch form is available at: MedWatch 3500 Form

- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection.

- The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to

aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.

- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision.

  The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAEform.

Pregnancies must be reported and submitted to BMS on any of the following form(s):

1. MedWatch or, CIOMS or
2. BMS Pregnancy Surveillance Form or,
3. Approved site SAE form

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow- up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

DEFINITIONS

The protocol must include a definition for Serious Adverse Events (SAE).

SERIOUS ADVERSE EVENTS

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

NOTE: (PI determines if this information regarding hospitalizations are considered SAEs and should be included in the protocol. This is supplemental information that is included in BMS-sponsored trials)

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead- in period or other observational period intended to establish a baseline status for the subjects.

A ***non-serious adverse event*** is an AE not classified as serious.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

Potential Drug Induced Liver Injury (DILI)

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, **or** approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for

Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

Laboratory Assessments

The following laboratory variables will be determined as outlined below:

Hematology: The following hematology parameters will be assessed: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (% and derived absolute values), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and absolute platelet count.

Clinical comprehensive metabolic test (CMP) : The following clinical chemistry parameters will be assessed per schedule of assessment: Total protein, sodium, potassium, calcium, chloride, bicarbonate (HCO3), albumin, glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hemoglobin A1C. Hemoglobin A1C will be used as a surrogate for pancreatic endocrine function. A fasting lipid panel and HbA1c will be performed during the GTI assessment visits**.**

Immunoglobulin: Serum IgM, IgG, and IgE will be assessed per schedule of assessment. Serum IgG subclasses will be measured per schedule of assessment

Complement levels: C3 and C4 levels will be assessed per schedule of assessment

Urinalysis and Urine protein/creatinine ratio: The following urinalysis parameters will be assessed per schedule of assessment: pH, glucose, ketones, specific gravity, nitrite, protein, bilirubin, urobilinogen, leukocytes and blood. Microscopic urinalysis will be performed if clinically indicated.

Serology: HBsAg, HBcAb, and HCV Ab will be performed at Screening. Not required if collected 6 months prior to screening visit.

Urine Pregnancy Test: Urine pregnancy testing will be performed in female subjects of childbearing age (if not surgically sterilized)

Mechanistic samples: Correlative Studies

Peripheral blood mononuclear cells (PBMCs) and plasma will be isolated and frozen from each subject at weeks 0, 1, 4, 12 and 24 corresponding with clinical blood draws. Flow cytometry looking at T cells will be assessed at weeks 0, 1, 4, 12 and 24. From 5 of the enrolled subjects

with known expansions of the respective cell type and clinical responsiveness to abatacept, terminally differentiated CD4+CTLs, terminally differentiated CD8+CTLs and activated B cells will be sorted by FACS at weeks 0, 12 and 24.

Blood Requirements:

Blood will be collected for clinical laboratory testing as outlined below:

Hematology: Blood (3 mL) will be collected into a lavender-top (EDTA) tube.

Chemistry: Blood (5.0 mL) will be collected into a serum gel (SST) tube.

Hepatitis serologies (HBsAg, HBcAb, HCVAb): Blood (4.0 mL) will be collected into a serum gel (SST) tube. Immunoglobulins (IgG, IgM, IgE, IgG4) and Complement C3 and C4: Blood (5 mL) will be collected into a serum gel (STT) tube.

Flow Cytometry B Cell and CD19 RO: Blood (3.0 mL) will be collected into a lavender-top tube and blood (5.0 mL) will be collected in a Cyto-Chex BCT glass streck CE marked tube.

Plasmablast and CD4+ CTL Assessment: Blood (5.0 mL) will be collected in a Cyto-Chex BCT glass streck CE marked tube.

Laboratory Values Outside Normal Range:

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the site. The Investigator or designee will indicate whether or not the value is of clinical significance. Laboratory values that are clinically significant and that are not explained by the subject's underlying disease or medications should be entered as AEs and the relationship to study drug assigned. A laboratory value of clinically significance typically requires a diagnostic or therapeutic intervention other than repeating the test. Additional testing during the study may be done if medically indicated. The study subject will be followed until the test(s) has (have) normalized or stabilized.

Physical Examination

Complete physical examinations will be performed at Screening, on Day 1 (could potentially be the same visit) and at EOS. Abbreviated PEs will be directed towards the symptoms of IgG4-RD that were previously defined and will be performed at all other visits.

The physical examination includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems).

Vital Signs

Vital signs will be assessed at Screening (Visit 1) and at each visit to the PI's office. The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg]);
- Heart rate (beats per minute [bpm]);
- Body temperature (°C);
- Respiratory rate (breaths per minute).

8. STATISTICAL EVALUATION

8.1 Analysis Population

The definitions of study populations are as follows:

- Efficacy Population: All subjects. This population will be used for the primary efficacy analysis and other efficacy analyses except where otherwise noted.
- Safety Population: All subjects treated with abatacept. This population will be used for safety analyses.
- Patient Reported Outcome Population (PRO): All randomized subjects who have a non-missing baseline and at least one post-baseline PRO assessment. Subjects in this subset will be analyzed according to their randomized treatment assignment, regardless of treatment received, except where otherwise noted.
- Pharmacokinetic Population: Subjects with at least one quantifiable trough concentration result will be included in this population.
- Pharmacodynamic Population: Subjects with a quantifiable baseline and at least one post-baseline assay result will be included in this population.
- Open-label Population: Subjects with contraindications to or who refuse glucocorticoid therapy may enter an open-label study and receive XmAb5871 if they otherwise meet all other inclusion and exclusion criteria. These subjects will follow the same schedule of assessments, but safety and efficacy will be reported separately.
- Continuing Glucorticoid Population: Subjects who continue on study after an unsuccessful glucocorticoid taper or who continue after receiving glucocorticoid rescue therapy following a successful taper.

8.2 Endpoints

Primary Efficacy Endpoint

The primary endpoint is complete remission at 24 weeks. Complete remission is defined as an IgG4-RD Responder Index Score of 0 and a prednisone dose of 0 mg/day and no flare since beginning treatment.

Secondary Efficacy Endpoints

- Disease response at 4, 12, 24, and 36 weeks. Disease response will be defined at 6 months as: 1) improvement of $\geq$ 1 point in the IgG4-RD RI score over baseline; 2) no glucocorticoid use following the week 4 visit; 3) no disease flares, as assessed by the IgG4-RD RI. Disease flare will be defined as recurrence of disease activity or demonstration of a disease exacerbation such that additional therapy beyond the trial protocol is indicated. Such additional therapy may include glucocorticoids or alternative immunosuppressive agents.
- Complete remission at 36 weeks.
- Time to disease remission (IgG4-RD RI = 0)
- Remission rates

- Number of disease flares per subject over time
- Cumulative corticosteroid doses and Glucocorticoid Toxicity Index
- Physician Global Assessment (PGA). A PGA consisting of a 10-centimeter visual analog scale is collected at each patient visit. Only active disease (as opposed to damage) is considered in the scoring of the PGA.
- Symptom Severity Index
- Serum immunoglobulin levels, IgG4 subclass concentrations, IgE levels, eosinophils, and serum C3 and C4

Safety Endpoints

Safety analyses will be performed using all treated subjects.

- The number and percent of subjects experiencing a treatment-emergent adverse event will be tabulated for each coded MedDRA system-organ class and preferred term. Treatment-emergent adverse events will also be tabulated according to intensity and causality.
- All SAEs, discontinuations due to AE, or deaths occurring during the course of the trial will be presented in subject listings.
- The number and percent of subjects experiencing a glucocorticoid-related AE will be tabulated for each coded MedDRA system-organ class and preferred term. Treatment-emergent adverse events will also be tabulated according to intensity and causality.
- Clinical laboratory tests (observed values) will be summarized descriptively in tabular format. Shift tables will be presented for select laboratory parameters. In the subject listings, values outside of the laboratory's reference limits will be identified, along with the Investigator's assessment of clinical significance. A list of all normal laboratory ranges will also be provided. Clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE listings.
- Vital signs (BP, pulse, temperature) will be summarized (observed and change from baseline) at each visit vital signs are collected using descriptive statistics and subject listings.
- Concomitant Medications will be summarized by the number and percentage of subjects in each therapeutic class and preferred term as coded using the WHODrug dictionary.

Physical Examinations will be presented in subject listings.

8.3 Quality of Life Assessments

Quality of life assessments will include the Physician Global Disease Activity Assessment Visual Analogue Scale (PhGA VAS), the Patient Global Disease Activity Assessment VAS (PtGA VAS), the Symptom Severity Index and the 36-item short form health survey (SF-36). Unless otherwise specified, the QOL analyses will include all randomized subjects who have a non-missing baseline and at least one post-baseline QOL assessment. Subjects in this subset

will be analyzed according to their randomized treatment assignment, regardless of treatment received.

The percentage of participants randomized to each treatment group who complete the QOL questionnaires at each assessment point after baseline (i.e., QOL completion rates) will be calculated and compared. If significant differences in QOL completion rates are observed, additional analyses may be performed to evaluate the potential for reporting biases.

For each QOL endpoint, descriptive statistics will be presented for recorded values at each visit, including mean, standard deviation, median, minimum, maximum, change from baseline and percent change from baseline.

8.4 Statistical Methods General

Considerations

Summary statistics will be presented by way of n, mean, standard deviation (SD), median, minimum and maximum for continuous variables and by way of group frequencies and percentages for categorical variables. Percentages will be calculated using the total subjects per arm in the planned analysis population, unless specified otherwise.
For listings, in the cases where a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.
Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible, data will be decimal aligned.
Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.
P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.

9 DIRECT ACCESS TO SOURCE DATA/NOTES

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject receiving IMP.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) to have direct access to all documents pertaining to the study.

10 QUALITY CONTROL AND QUALITY ASSURANCE

Data Quality Assurance

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's medical representative may review safety information as it becomes available throughout the study.
All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations.

The study may be audited to assess adherence to the Clinical Study Protocol. The Investigator/investigational site will permit study-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

During the conduct of the study, process-related audits may be performed as well. An audit certificate will be provided in the final study report outlining the audit performed and other related activities.

11 ETHICS

11.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with FDA ICH GCP and local requirements as applicable.

The IEC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures (e.g., advertisements), written information to be provided to the subjects, investigator's Brochure, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory Authority (Competent Authority) as applicable.

11.2 Good Clinical Practice

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the ICH guidelines on GCP as outlined in CPMP/ICH/135/95 and the Declaration of Helsinki (Version 2008). The clinical study also will be carried out in keeping with national and local legal requirements (in accordance with United States Investigational New Drug [IND] regulations [21 CFR Parts 50, 56 and 312]).

The Investigator will be responsible for the care of the subjects throughout the study. If the Investigator is not present at the study site, he/she will leave instructions for the staff and a telephone number where he/she can be reached.

11.3 Written Informed Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained from the subject according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The subject should be informed that he/she is free to withdraw from the study at any time. He/She will receive all information that is required by federal regulations and ICH guidelines. The Principal Investigator or designee will provide the Sponsor with a copy of the IRB/IEC-approved ICF prior to the start of the study.

The informed consent document must be signed and dated; one copy will be given to the subject, and the Investigator will retain a copy as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the informed consent document may need to be revised to reflect the changes to the protocol. If the informed consent document is revised, it must be reviewed and approved by the responsible IRB/IEC and signed by all subjects subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

11.4 Protocol Approval and Amendment(s)

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the IRB/IEC, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study.

This protocol is to be followed exactly. Any deviations should be agreed by both the Sponsor and the Investigator, with the appropriate written and approved protocol amendments made to reflect the changes agreed upon. Protocol amendments must be released by the responsible staff and receive IRB/IEC approval prior to implementation (as appropriate). Where the deviation occurs for the well-being of the subject, the Sponsor must be informed of the action agreed upon.

Administrative changes may be made without the need for a formal amendment but will also be mentioned in the integrated clinical study report. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

11.5 Confidentiality Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial or to comply with regulatory requirements.

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date, not by name. Documents that identify the subject (e.g., the signed informed consent document) must be maintained in confidence by the Investigator.

12 DATA HANDLING AND RECORD KEEPING

12.1Case Report Forms/Source Data Handling

The investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination reports.

12.2 Retention of Essential Documents

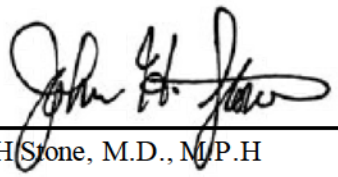
The sponsors must retain all study records and source documents for the maximum period required by applicable regulations and guidelines or institution procedures, or for the period specified by agreement with BMS, whichever is longer.

13 PUBLICATION POLICY

By signing the clinical study protocol, the Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the Investigator's name, address, qualifications and extent of involvement. An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

14 SIGNATURE OF INVESTIGATOR

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.



28 October 2018

Dr. John H Stone, M.D., M.P.H
Principal Investigator

Date (day/month/year)

15 REFERENCE LIST

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17 APPENDICES

Efficacy Assessments

A. IgG4-RD Responder Index (IgG4-RD RI)

The IgG4-RD RI is a tool designed to detect change in disease activity and identify improvements and worsening in the same or different organ systems (modified after Carruthers, 2012).

At each assessment, the physician enters a 0-3 score after the organ/site listed with;

0 = Normal or resolved

1 = Improved but still present

2 = New or recurrent disease activity while subject is off treatment, or unchanged from previous visit*

3 = Worsened or new disease manifestation despite treatment

*Unchanged from previous visit will often refer to disease manifestations that require follow-up imaging to assess accurately.

The second column is used to record symptomatic disease; yes=Y, no=N.

The third column records whether there is urgent disease in that site; yes=Y, no=N.

Damage in the organ/site is recorded in the fourth column; yes=Y, no=N.

The fifth column records whether damage in the organ/site is symptomatic; yes=Y, no=N.

Physician Global Assessment of disease activity is denoted on a 100 mm line as covered below.

IgG4-RD Responder Index (Version25July2016)

Scoring Rules

Scoring refers to manifestations of disease activity present in the last 28 days

Scoring: 0 Normal or resolved
1 Improved but still present
2 New / Recurrence while patient is off treatment or unchanged from previous visit*
3 Worsened or new disease manifestation despite treatment
*Unchanged from previous visit will often refer to disease manifestations that require follow-up imaging to assess accurately

Definitions

Organ/Site score: The overall level of IgG4-RD activity within a specific organ system

Symptomatic: Is the disease manifestation in a particular organ system symptomatic? (Y = yes; N = no)

Urgent disease: Disease that requires treatment immediately to prevent serious organ dysfunction (Y = yes; N = no) (*Presence of **urgent disease** within an organ leads to **DOUBLING** of that organ system score*)

Damage: Organ dysfunction that has occurred as a result of IgG4-RD and is considered permanent (Y = yes; N = no)

	Activity			Damage	
Organ/Site	Organ/Site Score (0-4)	Symptomatic (Yes/No)	Urgent (Yes/No)	Yes/No	Symptomatic (Yes/No)
Meninges					
Pituitary Gland					
Orbital lesion (specify location): _____					
Lacrimal Glands					
Parotid Glands					
Submandibular Glands					
Other Salivary Glands (specify): _____					
Mastoiditis / Middle ear disease					
Nasal Cavity Lesions					
Sinusitis					
Other ENT Lesions, e.g., tonsillitis, pharyngitis (specify): _____					
Thyroid					
Lungs					
Lymph Nodes (please circle site of involvement, below):					
Submental Submandibular Cervical Axillary Mediastinal Hilar Abdominal/Pelvic Inguinal Other lymph node chains:					

	Activity			Damage	
Organ/Site	Organ/Site Score (0-4)	Symptomatic (Yes/No)	Urgent (Yes/No)	Yes/No	Symptomatic (Yes/No)
Aorta / Large Blood Vessels					
Heart/Pericardium					
Retroperitoneal Fibrosis					
Sclerosing Mediastinitis					
Sclerosing Mesenteritis					
Pancreas					
Liver					
Bile ducts					
Kidney					
Skin					
Constitutional symptoms not attributable to involvement of a particular organ (weight loss, fever, fatigue caused by active IgG4-RD)					
Other involvement - specify: (Consider prostate, breast, gallbladder involvement; and other. Each "Other" item is counted separately.) _____ _____					

Total Activity Score

Organ/sites (x 2 if urgent): _____

Total **urgent** organs: _____

Total **symptomatic (active)** organs: _____

Total **damaged** organs: _____

Total **symptomatic (damage)** organs: _____

Total activity score is calculated as given in the lower left hand corner =

Sum of organ scores (any that are urgent are multiplied by 2).

Global Assessment of Disease Activity (VAS)

B. Physician's Global Assessment of Disease Activity (100 mm-VAS)

Place a mark on the line below to indicate disease activity (independent of the subject's self-assessment):

Very Good |——————————————————————| Very Bad

$VAS_{Physician\ Global\ Assessment\ of\ Disease\ Activity}$ =_____mm

C. Subject's Global Assessment of Disease Activity (VAS)

Subject's Global Assessment of Disease Activity (100 mm-VAS)

Place a mark on the line below to indicate disease activity:

Very Good |——————————————————————| Very Bad

$VAS_{Subject\ Global\ Assessment\ of\ Disease\ Activity}$ =_____mm

D. SF-36 Health Survey

SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. These measures rely upon patient self-reporting and are now widely utilized for routine monitoring and assessment of care outcomes in adult patients. The 36-Item Health Survey was developed at RAND as part of the Medical Outcomes Study (Ware et al. 1992, McHorney et al. 1994).

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

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

1 - Excellent

2 - Very good

3 - Good

4 - Fair

5 – Poor

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

1 - Much better now than one year ago

2 - Somewhat better now than one year ago

3 - About the same

4 - Somewhat worse now than one year ago

5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports

1)Yes, limited a lot 2)Yes, limited a little 3)No, not limited at all

4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

1)Yes, limited a lot 2)Yes, limited a little 3)No, not limited at all

5. Lifting or carrying groceries

1)Yes, limited a lot 2)Yes, limited a little 3)No, not limited at all

6. Climbing several flights of stairs

1)Yes, limited a lot 2)Yes, limited a little 3)No, not limited at all

7. Climbing one flight of stairs

1)Yes, limited a lot 2)Yes, limited a little 3)No, not limited at all

8. Bending, kneeling, or stooping

1)Yes, limited a lot 2)Yes, limited a little 3)No, not limited at all

9. Walking more than a mile

1)Yes, limited a lot 2)Yes, limited a little 3)No, not limited at all

10. Walking several blocks

1)Yes, limited a lot 2)Yes, limited a little 3)No, not limited at all

11. Walking one block

1)Yes, limited a lot 2)Yes, limited a little 3)No, not limited at all

12. Bathing or dressing yourself

1)Yes, limited a lot 2)Yes, limited a little 3)No, not limited at all

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

13. Cut down the amount of time you spent on work or other activities

1)Yes 2)No

14. Accomplished less than you would like

1)Yes 2)No

15. Were limited in the kind of work or other activities

1)Yes 2)No

16. Had difficulty performing the work or other activities (for example, it took extra effort)

1)Yes 2)No

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

17. Cut down the amount of time you spent on work or other activities

1)Yes 2)No

18. Accomplished less than you would like

1)Yes 2)No

19. Didn't do work or other activities as carefully as usual

1)Yes 2)No

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

1 - Not at all

2 - Slightly

3 - Moderately

4 - Quite a bit

5 - Extremely

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

1 - None

2 - Very mild

3 - Mild

4 - Moderate

5 - Severe

6 - Very severe

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

1 - Not at all

2 - A little bit

3 - Moderately

4 - Quite a bit

5 - Extremely

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

How much of the time during the past 4 weeks...

23. Did you feel full of pep?

1)All of the time 2)Most of the time 3)A good bit of the time 4)Some of the time 5)A little of the time 6)None of the time

24. Have you been a very nervous person?

1)All of the time 2)Most of the time 3)A good bit of the time 4)Some of the time 5)A little of the time 6)None of the time

25. Have you felt so down in the dumps that nothing could cheer you up?

1)All of the time 2)Most of the time 3)A good bit of the time 4)Some of the time 5)A little of the time 6)None of the time

26. Have you felt calm and peaceful?

1)All of the time 2)Most of the time 3)A good bit of the time 4)Some of the time 5)A little of the time 6)None of the time

27. Did you have a lot of energy?

1)All of the time 2)Most of the time 3)A good bit of the time 4)Some of the time 5)A little of the time 6)None of the time

28. Have you felt downhearted and blue?

1)All of the time 2)Most of the time 3)A good bit of the time 4)Some of the time 5)A little of the time 6)None of the time

29. Did you feel worn out?

1)All of the time 2)Most of the time 3)A good bit of the time 4)Some of the time 5)A little of the time 6)None of the time

30. Have you been a happy person?

1)All of the time 2)Most of the time 3)A good bit of the time 4)Some of the time 5)A little of the time 6)None of the time

31. Did you feel tired?

1)All of the time 2)Most of the time 3)A good bit of the time 4)Some of the time 5)A little of the time 6)None of the time

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

1 - All of the time

2 - Most of the time 3

- Some of the time 4 -

A little of the time

5 - None of the time

How TRUE or FALSE is each of the following statements for you.

33. I seem to get sick a little easier than other people

1)Definitely true 2)Mostly true 3)Don't know 4)Mostly false 5)Definitely false

34. I am as healthy as anybody I know

1)Definitely true 2)Mostly true 3)Don't know 4)Mostly false 5)Definitely false

35. I expect my health to get worse

1)Definitely true 2)Mostly true 3)Don't know 4)Mostly false 5)Definitely false

36. My health is excellent

1)Definitely true 2)Mostly true 3)Don't know 4)Mostly false 5)Definitely false

Date_____ **Pillai ID**_____

E. IgG4-Related Disease Symptom Distress Index

Survey Instructions

1. This should reflect any symptoms you may have experienced over the last 30 days. For each symptom, choose how often, if at all, you experience the symptom.
2. If present, choose how much the symptom causes you distress.
3. Of all the symptoms you identify on this survey, choose up to three which you would say are the most bothersome, severe, or important to you. Rank these three by marking a 1 for the most important, 2 as the next most important, and 3 as the least important of these three.
4. **Do not calculate the score. This will be done by your physician.**

Example:

	1.) Frequency (Check one)				2.) How much distress does the symptom cause you? (Check one)					Score
Symptom	**Never (0)**	**A few days a month (1)**	**A few days a week (2)**	**Every Day (3)**	**None (0)**	**A little bit (1)**	**Some-what (2)**	**Quite a bit (3)**	**Very much (4)**	
Swelling of salivary glands under or side of the jaw				X			X			8
Dry mouth	X									
Swelling around the eyes	X									
Change in vision			X			X				3

IgG4-Related Disease Symptom Distress Index

	Frequency (Checkone)				How much distress does the symptomcause you? (Checkone)					Score
Symptom	**Never** (0)	**A few days a month** (1)	**A few days a week** (2)	**Every Day** (3)	**None** (0)	**A little bit** (1)	**Some-what** (2)	**Quite a bit** (3)	**Very much** (4)	
Salivary Glands										
Swelling of salivary glands under or side of the jaw										
Dry mouth										
Orbit (Eye Area)										
Swelling around the eyes										
Change in vision										
Dry eyes										
Other Head and Neck										
Sinus congestion/discharge										
Sinus pain										
Loss of sense of smell										
Chest										
Shortness of breath										
Cough										
Abdomen										
Pain in the abdomen										
Loss of appetite										
Nausea and/or vomiting										
Loose stool and/or diarrhea										

	Frequency (Checkone)				How much distress does the symptomcause you? (Checkone)					Score
Symptom	**Never (0)**	**A few days a month (1)**	**A few days a week (2)**	**Every Day (3)**	**None (0)**	**A little bit (1)**	**Some-what (2)**	**Quite a bit (3)**	**Very much (4)**	
Genitourinary (male only)										
Pain in the groin										
Difficulty starting a urinary stream										
Urinating frequently										
Waking up at night to urinate										
Skin and Extremities										
Yellowing of the skin										
Swelling of the lower legs										
Other Symptoms										
1.										
2.										
3.										
Total Scores										

Of all the symptoms listed above, which three do you consider to be the most bothersome, severe, or important to you?

1.

2.

3.

Patient Survey (Subject should complete this form)

Instructions: Please rate your overall health related to your IgG4-Related Disease in the past week by selecting a whole number below, using the following scale: 1 = Extremely Poor and 10 = Excellent.

*Health problems due to a disease other than IgG4-related Disease should not be considered in this evaluation.

PARTICIPANT GLOBAL ASSESSMENT

Today's Date: |___|___| - |___|___| - |___|___|___|_ | **(MM-DD-YYYY)**

On a scale of 1-10, How was your overall health in the last week?

(Extremely Poor) ❑1 ❑2 ❑3 ❑4 ❑5 ❑6 ❑7 ❑8 ❑9 ❑10 (Excellent)

F. The Glucocorticoid Toxicity Index			
check if present	**Composite GTI**	**Item Weight**	**Specific List**
Body mass index			
	Improvement in BMI	-8	Major increase in BMI
	No change in BMI	0	
	Moderate increase in BMI	21	
	Major increase in BMI	36	
Glucose tolerance			
	Improvement in glucose tolerance	-8	Diabetic retinopathy
	No change in glucose tolerance	0	Diabetic nephropathy
	Worsening of glucose tolerance	32	Diabetic neuropathy
	Worsening of glucose tolerance despite treatment	44	
Blood pressure			
	Improvement in blood pressure	-10	Hypertensive emergency
	No change in blood pressure	0	Posterior reversible encephalopathy syndrome
	Worsening hypertension	19	
	Worsening hypertension despite treatment	44	
Lipids			
	Improvement in lipids	-9	
	No change in lipids	0	
	Worsening hyperlipidemia	10	
	Worsening hyperlipidemia despite treatment	30	
Bone density			
	Improvement in bone density	-1	Major decrease in bone density

	No change in bone density	0	Insufficiency fracture
	Decrease in bone density	29	
Steroid myopathy			
	No steroid myopathy	0	Severe steroid myopathy
	Mild steroid myopathy	9	
	Moderate steroid myopathy or greater	63	
Skin toxicity			
	No skin toxicity	0	Severe skin toxicity
	Mild skin toxicity	8	
	Moderate skin toxicity or greater	26	
Neuropsychiatric toxicity			
	No neuropsychiatric symptoms	0	Psychosis
	Mild neuropsychiatric symptoms	11	GG-induced violence
	Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection			
	No significant infection	0	Grade 4 infection
	Oral/vaginal candidiasis or uncomplicated zoster	19	Grade 5 infection
	Grade 3 infection or greater	93	
Endocrine			
			Adrenal insufficiency
Gastrointestinal			
			Perforation
			Peptic ulcer disease
Musculoskeletal			
			Avascular necrosis
			Tendon rupture
Ocular			

			Central serous retinopathy
			Intraocular pressure elevation
			Posterior subcapsular cataract
Total			
		-36 to 439	

G. The ACR/EULAR IgG4-RD Classification Criteria

Step			
1. Entry Criteria	Characteristic* clinical or radiologic involvement of a typical organ (e.g., pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges)		Yes or No**
2. Exclusion Criteria	Domains and Items		
	Clinical	**Check if Present**	☐ Yes ☐ No***
	Fever	☐	
	No objective response to glucocorticoids	☐	
	Serological		
	Leukopenia and thrombocytopenia with no explanation	☐	
	Peripheral eosinophilia	☐	
	ANCA positive (specifically against proteinase 3 or myeloperoxidase)	☐	
	Positive SS-A (Ro) or SS-B (La) Antibody	☐	
	Positive dsDNA, ribonucleoprotein, or Smith (Sm) Antibody	☐	
	Other disease-specific auto-antibody	☐	
	Cryoglobulinemia	☐	
	Radiology		
	Known radiologic findings suspicious for malignancy or infection that have not been sufficiently investigated	☐	
	Rapid radiologic progression	☐	
	Long bone abnormalities consistent with Erdheim-Chester disease	☐	
	Splenomegaly	☐	
	Pathology		
	Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated	☐	
	Markers consistent with inflammatory myofibroblastic tumor	☐	
	Prominent neutrophilic inflammation	☐	
	Necrotizing vasculitis	☐	
	Prominent necrosis	☐	
	Primary granulomatous inflammation	☐	
	Pathologic features of macrophage/histiocytic disorder	☐	
	Known Diagnoses of the Following		
	Multicentric Castleman's Disease	☐	
	Crohn's disease or Ulcerative Colitis (if only hepatopancreatobiliary disease is present)	☐	
	Hashimoto's thyroiditis (if only the thyroid is affected)	☐	

If case meets entry criteria and does not meet any exclusion criteria, proceed to step 3.

3. Inclusion Criteria	Domains and Items		
	Histopathology (Biopsies from lymph nodes, luminal tract, and the skin cannot be considered)	**Check if Present**	**Weight**
	Uninformative biopsy	☐	+ 0

	Dense Lymphoplasmacytic Infiltrate	☐	+ 3.7
	Dense Lymphoplasmacytic Infiltrate and Obliterative Phlebitis	☐	+ 6.1
	Dense Lymphoplasmacytic Infiltrate and Storiform Fibrosis with or without Obliterative Phlebitis	☐	+ 13.3
	Immunostaining (See Table Below and Enter Appropriate Weight)	☐ Done (use matrix to determine weight) ☐ Not done	_____

IgG4:IgG+ Ratio	IgG4+ Cells/HPF				
		0 to 9	Indeterminate	10 to 50	≥50
	0 to 40%	0	7.3	7.3	7.3
	Indeterminate	0	7.3	7.3	7.3
	41-70%	7.3	7.3	14.1	14.1
	≥70%	7.3	7.3	14.1	16

	Serum IgG4 Concentration		
	Normal or Not Checked	☐	+ 0
	> Normal but < 2x Upper Limit of Normal	☐	+ 3.7
	2x to 5x Upper Limit of Normal	☐	+ 6.1
	≥ 5x Upper Limit of Normal	☐	+ 10.8
	Bilateral Lacrimal, Parotid, Sublingual, and Submandibular Glands		
	No set of glands is involved	☐	+ 0
	One set of glands is involved	☐	+ 5.9
	Two or more sets of glands are involved	☐	+ 13.8
	Chest and Thoracic Aorta		
	Neither of the items listed is present	☐	+ 0
	Peribronchovascular and septal thickening	☐	+ 3.8
	Paravertebral Band-Like Soft Tissue in the Thorax	☐	+ 9.8
	Pancreas and Biliary Tree		
	None of the items listed is present	☐	+ 0
	Diffuse pancreas enlargement (loss of lobulations)	☐	+ 8.0
	Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	☐	+ 10.5
	Pancreas (either of above) and biliary tree involvement	☐	+ 18.7
	Kidney		
	None of the items listed is present	☐	+ 0
	Hypocomplementemia	☐	+ 5.8
	Renal pelvis thickening/soft tissue	☐	+ 8.1
	Bilateral renal cortex low density areas	☐	+ 9.8
	Retroperitoneum		
	Neither of the items listed is present	☐	+ 0
	Diffuse thickening of the abdominal aortic wall	☐	+ 4.1
	Circumferential or antero-lateral soft tissue around the infra-renal aorta or iliac arteries	☐	+ 7.8
4. Total Inclusion Points	A case meets the classification criteria for a diagnosis of IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥19		_____