AUTOIMMUNITY CENTERS OF EXCELLENCE
PROTOCOL NUMBER: AIG01
Elotuzumab in IgG4-Related Disease

VERSION 4.0 / 19May2023

IND# 147042

Study Sponsor	The National Institute of Allergy and Infectious Diseases (NIAID)
NIAID Funding Mechanism	Autoimmunity Centers of Excellence (ACE) cooperative network
IND Sponsor/Number	DAIT/NIAID, NIH / IND# 147042
Study Drug Manufacturer/Provider	Bristol-Myers Squibb

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PROJECT MANAGER – [redacted]	**REGULATORY FFICER –** [redacted]	**PHARMACEUTICAL SPECIALIST–** [redacted]	**RHO PROJECT MANAGER –** [redacted]

National Institute of Allergy and Infectious Diseases

SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: AIG01	**Version Number: 4.0 / Date: 19May2023**
Protocol Title: Elotuzumab in IgG4-Related Disease	
IND/IDE Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
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I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, 812 and in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) document entitled *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

*[*The site Principal Investigator should sign and date at the indicated location below. A written signature/date is acceptable (e.g., scanned and sent via email as a PDF version). An electronic signature is also acceptable (e.g., sent via email as a PDF version).]*

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Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	Elotuzumab in IgG4-Related Disease
Clinical Phase	II
Number of Sites	Part 1: approximately 3 Part 2: approximately 10
IND Sponsor/Number	DAIT/NIAID, NIH / IND# 147042
Study Objectives	**Primary Objectives** **Part 1:** To determine the safety and tolerability of the addition of elotuzumab to prednisone in participants with IgG4-RD. **Part 2:** To compare the effect of the addition of elotuzumab versus placebo to prednisone on the IgG4-RD RI at 48 weeks in participants with IgG4-RD. **Secondary Objectives** 1. To compare the effect of the addition of elotuzumab versus placebo to prednisone on complete remission at 48 weeks. 2. To compare the effect of the addition of elotuzumab versus placebo to prednisone on the number of disease flares (as defined in Section 3.5.3) per participant over time. 3. To compare the effect of the addition of elotuzumab versus placebo to prednisone on the change from baseline in Physician Global Assessment (PhGA) at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 weeks. 4. To compare the effect of the addition of elotuzumab versus placebo to prednisone on Patient Global Assessment (PGA) at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 weeks. 5. To compare the effect of the addition of elotuzumab versus placebo to prednisone on safety. **Exploratory Objectives** 1. To compare the effect of the addition of elotuzumab versus placebo to prednisone on serum immunoglobulin levels, IgG subclass concentrations, IgE levels, eosinophils, and serum C3 and C4 levels.

	2. To compare the effect of the addition of elotuzumab versus placebo to prednisone on participants' ELF scores. 3. To evaluate the effect of elotuzumab on CD4+ T cells and B cell subsets, specifically: a. CD4+ cytotoxic T lymphocytes b. CD8+ cytotoxic T lymphocytes c. CD4+ T follicular helper cells d. CD4+ peripheral helper T cells e. Plasmablasts f. Activated B cells, including double-negative (CD19+IgD-CD27-) B cells 4. To determine the kinetics of cell depletion induced by elotuzumab on disease-associated, SLAMF7-expressing lymphocyte subpopulations including CD4+ cytotoxic T cells and activated B cells, including plasmablasts. 5. To determine the effect of elotuzumab at the tissue level, using submandibular gland biopsies in participants with submandibular gland disease who consent separately to biopsies before and after treatment. 6. To determine the utility of using the clonally-expanded effector subset (CD57+CD28-) of CD4+CTLs as a biomarker of disease activity. 7. To determine the utility of soluble plasma SLAMF7 levels as indicators of disease activity and predictors of disease relapse. 8. To evaluate the longitudinal profile of patient reported outcomes on quality of life over the study period using the SF-36 health survey.
Study Design	This is a two-part multi-center clinical trial in participants with active IgG4-RD. Part 1 is an open-label, dose escalation phase to determine the safety of elotuzumab for investigation in IgG4-RD. If the addition of elotuzumab to prednisone is determined to be safe, Part 2 will be initiated as randomized, placebo-controlled, double-blinded trial. Part 2 will compare the effects of the addition of elotuzumab versus placebo to prednisone in participants with IgG4-RD. Approximately 75 participants with active IgG4-RD will be enrolled in the overall program, 12 in Part 1 and 63 in Part 2.
Primary Endpoint	**Part 1: Primary Safety Endpoint** The proportion of participants in each cohort who experience at least one Grade 3 or higher adverse event during study participation. **Part 2: Primary Efficacy Endpoint** Disease response at 48 weeks, defined as percent improvement in the IgG4-RD RI score over baseline.

Secondary Endpoints	**Part 2: Key Secondary Efficacy Endpoint** 1. Complete remission at 48 weeks, defined as an IgG4-RD RI Score of 0 and a glucocorticoid dose of 0 mg/day and no flare since beginning treatment. **Part 1 and Part 2: Additional Secondary Efficacy Endpoints** 1. The proportion of participants that reach the following threshold levels of IgG4-RD RI improvement at 48 weeks: 50% and 75%. 2. Number of disease flares, as defined in Section 3.5.3, by 24 and 48 weeks. 3. Change in PhGA from baseline. 4. Change in PGA from baseline. 5. Disease-related damage, as measured by the damage section of the IgG4-RD RI at 24 weeks. **Part 1 and Part 2: Secondary Safety Endpoints** 1. The proportion of participants who experience at least one Grade 2 or higher adverse event. 2. The proportion of participants with a Grade 3 or higher infection. 3. The proportion of participants who experience a malignancy. 4. The proportion of participants who experience a Hepatotoxicity, defined as an increase in the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) to elevations three times the upper limit of normal. 5. The proportion of participants who experience a serious adverse event. 6. The proportion of participants who experience infusion reactions, defined as any adverse reaction within 24 hours of infusion which are Grade 2 or higher events and at least possibly related to study drug. **Part 2: Secondary Safety Endpoint** 1. The proportion of participants who experience at least one Grade 3 or higher adverse event.
Exploratory Endpoints	**Part 1 and 2: Exploratory Endpoints** 1. Serum immunoglobulin levels, IgG subclass concentrations, IgE levels, eosinophils, and serum C3 and C4 levels. 2. ELF score (see Section 3.5.7). 3. Blood concentrations of T cells and B cell subsets of interest, specifically: a. CD4+ cytotoxic T lymphocytes b. CD8+ cytotoxic T lymphocytes c. CD4+ T follicular helper cells

	d. CD4+ peripheral helper T cells e. Plasmablasts f. Activated B cells, including double-negative (CD19+IgD-CD27-) B cells 4. Comparison of the kinetics of cell depletion induced by the addition of elotuzumab versus placebo to prednisone on disease-associated, SLAMF7-expressing lymphocyte subpopulations, including CD4+ cytotoxic T cells and activated B cells, including plasmablasts. 5. Comparison of elotuzumab and placebo with regard to the impact of the tissue concentrations of CD4+ cytotoxic T cells and activated B cells subsets of interest, pre- and post-treatment submandibular gland biopsies. 6. Correlation of the clonally-expanded effector subset (CD57+CD28-) of CD4+CTLs with disease activity. 7. Correlation of soluble plasma SLAMF7 levels with disease activity and risk of relapse. 8. SF-36 health survey.
Accrual Objective	Approximately 75 participants will be enrolled in the overall program, 12 in Part 1 and 63 in Part 2.
Study Duration	The rate of recruitment to AIG01 is anticipated to be 0.5 participants per week. • The duration target for Part 1A prior to initiation of Part 1B is 21 weeks (12 weeks of recruitment, 9 weeks of follow-up). • The duration target for Part 1B prior to initiation of Part 2 is 60 weeks (12 weeks of recruitment, 48 weeks of follow-up). • The duration target for Part 2 is 176 weeks (128 weeks of recruitment, 48 weeks of follow-up). The total study duration is estimated to be 257 weeks (approximately 5 years).
Treatment Description	**Part 1** <u>Elotuzumab</u> Participants receive either a 1-month or twelve-month regimen of elotuzumab, depending on enrollment phase (see Study Design Section 3). Each intravenous dose will be 10 mg/kg, to be determined based on participant's weight. Rounding is permissible within 5% of the nominal dose. The participant's actual weight will be used for dosing. At the Baseline/Day 0 visit, the participant's screening weight will be used for calculation of the Baseline/Day 0 infusion dose. For all subsequent infusions, weight from the previous visit may be used unless weight was

	obtained more than 42 days previously. If more than 42 days have elapsed since the previous visit, the participant's current weight should be used for calculation. The 1-month regimen consists of 4 weekly doses of elotuzumab (10 mg/kg) on days 0, 7, 14, and 21. The twelve-month regimen consists of 6 doses at Baseline/Day 0, Week 8, Week 16, Week 24, Week 32, and Week 40. Prednisone Participants will receive a standardized prednisone taper, starting at either 40 mg orally daily or 30 mg orally daily based on doses received during the screening period. This will be tapered to discontinuation over a 10-week period. **Part 2** Participants receive either elotuzumab or placebo for elotuzumab in a 2:1 ratio. <u>Elotuzumab/Placebo</u> It is anticipated that the twelve-month regimen from Part 1 will be used for the elotuzumab and placebo for elotuzumab dosing schedule, provided there is no safety signal detected. The pharmacist is the only site personnel not blinded to the treatment assignment. Placebo for elotuzumab will be investigational sites' stocked 0.9% normal saline prepared by the site pharmacist. <u>Prednisone</u> Participants will receive the same standard prednisone taper as described in Part 1.
Inclusion Criteria	1. Participant must be able to understand and provide informed consent and be willing to comply with study procedures and follow up. 2. Are at least 18 years of age and not older than 70 years of age at screening. 3. Meet the ACR/EULAR Classification Criteria for IgG4-RD. 4. Have active disease based at screening on an IgG4-RD RI ≥4, with disease manifestations in at least two organ systems. 5. May have newly-diagnosed or relapsing disease at screening. Relapsing disease is defined as IgG4-RD that has previously been in remission but is now active again. 6. May be on treatment or off treatment at the time of screening. If on treatment, must be willing to discontinue those other treatments before the baseline visit.

	7. No history of severe allergic reactions to monoclonal antibodies. 8. Female participants of childbearing potential must have a negative pregnancy test upon study entry. 9. Female participants of childbearing potential and male participants with a partner of childbearing potential must agree to consistently and correctly use FDA approved highly effective methods of birth control, as shown in **Appendix 8: Acceptable Contraception Methods for Females of Reproductive Potential**, for the entire duration of the study and 6 months after last elotuzumab infusion. 10. Immunization with one of the FDA authorized or licensed SARS-CoV-2 vaccines as per CDC recommendations at the time of informed consent is required for study entry. Vaccination series must have been completed at least 2 weeks prior to start of study therapy.
Exclusion Criteria	1. Presence of a condition other than IgG4-RD that (e.g., asthma) is likely to require systemic Glucocorticoids (GC) for disease control during the period of the trial. 2. Malignancy within 5 years (except successfully treated in situ cervical cancer, resected squamous cell or basal cell carcinoma of the skin.) 3. The following lab values as indicators of hepatic dysfunction: a. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than three times the upper limit of normal (ULN) b. Total bilirubin > two times the ULN unless caused by Gilbert's disease. Gilbert's disease with total bilirubin > three times ULN. c. Serum albumin < 2.5 gm/dL. 4. Evidence of another uncontrolled condition which, in the judgment of the investigator, could interfere with participation in the trial according to the protocol. 5. Active infection requiring hospitalization or treatment with systemic antimicrobial agents within the 30 days prior to treatment allocation/randomization. 6. Prior use of rituximab or other B cell depleting agents within 9 months of enrollment unless B cells have been demonstrated to have repopulated. 7. Use of any investigational agent or biologic and non-biologic DMARDS within 5 half-lives of the agent (or 6 months if the half-life is unknown) prior to enrollment. 8. Any of the following laboratory tests at the Screening Visit: a. White blood cell (WBC) count < 3.0 x 10^3/µL. b. Absolute neutrophil count (ANC) < 1.5 x 10^3/µL. c. Hemoglobin < 10 g/dL. d. Platelet count < 75 x 10^9/L.

	e. Estimated glomerular filtration rate (eGFR) ≤ 45 ml/minute/1.73m^2. 9. The use of supplemental oxygen at baseline. 10. At or within 90 days of screening: Positive Interferon-Gamma Release Assay (IGRA). Indeterminate IGRAs must be repeated (with same or other IGRA per local policy) and shown to be negative. Alternatively, if the assay remains indeterminant, a participant must have a negative PPD. Finally, if the participant has had the Bacille Calmette-Guerin (BCG) vaccine or has some other condition complicating the interpretation of TB testing, consultation with infectious disease specialist must be obtained before receipt of the first investigational infusion. a. Participants diagnosed with latent TB are eligible but must have received appropriate prophylaxis for 30 days before their first investigational infusion. 11. Medical history or serologic evidence at Screening of chronic infections including: a. Human immunodeficiency virus infection. b. Hepatitis B as indicated by surface antigen or hepatitis B core antibody positivity c. Hepatitis C as indicated by anti-hepatitis C antibody positivity; if a participant is Hepatitis C antibody positive, they will be eligible to participate in the study if he/she is negative for viral load at Screening. 12. Live vaccines within 8 weeks of initiating study therapy. 13. Participant is pregnant or breastfeeding, or planning a pregnancy while enrolled in the study. 14. Substance use disorder, including the recurrent use of alcohol and/or drugs within the past year associated with clinically significant impairment associated with failure to meet major responsibilities at work, school, or home. 15. IgG4-RD that is dominated primarily by advanced fibrotic lesions. Specifically, participants whose disease manifestations consist only of a. retroperitoneal fibrosis, b. fibrosing mediatinitis, c. sclerosing mesenteritis, and d. Riedel's thyroiditis. Participants with these disease manifestations can be included, however, only if they have disease in 2 organ systems that is not of an advanced fibrotic nature and otherwise meet the Inclusion and Exclusion Criteria. 16. Evidence a SARS-CoV-2 (COVID-19) infection started within the 30 days prior to treatment allocation/randomization. Participants

	diagnosed with SARS-CoV-2 (COVID-19) infection more than 30 days prior to treatment allocation/randomization must have symptoms resolved and be deemed fit to participate in the trial.
Safety Stopping Guidance	The following events will trigger an ad hoc DSMB review (Section 12.11.3): • Any death that is at least possibly related to elotuzumab, IgG4-RD, or a study-mandated procedure; • Any grade 4 adverse event, including infection, that is a clinical event such as a sign/symptom, diagnosis, or laboratory abnormality with clinical consequence and at least possibly related to use of the investigational study medication. Any life-threatening infusion reactions during infusion of study treatment or within the two-hour observation period after study treatment that lead to permanent discontinuation of the infusion, including anaphylaxis; • Two or more of the first 6 treated participants within a given cohort (cohorts 1a, 1b or 2) experience a drug-related adverse event resulting in the permanent discontinuation of study treatment; subsequently, if >20% of participants on study or within a cohort experience a drug-related adverse event resulting in the permanent discontinuation of study treatment; • The occurrence of a Grade 3 or higher related and unexpected SAE in three or more of the study participants who have received a study treatment; • Malignancy • Any event which in the opinion of the Protocol Chair or Medical Monitor merits DSMB review. Events that trigger an ad hoc DSMB review will be cumulative over Parts 1 and 2 of the study.

Table of Contents

Glossary of Abbreviations

ACE	Autoimmunity Centers of Excellence
ACR/EULAR	American College of Rheumatology/European League Against Rheumatism
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BCG	Bacille Calmette-Guerin
BMS	Bristol-Myers Squibb Co.
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology
CRP	C-Reactive protein
CTL	Cytotoxic T lymphocytes
DAIT	Division of Allergy, Immunology, and Transplantation
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
ELF	Enhanced Liver Fibrosis
ESR	Erythrocyte sedimentation rate
EUA	Emergency Use Authorization
FACS	Fluorescence-activated cell sorting
FDA	Food and Drug Administration
HA	Hyaluronic acid
HCG	Human chorionic gonadotropin
ICH	International Conference on Harmonisation
IgG4-RD	IgG4-related disease
IgG4-RD RI	IgG4-RD Responder Index
IGRA	Interferon gamma release assay
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
mAb	Monoclonal antibody
MCAR	Missing-completely-at-random
MGH	Massachusetts General Hospital
MIT	Massachusetts Institute of Technology
mITT	Modified intent-to-treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institute of Health
NK	Natural killer
PBMC	Peripheral blood mononuclear cells
PGA	Patient Global Assessment
PhGA	Physician Global Assessment
PI	(Site) Principal investigator
PIIINP	Propeptide of type III procollagen
PMA	Phorbol myristate acetate

PP	Per protocol
RT-PCR	Reverse transcription polymerase chain reaction
SCCC	Statistical and Clinical Coordinating Center
SAE	Serious adverse event
SAR	Suspected adverse reaction
SF-36	36-Item Short Form Health Survey
SLAMF7	Signaling lymphocyte activation molecule family 7
SRC	Safety Review Committee
SUSAR	Serious unexpected suspected adverse reaction
TCR/BCR	T cell receptor/B cell receptor
TFH	T follicular helper
TIMP-1	Tissue inhibitor of metalloproteinases 1
TPH	Peripheral helper T
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell

1 Background and Rationale

1.1 Background and Scientific Rationale

1.1.1 IgG4-Related Disease (IgG4-RD)

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. It may also involve the retroperitoneum. This multi-organ immune-mediated condition, once regarded as a group of isolated, single-organ diseases, is now recognized to be an overarching, single-disease 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. Immunostaining of affected tissues generally demonstrates a ratio of ≥40% IgG4/IgG+ plasma cells [1]. Serum IgG4 concentrations are elevated in at least 50-60% of cases before the initiation of treatment [2].

IgG4-RD tends to afflict middle-aged to elderly individuals. Although IgG4-RD can affect a single organ at presentation, it is not uncommon for participants 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:

- A CD4+ cytotoxic T lymphocyte (CTL) bearing signaling lymphocyte activation molecule family 7 (SLAMF7) on its surface, secreting profibrotic cytokines IL-1B and transforming growth factor-B1 (TGF-B1) and interferon-gamma (IFN-gamma), as well as cytotoxic molecules such as perforin and granzyme B.
- A CD4+ T follicular helper (TFH) cell, known to drive the class switch within lymph nodes and extra-nodal germinal centers [3]

In addition, several B cell subsets have recently been described by flow cytometry to be elevated in the peripheral blood of IgG4-RD participants. Circulating IgG4+ plasmablasts (CD19lowCD38+CD20-CD27+) are elevated in active disease as compared to individuals with other diseases and normal controls, even in IgG4-RD participants with normal IgG4 serum levels. Total plasmablasts can therefore be utilized as a diagnostic feature of IgG4-RD [4, 5].

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

The goals of IgG4-RD treatment are to reduce inflammation and organ swelling and to prevent or reverse tissue fibrosis. 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 the endocrine pancreas, exocrine pancreas, or both; and IgG4-related tubulointerstitial nephritis can lead to renal failure.

At the present time, glucocorticoids at daily doses of 0.6 mg/kg daily for 2 to 4 weeks followed by tapering to low doses (or discontinuing altogether) over a total of 2-4 months is the first line of therapy. Although this approach is effective initially in most participants, the relapse rate upon tapering or discontinuation is high [6]. 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 weight gain, diabetes, osteoporosis, bone fracture, hypertension, and infection.

In an open-label trial from Japan in which 60 participants were treated with prednisone alone for one year, the protocol called for participants to continue on maintenance prednisone between 5 mg/day and 10 mg/day after achieving disease stability. Despite the continuation of prednisone in all participants at doses closer to 10 mg/day than 5 mg/day, only 66% of the participants treated according to this protocol achieved and maintained disease remission at one year [7]. Another trial from China compared participants treated with prednisone alone (tapered to between 5 mg/day and 10 mg/day) to the combination of cyclophosphamide and prednisone [8]. Despite the fact that participants in the prednisone only arm continued their prednisone throughout the observation period, disease relapses occurred in 39% of the participants. Twelve percent of the participants in the cyclophosphamide/prednisone arm failed, but the known toxicities of this combination of therapies are unappealing for broad clinical use. These trials underscore the shortcomings of glucocorticoids as monotherapy for IgG4-RD and emphasize the importance of identifying new treatment approaches.

Immunosuppressive medications such as azathioprine, mycophenolate mofetil, and methotrexate have been used as glucocorticoid-sparing agents, with no clear evidence of efficacy [6, 9, 10]. A high disease response rate has been observed in one 30-participant open-label trial with rituximab, utilizing the IgG4-RD Responder Index (IgG4-RD RI) as a measure of disease response [11]. A single case report from Japan described efficacy of abatacept in a participant with multi-organ IgG4-RD whose symptoms and signs of disease were refractory to B cell depletion with rituximab [12].

1.2 Rationale for Selection of Investigational Product or Intervention

Elotuzumab (Bristol-Myers Squibb) is a humanized, IgG1 monoclonal antibody (mAb) targeted against SLAMF7, a glycoprotein expressed on myeloma cells as well as on cells of the normal B lymphocyte lineage, natural killer (NK) cells, and a number of CD4+ and CD8+ T cell subsets. SLAMF7 has been not been detected on either hematopoietic stem cells or on other normal tissues. SLAMF7 is highly expressed on myeloma cells independent of cytogenetic abnormalities. It is also expressed on the CD4+ CTL that we believe to be the crucial driver of the fibroinflammatory processes central to IgG4-RD, and on cells of the B lymphocyte lineage that also play crucial roles in IgG4-RD [3-5, 13].

In participants with myeloma, elotuzumab is known to interact directly with NK cells. This enhances the anti-myeloma activity of these cells through both the SLAMF7 pathway and Fc receptors. Elotuzumab also targets SLAMF7 on myeloma cells and facilitates the interaction with NK cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC). The presence of SLAMF7 on two types of cells considered crucial to the pathophysiology of IgG4-RD, namely cells of the B lymphocyte lineage and CD4+CTLs, suggest that this therapy may be highly effective in IgG4-RD [3-5, 14-16].

An overview of the pathophysiology of IgG4-RD is shown in **Figure 1** below [17]. The cellular interaction believed critical to the disease is that involving cells of the B lymphocyte lineage and a CD4+CTL, both of which express SLAMF7 on their surface:

Figure 1. Overview of the Pathophysiology of IgG4-RD

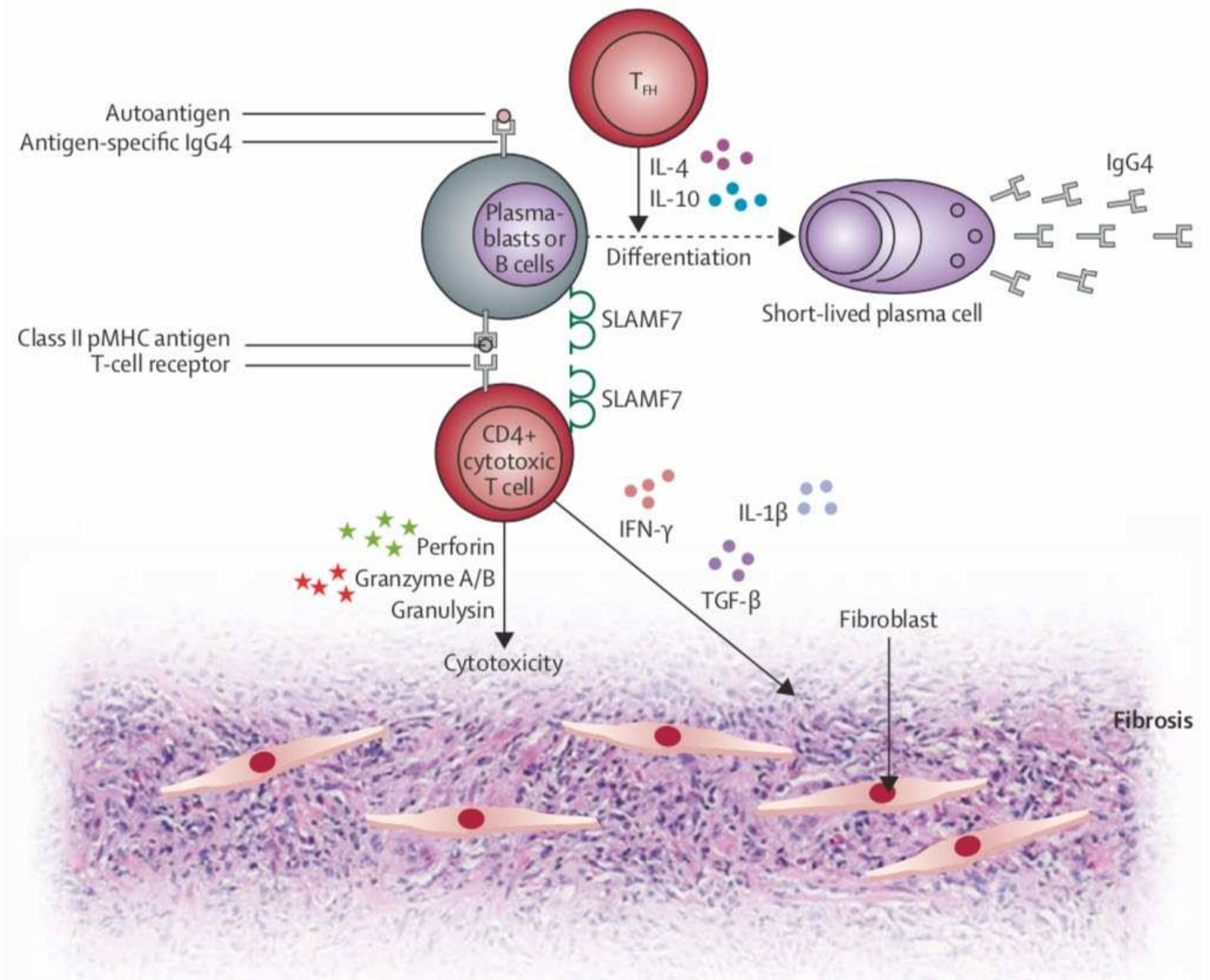


Figure 1 Legend. The central pathophysiologic event in IgG4-RD is believed to be the presentation of antigen by cells of the B-lymphocyte lineage (plasmablasts and some double negative [CD19+IgD-CD27-] B cells) to CD4+ cytotoxic T lymphocytes. Both these CD4+CTLs and the antigen-presenting cells are SLAMF7-positive, making SLAMF7 an appealing therapeutic target. The class switch to IgG4 production by cells of the B lineage appears to be driven by T follicular helper cells (TFH cells) via the secretion of IL-4 and IL-10. The role of serum IgG4 in IgG4-RD may be a counter-regulatory one but in some cases of extremely high serum IgG4 concentrations immune complexes appear to contribute to tissue injury [17].

The CD4+ CTLs in IgG4-RD secrete several pro-fibrotic cytokines, including IL-1beta and transforming growth factor-beta [3]. Moreover, they are also capable of perforin- and granzyme B-mediated cytolysis. We have demonstrated that: 1) these CD4+CTLs accumulate within tissue lesions; 2) that they represent the dominant T cell population in these affected tissues; and that they actively produce these mediators in situ [3].

Our group has also demonstrated that participants with IgG4-RD have elevations in circulating plasmablasts [4, 5]. Because B-cell depleting therapy with anti-CD20 monoclonal antibody rituximab leads to both profound clinical responses and to declines in CD4+CTLs [11, 18, 19], we suspect that activated B cells within affected tissues drive the activation of cytotoxic CD4+T cells at sites of disease. Elotuzumab will also eliminate B lymphocyte lineage cells, which bear SLAMF7 on their surface and provide essential support to the CD4+SLAMF7+CTL [4, 5, 15, 16]. Thus, this trial will

address a fundamental and important question in IgG4-RD: do CD4+SLAMF7+CTLs and their interaction with SLAMF7+ B cells truly drive the critical fibroinflammatory mechanisms of IgG4-RD?

1.3 Preclinical Experience

Elotuzumab is approved for use in multiple myeloma but has not been used before in participants with IgG4-RD or in participants with other autoimmune disease. An in vitro study using T lymphocytes from a participant with IgG4-RD was performed to gain insight into the potential effect of elotuzumab on IgG4-RD. This experiment, performed in the laboratory of Dr. Shiv Pillai at the Ragon Institute in Cambridge, MA, is described below.

The objective was to understand the *in vitro* effects of elotuzumab on CD4+CTLs (and the small subset of TFH cells expressing SLAMF7 in terms of cell death and activation).

A co-culture experiment using peripheral blood mononuclear cells (PBMCs) from an IgG4-RD participant with a large expansion of CD4+CTLs was performed. Cells were thawed and incubated overnight in medium. PBMCs alone were used as a negative control. Varying doses of elotuzumab (0.0001, 0.01 and 1.0 ug/mL) were compared to positive controls (phorbol myristate acetate (PMA)/ionomycin & CD3/CD28 for T cell activation, staurosporine for apoptosis). Cells were incubated for 4 hours and then stained for flow cytometry. Annexin and 7-AAD were used to quantify apoptosis and cell death. CD69 and CD40L were used as surface markers of T cell activation.

Figure 2A below illustrates marked cell death induced by elotuzumab in a dose-dependent manner. Cell death only occurred in the SLAMF7-expressing T cell populations, and it occurred quickly (this was a 4-hour assay). This suggests that elotuzumab induces cell death by its specific affinity to SLAMF7. To ensure the administration of elotuzumab would not result in activation of autoreactive T cells in IgG4-RD participants, we also measured surface expression of T cell activation markers following this co-culture experiment.

Figure 2B below demonstrates the dose-dependent decline in CD69 expression as a percentage of the total CD4+CTLs following elotuzumab exposure. Positive controls using CD3/CD28 Dynabeads and PMA/ionomycin were used to demonstrate the capacity of the cells to express activation markers with a 4-hour incubation. Taken together, these data support the idea that elotuzumab does not activate CD4+CTLs. On the contrary, elotuzumab induces profound cell death of the SLAMF7-expressing CD4 CTLs as well the as SLAMF7-expressing TFH cells.

Figure 2A. Dose vs Response

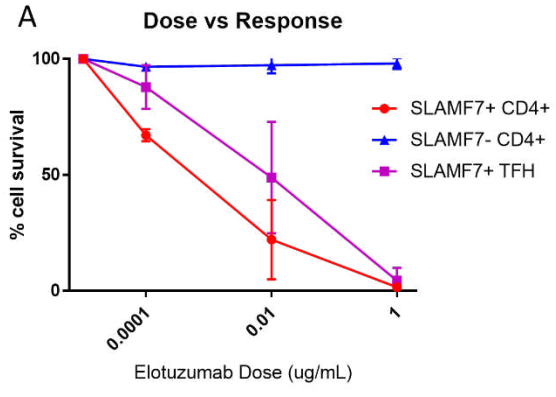


Figure 2B. CD4+CTL Activation vs Elotuzumab Dose

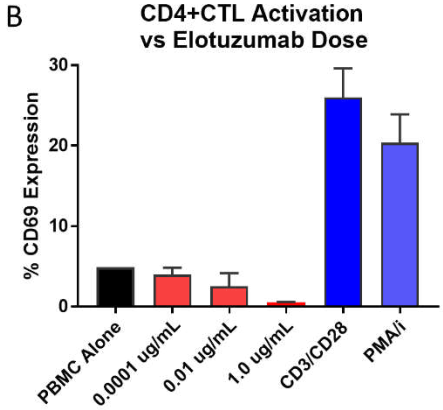


Figure 2A. Dose-dependent cell death induced by elotuzumab only affecting SLAMF7-expressing CD4+ T cells (CD4+CTLs, red; SLAMF7+TFH cells, purple; SLAMF7-CD4+ T cells in blue).

Figure 2B. CD4+CTLs were not activated by elotuzumab exposure but rather the percent activation was reduced as demonstrated by the red columns compared to PBMCs alone (black column). Two different positive controls were used (CD3/CD28 and PMA/ionomycin) to ensure CD4+CTLs were capable of activation in this 4-hour assay.

1.4 Rationale for Study Population

IgG4-RD is a recently-described disease for which no approved therapy exists. IgG4-RD causes important end-organ damage, including failure of both the exocrine and endocrine pancreas (autoimmune pancreatitis); hepatic failure (cholangitis); kidney failure from intrinsic renal disease (tubulointerstitial nephritis); obstructive nephropathy and chronic pain (retroperitoneal fibrosis); dysfunction of other organs (orbits, lung); and death from a variety of causes (complications of aortitis, pulmonary disease, meningeal involvement, other). Prednisone is an effective therapy in many participants but does not cure the disease. Moreover, the use of glucocorticoids in a disease that affects a middle-aged to elderly population and has a predilection for causing endocrine pancreatic failure (i.e., diabetes) is problematic.

The SLAMF7 molecule, expressed on both multiple B cell subsets and a crucial CD4+CTL, offers a promising targeted approach to the treatment of IgG4-RD. The administration of elotuzumab should eliminate the cell types that are central to the critical cellular interaction that drives the pathophysiology of IgG4-RD, offering a potentially glucocorticoid-free approach to remission induction. We have therefore designed a two-part trial, which will first (Part 1) gather data about the safety of this treatment approach in this participant population and then (Part 2) help understand the efficacy of this intervention.

This study plans to enroll adult participants who meet the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria for IgG4-RD, and who have active IgG4-RD with disease manifestations in at least two organ systems. The study will not restrict enrollment to the subset of patients with elevated serum IgG4 level; however, patients with normal serum IgG4 concentrations typically have disease limited to a single organ or body area, and we therefore anticipate enrichment in the percentage of patients with elevated serum IgG4 concentrations greater than the 50-60% of cases reported in previous cohort studies [2]. A planned subgroup analysis will evaluate the efficacy of elotuzumab in participants with elevated serum IgG4 level that is detected in the 6 months prior to initiation of study therapy.

The total duration of follow-up in this trial will be 48 weeks. The purpose of this extended follow-up is to provide data on the duration of effect of elotuzumab that are comparable to those available for prednisone[7], cyclophosphamide [8], and rituximab[11], as other therapies employed for the treatment of IgG4-RD. In a 30-patient open-label trial of rituximab, for example, 40% of the patients treated with rituximab remained in sustained remission 12 months after induction therapy.

1.5 Clinical Studies

Elotuzumab, a humanized, IgG1 monoclonal antibody, targets SLAMF7 and is approved for use in refractory multiple myeloma. The drug is the first therapy ever awarded a breakthrough designation for any indication by the U.S. Food & Drug Administration (FDA). Elotuzumab has been a well-tolerated therapy in multiple myeloma [20-23]. Myeloma participants are typically elderly, frequently have substantial co-morbidities, and generally undergo intensive treatment regimens consisting not only of elotuzumab but also high-dose glucocorticoids and chemotherapeutic agents. The chief concern stems from the potential for infusion reactions, which are reported in only 10% of myeloma participants and are nearly always only grade 1 or 2 (1% of reactions are grade 3) [21].

Elotuzumab has been administered to participants with multiple myeloma in 16 clinical studies that are either completed (fully or for the primary endpoint) or ongoing. Elotuzumab has been combined with other agents in most of these studies, aside from dose-ranging studies of elotuzumab alone. These studies include:

- Elotuzumab plus thalidomide and dexamethasone
- Elotuzumab plus lenalidomide and dexamethasone
- Elotuzumab plus pomalidomide and dexamethasone
- Elotuzumab plus pomalidomide, nivolumab, and dexamethasone
- Elotuzumab plus bortezomib and dexamethasone

For the purpose of treating multiple myeloma, elotuzumab is used invariably in combination with one of these or other therapies.

The elotuzumab dose that we will use in IgG4-RD is 10 mg/kg, administered in two regimens, one regimen that is one month long (four administrations) and the other that is twelve months long (six administrations). The dose of 10 mg/kg is the FDA approved dose for refractory multiple myeloma, a malignancy of plasma cells. Patients with multiple myeloma begin their treatment by receiving one elotuzumab infusion weekly for eight doses and then transition to receiving the medication every two weeks on an ongoing basis until disease progression or unacceptable toxicity. The rationale for the continued infusions in multiple myeloma is to maintain a steady state of plasma cell depletion. Although we will employ the same FDA-approved dose in our IgG4-RD population, the regimens we will employ have significantly fewer doses than those used in multiple myeloma because we anticipate a more prolonged treatment response in IgG4-RD, a non-malignant condition. We believe that these regimens will heighten the safety of elotuzumab in this IgG4-RD participant population compared to the myeloma populations in which it has been tested previously. For the purposes of assessing safety, we discuss below the outcomes of two trials in multiple myeloma using elotuzumab monotherapy. These were known as CA204011 and HuLuc63-1701**.** Both of the trials discussed below were small, early phase studies. A more complete discussion of risks as described in the package insert and Investigator's Brochure for elotuzumab are discussed in Section 5.1.

CA204011 (NCT01441973)

This study was entitled: "A Phase 2 Biomarker Study of Elotuzumab (Humanized anti-SC1 Monoclonal IgG1 Antibody) Monotherapy to Assess the Association Between NK Cell Status and Efficacy in High Risk Smoldering Myeloma". The trial enrolled 31 participants. Participants received elotuzumab 20 mg/kg intravenous (IV) on Days 1 and 8 of Cycle 1 and Day 1 of Cycle 2 and beyond in Arm 1 and elotuzumab 10 mg/kg weekly for 4 weeks in Cycles 1 and 2 and every other week in Cycles 3 and above in Arm 2.

No deaths occurred on treatment or within 60 days after end of treatment. Two participants died more than one year after receiving the study drug: specifically, at 685 days (22.5 months) and at 1183 days (38.9 months) after the last dose. Serious adverse events (SAEs) were reported in a total of 15 participants: 8 (53.3%) participants in the 20-mg/kg dose arm and 7 (43.8%) of those in the 10-mg/kg dose arm. SAEs deemed related to study drug occurred in 1 (6.7%) participant in the 20-mg/kg dose arm (Grade 2 infusion-related reactions) and in 2 (12.5%) participants in the 10-mg/kg dose arm (Grade 3 pneumonia and Grade 4 dyspnea). The pneumonia and dyspnea events were the only Grade 3 to 4 study drug-related SAEs.

Adverse events (AEs) leading to discontinuation from study drug regardless of causality occurred in a total of 6 participants, of whom 5 participants had Grade 3 to 4 AEs. No AE that led to discontinuation was considered related to study drug.

All infusion reactions were Grade 1 to 2 in intensity, and at least 1 infusion reaction occurred in 4 (26.7%) participants in the 20-mg/kg dose arm and 1 (6.3%) participant in the 10-mg/kg dose arm. No participant discontinued study drug due to an infusion reaction.

Second primary malignancies were reported in 1 (6.7%) participant in the 20-mg/kg dose arm and in 3 (18.8%) participants in the 10-mg/kg dose arm. The second primary malignancy occurring in the 20-mg/kg dose arm was a squamous cell carcinoma that occurred >1.5 years after last dose of study drug. The study-drug-unrelated Grade 3 malignancy AEs in the 10-mg/kg dose arm renal cell carcinoma, prostate cancer, and endometrial cancer.

Few or no Grade 3 to 4 hematology, chemistry, liver, or renal laboratory test results were reported. No instances of possible drug-induced liver injury occurred.

HuLuc63-1701 (NCT00425347)

This trial was entitled: "Phase 1, Multi-Center, Open-label, Dose Escalation Study of Elotuzumab (Humanized anti-CS1 Monoclonal IgG1 antibody) in Participants with Advanced Multiple Myeloma". The trial enrolled 35 participants. Four doses of elotuzumab IV infusion given every other week in 1 of the following dose arms: 0.5, 1, 2.5, 5, 10, and 20 mg/kg.

In Study HuLuc63-1701, the safety profile was favorable at all doses. In the 2.5-mg/kg dose arm, 1 out of the first 3 participants dosed experienced a dose-limited toxicity, a grade 3 serum creatinine elevation. Subsequently, the dose arm was expanded to include another 3 participants. No further dose-limiting toxicities occurred in the 2.5-mg/kg dose arm, and dosing continued up to the 20-mg/kg dose arm. In the 20-mg/kg dose arm, 1 participant experienced a dose-limiting toxicity, a grade 3 hypersensitivity following the first elotuzumab infusion. Thus, no maximum tolerated dose of elotuzumab has been identified. Doses as high as 20 mg/kg have been tolerated in participants with multiple myeloma. This is two times higher than the FDA-approved dose (10 mg/kg), which is the dose we will employ in this IgG4-RD trial.

The most common AEs reported in HuLuc63-1701 were chills (38.2%), fatigue (38.2%), pyrexia (38.2%), cough (29.4%), headache (29.4%), and anemia (26.5%). There was no dose-dependent pattern observed with respect to the type or frequency of SAEs. AEs that led to discontinuation included Grade 3 migraine and Grade 4 congestive cardiac failure (1 participant in the 0.5 mg/kg group) and Grade 3 hypersensitivity (1 participant in the 20 mg/kg group).

The primary causes of death were disease progression (1 participant each in the 0.5, 5, and 20 mg/kg groups) and renal failure (1 participant in the 5 mg/kg group).

1.5.1 Rationale for Elotuzumab Dosing Schedule Change following Part 1A of Protocol AIG01

Prior to this study, elotuzumab had not been administered to patients beyond oncology indications. Evidence about the duration of elotuzumab's effect in IgG4-RD, therefore, need to be derived from Parts 1A and 1B. Experience with elotuzumab in the six patients enrolled Part 1A led to important protocol modifications. The intent of these modifications is to optimize the potential for treatment efficacy in remission maintenance over 48 weeks. The modifications designed to enhance efficacy are discussed below. The goal is to establish safety and gain insight into potential treatment efficacy into Part 1B, and then to test this hypothesis definitively in Part 2, a randomized, double-blind, placebo-controlled trial.

Experience in Part 1A suggests that in IgG4-RD, as in multiple myeloma, elotuzumab needs to be re-administered at some interval. A common pattern was observed in the first six patients enrolled and treated with four weekly elotuzumab infusions. Approximately 1-3 months following the fourth elotuzumab infusion, the start of elevations in serum IgG4 concentrations was observed. This implies the possibility of recurrent immunologic activity. Clinical experience outside AIG01 suggests that immunological activity is likely to be followed by the resumption of clinical activity, usually over a period of a few months [2, 17].

Four patients treated with the Part 1A regimen remain without clinical signs of disease activity: two have completed 48 weeks of follow-up with no clinical signs of disease, and the other two continue in follow-up at this time with no clinical signs of active disease. Each of these patients, however, had evidence of recurrent immunological activity as evidenced by rises in serum IgG4 concentrations between 1 and 3 months after their final elotuzumab infusion. In addition, one patient had an excellent response to remission induction, but had a mild clinical relapse characterized by a recurrent cough at 23 weeks; one patient, who had multi-organ disease at baseline and the highest serum IgG4 concentration of any patient, had a clinical relapse at 10 weeks.

The serological findings related to IgG4 concentrations are supported by flow cytometry investigations. Serial flow cytometry studies on all six patients demonstrate swift, nearly complete depletions of the cell types of interest: namely, the CD4+ and CD8+ cytotoxic T lymphocytes, plasmablasts, and DN3 B cells. Steep declines of each cell type were observed quickly following receipt of elotuzumab, often by 48 hours following the first infusion. These cells begin to re-constitute at varying intervals, averaging approximately 6 weeks across the 6 patients and occurring earlier for the patient with early clinical relapse.

The transient depleting effect of elotuzumab observed in IgG4-RD is consistent with the therapeutic strategy developed for multiple myeloma. Our observations in Part 1A suggest that re-treatment of patients with elotuzumab at some regular interval will be required. This fits the pattern of treatment with other monoclonal antibodies for other autoimmune diseases, most of which require re-treatment on some regular basis. As examples, re-treatment with infliximab every six weeks is a standard treatment approach for Crohn's disease, rheumatoid arthritis, and ankylosing spondylitis.

Because clinical manifestations of active IgG4-RD generally trail serological elevations in IgG4 concentrations, modifications to Parts 1B and 2 of the protocol will include the infusion of elotuzumab every eight weeks starting at Baseline/Day 0, and followed by infusions at Weeks 8, 16, 24, 32, and 40. This elotuzumab + 10-week prednisone taper appears likely to establish disease control in a substantial majority of patients treated in this fashion. Regularly planned re-treatment of patients in Part 1B will permit important insights into the potential efficacy of every 8-week elotuzumab infusions for the maintenance of remission.

Finally, the observations from Part 1A also underscore the importance of blinding both the investigators and participants to serum IgG4 concentrations in the randomized, double-blind part of the elotuzumab in IgG4-RD trial program.

2 Study Hypotheses/Objectives

2.1 Hypotheses

1. Elotuzumab is safe in IgG4-RD. To provide initial confirmation that targeting SLAMF7 is a safe therapeutic strategy in IgG4-RD, we will enroll 12 participants in Part 1 of this proposal to receive elotuzumab in one of two regimens differing in both intensity and duration, with protocolized monitoring for treatment-related adverse effects.
2. A twelve month course (six administrations) of elotuzumab will induce reduction in disease activity in IgG4-RD. This hypothesis will be tested in Part 2 of this proposal, a randomized, double-blind, placebo-controlled trial. The IgG4-RD RI will be used to quantify disease activity [24].
3. Because elotuzumab will eliminate effector cells with pro-fibrotic function, elotuzumab-induced remission will correlate with declining Enhanced Liver Fibrosis (ELF) scores. The ELF score is an indirect measure of fibroblast activation and extracellular matrix deposition [14, 25, 26].

2.2 Mechanistic Hypotheses

1. CD4+CTLs will decline at a slower rate compared to activated B cells. This is because cytotoxic T lymphocytes are evolutionarily resistant to cytotoxicity, as evidenced by their capacity for serial killing and ability to endocytose cytotoxic granules [27, 28]. We also acknowledge an alternative hypothesis: namely that activated B cells will decline at a slower rate compared to CTLs. This is because SLAMF7 engagement on activated B cells results in B cell growth and survival [29].
2. Elotuzumab achieves tissue-level depletion of SLAMF7-expressing lymphocyte sub-populations.
3. Expansion of the effector (CD57+CD28-) CD4+CTL subset and oligoclonality correlate with disease activity and decline in a manner concordant with elotuzumab-induced clinical improvement.
4. Elotuzumab failure will be predicted by the failure to eliminate (CD57+CD28-) CD4+CTLs as determined by peripheral blood flow cytometry.
5. Soluble SLAMF7 levels correlate with disease activity.

2.3 Primary Objectives

Part 1: To determine the safety and tolerability of the addition of elotuzumab to prednisone in participants with IgG4-RD.

Part 2: To compare the effect of the addition of elotuzumab versus placebo to prednisone on the IgG4-RD RI at 48 weeks in participants with IgG4-RD.

2.4 Secondary Objectives

1. To compare the effect of the addition of elotuzumab versus placebo to prednisone on complete remission at 48 weeks.
2. To compare the effect of the addition of elotuzumab versus placebo to prednisone on the number of disease flares (as defined in Section 3.5.3) per participant over time.
3. To compare the effect of the addition of elotuzumab versus placebo to prednisone on the change from baseline in Physician Global Assessment (PhGA) at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 weeks.
4. To compare the effect of the addition of elotuzumab versus placebo to prednisone on Patient Global Assessment (PGA) at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 weeks.
5. To compare the effect of the addition of elotuzumab versus placebo to prednisone on safety.

2.5 Exploratory Objectives

1. To compare the effect of the addition of elotuzumab versus placebo to prednisone on serum immunoglobulin levels, IgG subclass concentrations, IgE levels, eosinophils, and serum C3 and C4 levels.
2. To compare the effect of the addition of elotuzumab versus placebo to prednisone on participants' ELF scores.
3. To evaluate the effect of elotuzumab on CD4+ T cells and B cell subsets, specifically:
    a. CD4+ cytotoxic T lymphocytes
    b. CD8+ cytotoxic T lymphocytes
    c. CD4+ T follicular helper cells
    d. CD4+ peripheral helper T cells
    e. Plasmablasts
    f. Activated B cells, including double-negative (CD19+IgD-CD27-) B cells
4. To determine the kinetics of cell depletion induced by elotuzumab on disease-associated, SLAMF7-expressing lymphocyte subpopulations including CD4+ cytotoxic T cells and activated B cells, including plasmablasts.
5. To determine the effect of elotuzumab at the tissue level, using submandibular gland biopsies in participants with submandibular gland disease who consent separately to biopsies before and after treatment.

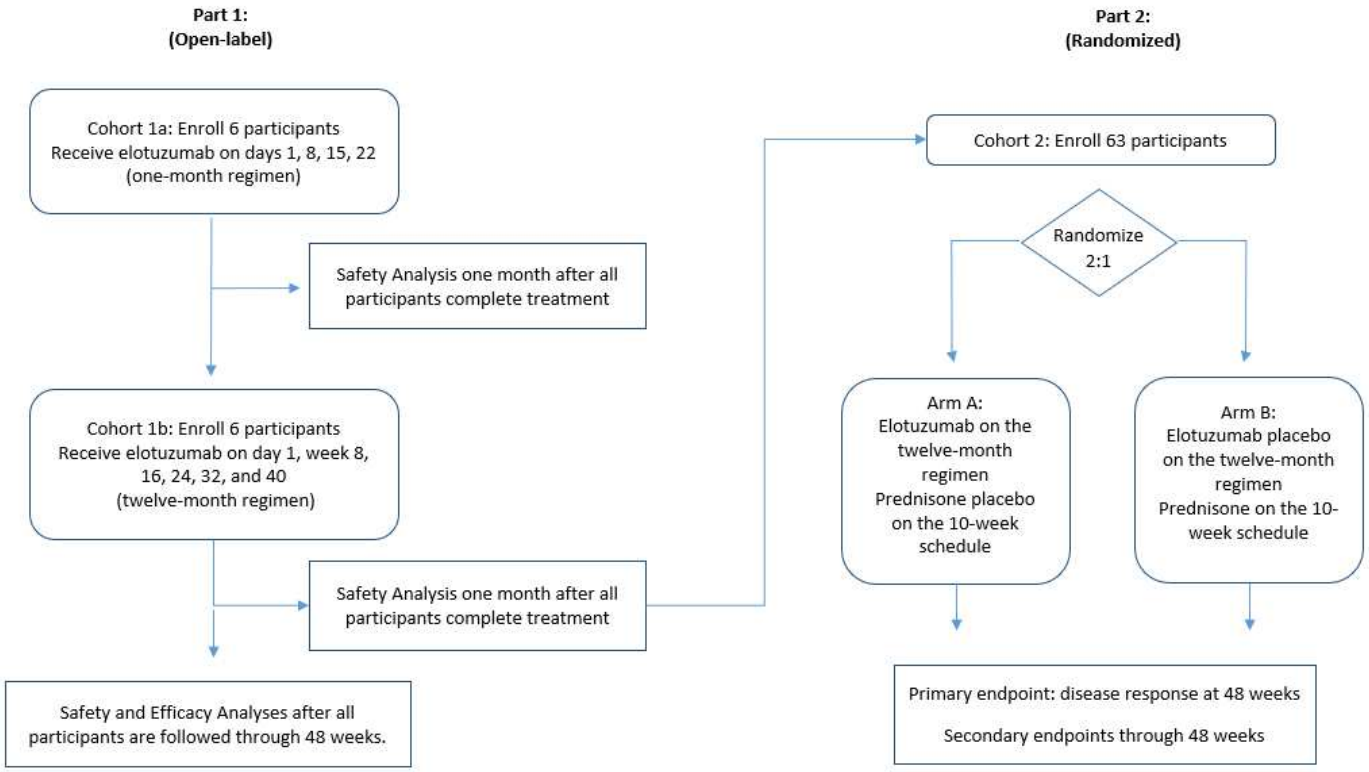
6. To determine the utility of using the clonally-expanded effector subset (CD57+CD28-) of CD4+CTLs as a biomarker of disease activity.
7. To determine the utility of soluble plasma SLAMF7 levels as indicators of disease activity and predictors of disease relapse.
8. To evaluate the longitudinal profile of patient reported outcomes on quality of life over the study period using the SF-36 health survey.

3 Study Design

3.1 Description of Study Design

This is a two-part multi-center clinical trial in participants with active IgG4-RD. Part 1 is an open-label, dose escalation phase to determine the safety of elotuzumab for investigation in IgG4-RD. If the addition of elotuzumab to prednisone is determined to be safe, Part 2 will be initiated as a randomized, placebo-controlled, double-blinded trial. Part 2 will compare the effects of the addition of elotuzumab versus placebo to prednisone in participants with IgG4-RD. Approximately 75 participants with active IgG4-RD will be enrolled in the overall program, 12 in Part 1 and 63 in Part 2.

Figure 3. Overall Study Design Schema



3.1.1 Part 1: Open-label Phase

In Part 1, approximately 12 participants will be enrolled into one of two elotuzumab treatment regimens. The first six participants will receive 1 month of treatment (Cohort 1a). One month after the last participant in Cohort 1a has completed the one-month regimen and the week 9 visit has occurred, a Safety Review Committee (SRC) review will

be performed to determine the safety of moving to Cohort 1b, where six participants will receive the twelve-month regimen. Elotuzumab will be administered as follows:

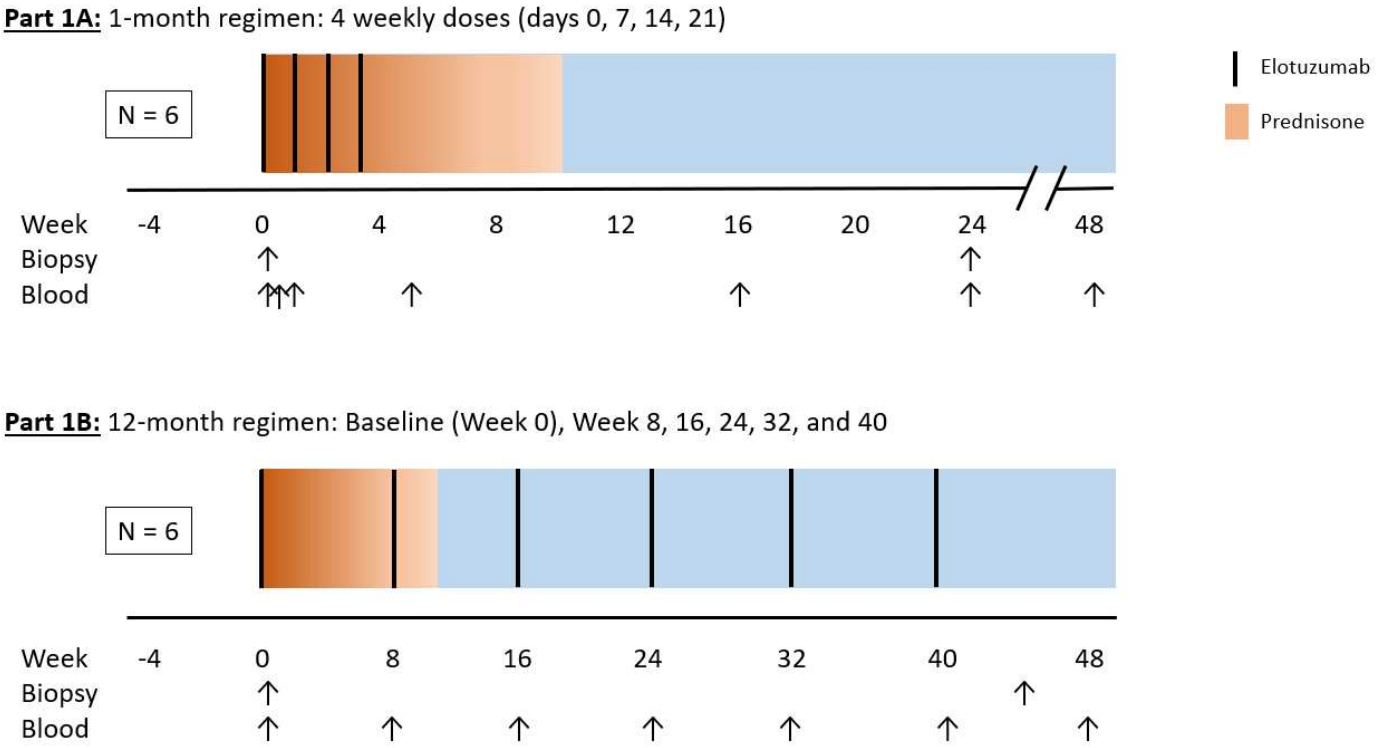
Cohort 1a: One-month regimen: four weekly doses at 10 mg/kg on Days 0, 7, 14, 21
Cohort 1b: Twelve-month regimen: six doses at 10 mg/kg on Baseline/Day 0 and Weeks 8, 16, 24, 32, and 40.

All participants will also receive a standardized prednisone taper, starting at either 40 mg orally daily or 30 mg orally daily based on doses received during the screening period (see 7.1.1.3). This will be tapered to discontinuation over a 10-week period.

The schema for Part 1 is shown below **(Figure 4)**.

Figure 4. Trial Schema, Part 1

AIG01: Participant flow in Part 1



Immunosuppressive Treatment During the Screening Period

It is anticipated that some participants will be on immunosuppressive treatment and/or prednisone during the screening period. Based on the investigator's judgement, participants who present with aggressive disease or who require a higher starting dose of prednisone because of a large body mass index may be placed on up to 60 mg prednisone daily during the screening period. The dose will need to be decreased to 40 mg prednisone /day by the baseline visit.

Prednisone Dosing

Participants in Part 1 will begin dosing with prednisone on the day of their first elotuzumab infusion. The ten-week dosing taper is described in Section 7.1.1.3.

Sampling for Mechanistic Studies in Part 1A. All participants in Part 1A will undergo blood sampling for mechanistic studies beyond routine flow cytometry at the following time points:

- Baseline/Day 0
- Two days after the first infusion
- Day 7
- Weeks 5, 16, 24 and 48

Sampling for Mechanistic Studies in Part 1B. All participants in Part 1B will undergo blood sampling for mechanistic studies beyond routine flow cytometry at the following time points:

- Baseline/Day 0
- Weeks 8, 16, 24, 32, 40 and 48

Participants will be followed for a total study period of up to 48 weeks.

3.1.2 Transition to Part 2

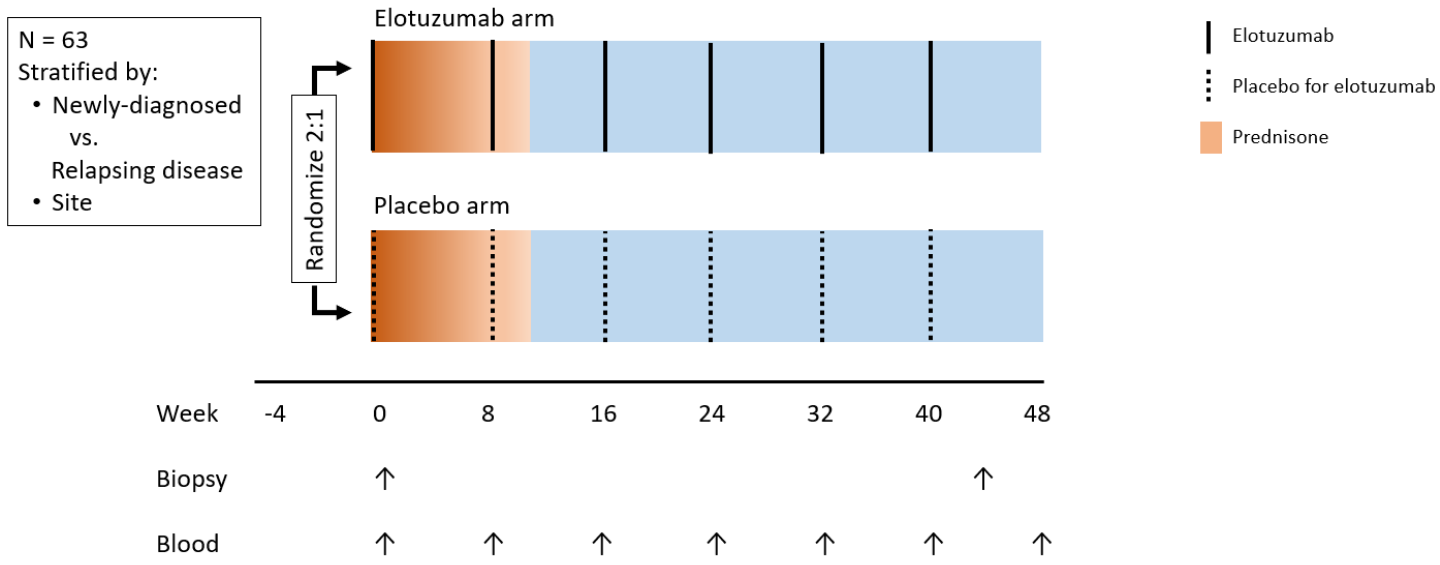
Once the last participant in Cohort 1b has completed the week 48 visit, a Safety Review Committee (SRC) review will be performed to determine the safety of moving to Part 2 of the trial as described in Section 12.11.2. If the SRC determines the longer duration of elotuzumab is safe, the twelve-month dosing regimen will be used in Part 2. If there are safety concerns with the longer regimen of elotuzumab, the SRC may make recommendations for protocol revision.

3.1.3 Part 2: Randomized Phase

Part 2 will enroll a total of 63 participants. Part 2 is a randomized double blind, placebo-controlled trial. Sixty-three participants will be enrolled and randomized in a 2:1 ratio to two treatment arms. Arm A: approximately 42 participants will be randomized to receive elotuzumab; Arm B: approximately 21 participants will be randomized to receive placebo elotuzumab. It is anticipated that the twelve-month regimen from Part 1 will be used for the elotuzumab/placebo elotuzumab dosing schedule provided there is no safety signal detected. All randomized participants will receive a standardized prednisone taper starting at either 40 mg orally daily or 30 mg orally daily based on doses received during the screening period (see 7.1.1.3). This will be tapered to discontinuation over a 10-week period. The trial schema for Part 2 is shown in **Figure 5**, below.

Figure 5. Trial Schema, Part 2

AIG01: Participant flow in Part 2



Immunosuppressive Treatment During the Screening Period

It is anticipated that some participants will be on immunosuppressive treatment and/or prednisone during the screening period. Based on the investigator's judgement, participants who present with aggressive disease or who require a higher starting dose of prednisone because of a large body mass index may be placed on up to 60 mg prednisone daily during the screening period. The dose will need to be decreased to 40 mg prednisone /day by the baseline visit.

Prednisone Dosing

Participants in Part 2 will begin dosing with prednisone on the day of their first /placebo elotuzumab infusion. The ten-week dosing taper is described in Section 7.1.1.3.

Sampling for Mechanistic Studies in Part 2. All participants in Part 2 will undergo blood sampling for mechanistic studies beyond routine flow cytometry at the following time points:

- Baseline/Day 0
- Weeks 8, 16, 24, 32, 40 and 48

3.1.4 Study Duration

The rate of recruitment to AIG01 is anticipated to be 0.5 participants per week.

- The duration target for Part 1A prior to initiation of Part 1B is 21 weeks (12 weeks of recruitment, 9 weeks of follow-up).
- The duration target for Part 1B prior to initiation of Part 2 is 60 weeks (12 weeks of recruitment, 48 weeks of follow-up).
- The duration target for Part 2 is 176 weeks (128 weeks of recruitment, 48 weeks of follow-up).

The total study duration is estimated to be 257 weeks (approximately 5 years).

3.2 Primary Endpoints

Part 1: Primary Safety Endpoint

The proportion of participants in each cohort who experience at least one Grade 3 or higher adverse event during study participation.

Part 2: Primary Efficacy Endpoint

Disease response at 48 weeks, defined as percent improvement in the IgG4-RD RI score over baseline.

3.3 Secondary Endpoints

Part 2: Key Secondary Efficacy Endpoint

1. Complete remission at 48 weeks, defined as an IgG4-RD RI Score of 0 and a glucocorticoid dose of 0 mg/day and no flare since beginning treatment.

Part 1 and Part 2: Additional Secondary Efficacy Endpoints

1. The proportion of participants that reach the following threshold levels of IgG4-RD RI improvement at 48 weeks: 50% and 75%.
2. Number of disease flares, as defined in Section 3.5.3.
3. Change in PhGA from baseline.
4. Change in PGA from baseline.
5. Disease-related damage, as measured by the damage section of the IgG4-RD RI.

Part 1 and Part 2: Secondary Safety Endpoints

1. The proportion of participants who experience at least one Grade 2 or higher adverse event.
2. The proportion of participants with a Grade 3 or higher infection.
3. The proportion of participants who experience a malignancy.
4. The proportion of participants who experience a Hepatotoxicity, defined as increase in the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) to elevations three times the upper limit of normal.
5. The proportion of participants who experience a serious adverse event.
6. The proportion of participants who experience infusion reactions, defined as any adverse reaction within 24 hours of infusion which are Grade 2 or higher events and at least possibly related to study drug.

Part 2: Secondary Safety Endpoint

1. The proportion of participants who experience at least one Grade 3 or higher adverse event.

3.4 Exploratory Endpoints

Part 1 and 2: Exploratory Endpoints

1. Serum immunoglobulin levels, IgG subclass concentrations, IgE levels, eosinophils, and serum C3 and C4 levels.
2. ELF score (see 3.5.7).
3. Blood concentrations of T cells and B cell subsets of interest, specifically:
    a. CD4+ cytotoxic T lymphocytes
    b. CD8+ cytotoxic T lymphocytes
    c. CD4+ T follicular helper cells
    d. CD4+ peripheral helper T cells
    e. Plasmablasts
    f. Activated B cells, including double-negative (CD19+IgD-CD27-) B cells

4. Comparison of the kinetics of cell depletion induced by the addition of elotuzumab versus placebo to prednisone on disease-associated, SLAMF7-expressing lymphocyte subpopulations, including CD4+ cytotoxic T cells and activated B cells, including plasmablasts.
5. Comparison of elotuzumab and placebo with regard to the impact of the tissue concentrations of CD4+ cytotoxic T cells and activated B cells subsets of interest, pre- and post-treatment submandibular gland biopsies.
6. Correlation of the clonally-expanded effector subset (CD57+CD28-) of CD4+CTLs with disease activity.
7. Correlation of soluble plasma SLAMF7 levels with disease activity and risk of relapse.
8. SF-36 health survey.

3.5 Description of Outcome Variables and Instruments

3.5.1 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria

The 2019 ACR/EULAR Classification Criteria for IgG4-RD [30, 31] will be used as part of the Inclusion Criteria. These criteria were developed by an international, multi-specialty collaboration of 86 physicians. Investigators used consensus exercises, existing literature, derivation and validation cohorts of 1,879 participants (n=1,086 cases, n=793 mimickers), and multi-criterion decision analysis to identify, weight, and test potential classification criteria. There are three steps to classification. First, a potential IgG4-RD case must demonstrate involvement of at least one of eleven possible organs in a manner consistent with IgG4-RD. Second, Exclusion Criteria consist of a total of 32 clinical, serological, radiological, and pathological items which, if present, eliminate the participant from IgG4-RD classification. Third, eight weighted Inclusion Criteria domains address clinical findings, serologic results, radiology assessments, and pathology interpretations. A sample assessment form is included in **Appendix 2: ACR/EULAR**. Investigators will obtain the biopsy reports from tissue biopsies previously performed for diagnosis.

3.5.2 IgG4-RD Responder Index

The IgG4-RD RI is based on the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis [32], utilized for the evaluation and licensure of rituximab in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [33]. The IgG4-RD RI detects change in disease activity and identifies improvements and worsening in the same or different organ systems. The IgG4-RD RI has been used in prior clinical trials to monitor IgG4-RD disease activity [11, 18, 34].

During Part 1A, disease activity will be measured by the IgG4-RD RI at Screening, Baseline/Day 0 if necessary, and at Week 24. During Part 1B and 2, disease activity will be measured by the IgG4-RD RI at Screening, Baseline/Day 0 if necessary, and at Week 48. The IgG4-RD RI does not need to be repeated at Baseline unless there has been a change in Prednisone or other DMARD or if there has been an apparent change in disease activity between Screening and Baseline. The RI will also be measured at any interim visit conducted because of the possibility of recurrent disease or for the purpose of assessing a potential AE.

Imaging required to complete a full IgG4-RD RI assessment will be performed at the Screening visit. Specifically, all participants will undergo either a CT or MRI of the chest, abdomen, and pelvis within 6 weeks of the Screening visit. Participants with clinical evidence of orbital disease will also undergo CT or MRI of that area. If abnormalities in a particular area are detected at Screening, the participant will have the same type of study repeated at Week 24 (Part 1A) or Week 48 (Part 1B and 2) unless there are contraindications to use of the same imaging technique. Imaging at Week 24 (Part 1A) and Week 48 (Part 1B and 2) will be performed if there is a clinical reason to suspect disease activity at that site. Imaging may also be repeated at the discretion of the investigator at a visit other than those two time points if required to assess disease activity because of a potential disease flare or to assess an adverse event. If

participants have received prednisone or another glucocorticoid agent for a total of more than 21 days in the interval between the time of qualifying imaging and the Screening visit, the imaging will be repeated at Screening.

An assessment of damage caused by IgG4-RD in each affected organ is part of the RI. Activity and damage are considered separately from the standpoint of scoring, because only disease activity can be expected to respond to treatment. A sample assessment form is included in **Appendix 3: IgG4-RD RI**.

3.5.3 Disease Flare Definition

Disease flare will be defined as recurrence of disease activity such that additional immunosuppressive therapy beyond the trial protocol is indicated. Such additional therapy may include glucocorticoids or alternative immunosuppressive agents. At the time of a potential disease flare, investigators will document the features of the disease flare by performing the assessments outlined in the **Flare Documentation Guidance (Appendix 5: Flare Documentation Guide).** A disease flare must be reported by the site investigators to the Division of Allergy, Immunology, Transplantation – Statistical and Clinical Coordinating Center (SCCC) within 24 hours of discovery (Section 12.5.2).

3.5.4 Physician and Patient Global Assessment Visual Analog Scale (VAS)

The PhGA of the participant's current disease activity is 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). Only active disease (as opposed to damage) is considered in the scoring of the PhGA. The PGA of current disease activity will be assessed on an identical VAS. During Part 1A, assessments will be performed at Screening, Baseline/Day 0, Weeks 1, 5, 9, 16, 24 and 48, as well as at any interim visit conducted because of the possibility of recurrent disease or for the purpose of assessing a potential AE. During Part 1B and 2, assessments will be performed at Screening, Baseline/Day 0, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, as well as at any interim visit conducted because of the possibility of recurrent disease or for the purpose of assessing a potential AE. A sample assessment form is included in **Appendix 4: PhGA and PGA VAS**.

3.5.5 Flare Guidance Document

The Flare Guidance Document (FGD) provides guidance with regard to the evaluation of potential disease flares and outlines appropriate work-ups for IgG4-RD activity in each organ. Investigators will complete a disease activity assessment only in the organs involved in the flare. The suggested laboratory evaluation, radiology studies, and other procedures (e.g., biopsy) as well as the minimum criteria for diagnosis of a disease flare are provided for each organ system. Following the documentation of evidence supporting a flare in a given organ, the investigator will complete a short narrative justifying the diagnosis of a flare in that organ. A sample assessment form is included in **Appendix 5: Flare Documentation Guide**.

3.5.6 36-Item Short Form (SF-36) 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 participant's perspective of the effect that the disease plays in their activities of daily life. These measures rely upon participant self-reporting and are now widely utilized. During Part 1A, this assessment will be performed at Baseline/Day 0 and on Weeks 5, 16, 24 and 48. During Part 1B and 2, this assessment will be performed at Baseline/Day 0, Weeks 8, 16, 24, 32, 40, and 48. A sample assessment form is included in **Appendix 6: SF-36 Health Survey.**

3.5.7 ELF Score

The ELF score is a set of serological biomarkers consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA) that shows good correlations with fibrosis within organs. During Part 1A, this assessment will be performed at Baseline/Day 0 and on Weeks 5 and 24. During Part 1B and 2, this assessment will be performed at Baseline/Day 0 and at Week 8, 16, 24, 32, and 40.

3.6 Criteria for Evaluation

3.6.1 Disease Activity

The following disease activity parameters will be recorded at scheduled intervals throughout the study:

- IgG4-RD RI Activity Score
- Physician Global Assessment of Disease Activity VAS

3.6.2 Disease-Related Damage

- IgG4-RD RI Damage Score

3.6.3 Patient-Reported Outcomes

- SF-36
- Patient Global Assessment VAS

3.6.4 Safety

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

- All adverse events using the grading criteria described in Section 12.3.1
- Clinical laboratory testing (clinical chemistry, hematology, and urinalysis)
- Concomitant medications: Any medication related to IgG4-RD taken at any point should be recorded. Other non-IgG4-RD related concomitant medications taken 30 days prior to screening through study completion or termination should be reported.

3.6.5 Serologic Indicators of Response

- Immunoglobulin levels
- IgG subclasses
- IgE
- Eosinophil levels
- C3 and C4 levels
- ELF score

3.6.6 Mechanistic Studies

Mechanistic studies will be conducted at the Ragon Institute of Harvard, Massachusetts General Hospital (MGH), Massachusetts Institute of Technology (MIT), and at Emory University.

Briefly, PBMCs and plasma will be isolated and frozen from each participant on the following schedules. During Part 1A, samples will be collected at Baseline/Day 0 and then two days after the first elotuzumab infusion. Subsequent samples will also be obtained at 1, 5, 16, 24 and 48 weeks, corresponding with clinical blood draws. During Part 1B and 2, samples will be collected at Screening or Baseline/Day 0 and Weeks 8, 16, 24, 32, 40 and 48, corresponding with clinical blood draws. Mechanistic assessments should not be collected at Screening if the participant is taking glucocorticoids on the day of the Screening Visit. If Mechanistic Assessments were not collected at the Screening

Visit, they must be collected at Baseline/Day 0. PBMCs and plasma will be stored in liquid nitrogen for preservation. The following experiments will be carried out in batches of 10 participant time points per experiment:

1. Flow cytometric quantification of plasmablasts, activated B cells, terminally differentiated CD4+CTLs, terminally differentiated CD8+CTLs, activated 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 on the schedules noted above 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 elotuzumab.
3. Participants with known expansions of the respective cell type and clinical responsiveness to elotuzumab, terminally differentiated CD4+CTLs, terminally differentiated CD8+CTLs, and activated B cells will be sorted by fluorescence-activated cell sorting (FACS) at weeks 0, 16, 24, and 48. RNA will be isolated to undergo reverse transcription polymerase chain reaction (RT-PCR) amplification of the TCR-β/IgH. Next-Generation Sequencing will be used to define the diversity of the T cell receptor/B cell receptor (TCR/BCR) repertoire longitudinally to ascertain how elotuzumab may impact clonality.

Mechanistic studies will also be performed on a subset of participants (MGH participants only) with submandibular gland involvement at baseline who consent to follow-up submandibular gland biopsies. Biopsies for immunohistochemical studies will be performed using standard core needle biopsy techniques. The purpose of these studies will be to determine the effects of study therapy on the chronic inflammatory response at a site of tissue inflammation in submandibular glands. For Part 1A, submandibular gland samples will be obtained prior to Baseline/Day 0 and between Weeks 16 and 24 following the Baseline/Day 0 visit. For Part 1B and 2, submandibular gland samples will be obtained prior to the Baseline/Day 0 Visit, following eligibility confirmation ,and between Weeks 40 and 44 following the Baseline/Day 0 visit. Paraffin-embedded sections will be stained with antibodies to identify T cells, B cells, macrophages, dendritic cells, cytokines, and chemokines.

3.7 Stratification, Randomization, and Blinding/Masking

In Part 2, after participants sign the consent form, those eligible will be randomized in a 2:1 ratio to receive elotuzumab versus placebo. Randomization will be stratified by whether participants have newly-diagnosed or relapsing disease at entry.

Randomization will be accomplished through a password-protected, web-based, randomization system. The investigators, clinic personnel, and participants will not be informed regarding the intervention assignment until the study is unblinded. Laboratories performing assays for this protocol will be masked to the identity and group assignment of biological materials to be studied.

3.7.1 Procedure for Unblinding/Unmasking

Procedures for unblinding are only applicable for Part 2. Unblinding before the study is completed will occur only if a participant's well-being is threatened and the site investigator believes unblinding is necessary for the participant's safety. Unblinding may also occur in the event of pregnancy in a female participant or a male participant's partner.

Whenever possible, before treatment assignment for an individual participant is unblinded, the site investigator must confer with the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor and the protocol chair. If emergency unblinding is required for a participant's well-being during non-business hours, the site principal investigator or designee (i.e., sub-investigator specified on Form FDA 1572) must notify the investigative pharmacy of the need for the treatment assignment. A full account of the event will be recorded, including the date and time of

the emergency, the reason for the decision to unblind, and the names of those notified/consulted with. The site investigator will notify the protocol chair and the study Statistical and Clinical Coordinating Center of the unblinding event on the next business day. The emergency unblinding will be reported to the Data and Safety Monitoring Board (DSMB). The reasons for unblinding of a participant's treatment assignment will be included in the final study report to the FDA.

Unblinding of treatment assignments for an individual participant or subgroups of participants for planned or unplanned interim analyses to support DSMB reviews will require NIAID approval. Study-derived Investigational New Drug (IND) Safety Reports will be reported to the FDA, DSMB, and Institutional Review Board (IRB) in an unblinded fashion as per International Conference for Harmonisation (ICH) and local guidance after approval by the NIAID medical monitor.

4 Selection of Participants

4.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Participant must be able to understand and provide informed consent and be willing to comply with study procedures and follow up.
2. Are at least 18 years of age and not older than 70 years of age at screening.
3. Meet the ACR/EULAR Classification Criteria for IgG4-RD [30, 31].
4. Have active disease based at screening on an IgG4-RD RI ≥4, with disease manifestations in at least two organ systems.
5. May have newly-diagnosed or relapsing disease at screening. Relapsing disease is defined as IgG4-RD that has previously been in remission but is now active again.
6. May be on treatment or off treatment for IgG4-RD at the time of screening. If on treatment, must be willing to discontinue those other treatments before the baseline visit.
7. No history of severe allergic reactions to monoclonal antibodies.
8. Female participants of childbearing potential must have a negative pregnancy test upon study entry.
9. Female participants of childbearing potential and male participants with a partner of childbearing potential must agree to consistently and correctly use FDA approved highly effective methods of birth control, as shown in **Appendix 8: Acceptable Contraception Methods for Females of Reproductive Potential**, for the entire duration of the study and 6 months after last elotuzumab infusion.
10. Immunization with one of the FDA authorized or licensed SARS-CoV-2 vaccines as per CDC recommendations at the time of informed consent is required for study entry. Vaccinations must have been completed at least 2 weeks prior to start of study therapy.[1]

4.2 Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Presence of a condition other than IgG4-RD that (e.g., asthma) is likely to require systemic Glucocorticoids (GC) for disease control during the period of the trial.

[1] *Vaccination status must conform to CDC recommendations for immunocompromised individuals. These recommendations are subject to change, but are updated at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html.*

2. Malignancy within 5 years (except successfully treated in situ cervical cancer, resected squamous cell or basal cell carcinoma of the skin.)
3. The following lab values as indicators of hepatic dysfunction:
    a. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than three times the upper limit of normal (ULN)
    b. Total bilirubin > two times the ULN unless caused by Gilbert's disease. Gilbert's disease with total bilirubin > three times ULN.
    c. Serum albumin < 2.5 gm/dL.
4. Evidence of another uncontrolled condition which, in the judgment of the investigator, could interfere with participation in the trial according to the protocol.
5. Active infection requiring hospitalization or treatment with systemic antimicrobial agents within the 30 days prior to treatment allocation/randomization.
6. Prior use of rituximab or other B cell depleting agents within 9 months of enrollment unless B cells have been demonstrated to have repopulated.
7. Use of any investigational agent or biologic and non-biologic DMARDs within 5 half-lives of the agent (or 6 months if the half-life is unknown) prior to enrollment.
8. Any of the following laboratory tests at the Screening Visit:
    a. White blood cell count (WBC) < 3.0 x 10^3/µL.
    b. Absolute neutrophil count (ANC) < 1.5 x 10^3/µL.
    c. Hemoglobin < 10 g/dL.
    d. Platelet count < 75 x 10^9/L.
    e. Estimated glomerular filtration rate (eGFR) ≤ 45 ml/minute/1.73 m^2.
9. The use of supplemental oxygen at baseline.
10. At or within 90 days of screening: Positive Interferon-Gamma Release Assay (IGRA). Indeterminate IGRAs must be repeated (with same or other IGRA per local policy) and shown to be negative. Alternatively, if the assay remains indeterminant, a participant must have a negative PPD. Finally, if the participant has had the Bacille Calmette-Guerin (BCG) vaccine or has some other condition complicating the interpretation of TB testing, consultation with infectious disease specialist must be obtained before receipt of the first investigational infusion.
    a. Participants diagnosed with latent TB are eligible but must have received appropriate prophylaxis for 30 days before their first investigational infusion.
11. Medical history or serologic evidence at Screening of chronic infections including:
    a. Human immunodeficiency virus infection.
    b. Hepatitis B as indicated by surface antigen or hepatitis B core antibody positivity
    c. Hepatitis C as indicated by anti-hepatitis C antibody positivity; if a participant is Hepatitis C antibody positive, they will be eligible to participate in the study if he/she is negative for viral load at Screening.
12. Live vaccines within 8 weeks of initiating study therapy.
13. Participant is pregnant or breastfeeding, or planning a pregnancy while enrolled in the study.
14. Substance use disorder, including the recurrent use of alcohol and/or drugs within the past year associated with clinically significant impairment associated with failure to meet major responsibilities at work, school, or home.
15. IgG4-RD that is dominated primarily by advanced fibrotic lesions. Specifically, participants whose disease manifestations consist only of
    a. retroperitoneal fibrosis,
    b. fibrosing mediatinitis,

c. sclerosing mesenteritis, or
d. Riedel's thyroiditis.

Participants with these disease manifestations can be included, however, only if they have disease in 2 organ systems that is not of an advanced fibrotic nature and otherwise meet the Inclusion and Exclusion Criteria.

16. Evidence a SARS-CoV-2 (COVID-19) infection started within the 30 days prior to treatment allocation/randomization. Participants diagnosed with SARS-CoV-2 (COVID-19) infection more than 30 days prior to treatment allocation/randomization must have symptoms resolved and be deemed fit to participate in the trial.

4.3 Co-enrollment Guidelines

While participating in AIG01, participants may not be in another interventional trial, but may be in observational registries or cohorts as long as the total combined volume of blood to be drawn does not exceed the National Institutes of Health (NIH) limit of and objectives do not confound the current study.

5 Known and Potential Risks and Benefits to Participants

5.1 Risks of Investigational Product or Intervention as cited in Investigator Brochure or Package Insert

Common risks include infusion reactions, immunogenicity, and infections.

5.1.1 Infusion Reactions

Elotuzumab can cause infusion reactions. The infusion reactions associated with elotuzumab are mitigated with a standard premedication regimen.

Infusion reactions were reported in approximately 10% of participants treated with elotuzumab, lenalidomide, and dexamethasone (Study CA204004); in 5.4% of participants treated with elotuzumab, bortezomib, and dexamethasone (Study CA204009); and in 2.5% of participants treated with elotuzumab, lenalidomide, and dexamethasone (Study CA204116). All reports of infusion reaction were ≤ Grade 3.

Grade 3 infusion reactions occurred in 1.3 % of participants in Study CA204004 and in no participants in Study CA204009 or Study CA204116. The most common symptoms of an infusion reaction included fever, chills, and hypotension. In Study CA204004, 5% of participants required interruption of the administration of elotuzumab due to infusion reactions for a median of 25 minutes and 1% of participants discontinued due to infusion reactions. In Study CA204009, 20% of participants required interruption of the administration of elotuzumab for a median of 40 minutes but no participants discontinued due to infusion reactions. Of the participants who experienced an infusion reaction, 70% (23/33) in Study CA204004 and 80% (4/5) in Study CA204009 had them during the first dose. [35-38]

5.1.2 Pregnancy & Lactation

Animal reproduction studies have not been conducted with elotuzumab. It is also not known whether elotuzumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Elotuzumab is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk. Study participants should be advised to avoid pregnancy while receiving treatment with elotuzumab.

It is not known whether elotuzumab is secreted into human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. However, because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue breastfeeding or to discontinue from elotuzumab therapy, taking into account the benefit of breastfeeding for the child and the benefit of elotuzumab therapy for the woman.

5.1.3 Infections

The incidence of infections, including pneumonia, was higher with elotuzumab treatment than with controls. In the largest clinical study of elotuzumab in participants with multiple myeloma, Study CA204004; N = 635), infections were reported in 81.4% of participants in the elotuzumab/lenalidomide arm and 74.4% in the lenalidomide arm. Grade 3 to 4 infections were noted in 28% and 24.3% of elotuzumab/lenalidomide-treated participants and lenalidomide-treated participants, respectively. Fatal infections were infrequent, reported in 2.5% of the elotuzumab/lenalidomide group and 2.2% of the lenalidomide group.

In the same trial (CA204004) opportunistic infections occurred in 22% of participants in the elotuzumab/ lenalidomide arm and in 13% of participants in the lenalidomide arm. Fungal infections occurred in 10% of the participants in the elotuzumab/ lenalidomide arm and 5% of participants in the lenalidomide arm. Herpes zoster occurred in 14% of the participants in the elotuzumab/lenalidomide arm and 7% of participants in the lenalidomide arm.

Elotuzumab may also increase the risk of SARS-CoV-2 (COVID-19) infections. This is because of the drug's broad effects on B-lymphocytes as well as CD4+ and CD8+ T-lymphocytes and NK cells. As of the date of this amendment, Bristol-Myers Squibb has not recognized a safety signal in COVID-19 infection in their worldwide safety database (personal communication). In view of the worldwide surge in SARS-CoV-2 (Omicron variant) infections in the winter of 2021-2022, the AIG01 protocol was adjusted accordingly as described in section 6.4.2: Toxicity Prevention & Management.

5.1.4 Hepatotoxicity

In study CA201004, elevations in liver enzymes greater than 3 times the ULN and total bilirubin greater than 2 times the ULN and alkaline phosphatase less than 2 times the ULN consistent with hepatotoxicity were see in 2.5% of participants in the elotuzumab/ lenalidomide arm and 0.6% of participants in the lenalidomide arm. Two of the 8 affected participants were not able to continue treatment with elotuzumab. No meaningful difference in hepatic function tests between the arms was reported.

IgG4-RD seldom affects hepatocytes directly. Abnormalities of the liver noted in IgG4-RD are usually the result of biliary tract disease. We do not anticipate, therefore, an increased propensity to liver injury among the IgG4-RD participants in this trial.

5.1.5 Malignancies

There are no consistent reports of the use of elotuzumab associated with the development of secondary malignancies in the setting of individuals treated for multiple myeloma. However, in study CA204004, invasive secondary primary malignancies were observed in 12.3% of participants in the elotuzumab/ lenalidomide arm and 8.8% of participants in the lenalidomide arm.

5.1.6 Immunogenicity (Anti-Elotuzumab Antibodies)

There is a potential for immunogenicity to elotuzumab. Of 390 participants across 4 clinical studies who were treated with elotuzumab and were evaluable for the presence of anti-product antibodies, 72 (18.5%) participants tested

positive for treatment-emergent anti-product antibodies by an electrochemiluminescent assay. Neutralizing antibodies were detected in 19 of 299 participants in Study CA204004. In the majority of participants, immunogenicity started early, was transient, and resolved by 2 to 4 months. There was no clear causal evidence of altered protein kinase (PK), efficacy, or toxicity profiles with anti-product antibody development.

5.1.7 Other Frequently-reported Adverse Events

The most common AEs (≥ 40%) were diarrhea (67.1%), muscle spasms (61.6%), fatigue (57.5%), constipation (50.7%), nausea (47.9%), upper respiratory tract infection (46.6%), pyrexia (42.5%), back pain (42.5%), and anemia (41.1%). The majority of these were Grade 1 or 2 in severity. Grade 3 to 4 treatment emergent adverse events (TEAEs) were reported in 57 (78.1%) participants. The most common (≥ 10%) were lymphopenia (19.2%), neutropenia (19.2%), thrombocytopenia (17.8%), anemia (15.1%), and pneumonia (11.0%). SAEs reported in more than 2 participants were pneumonia (12.3%), sepsis (6.8%), and bronchitis, cellulitis, and febrile neutropenia (4.1% each).

5.2 Risks of Other Protocol Specified Medications

5.2.1 Corticosteroids

Corticosteroids (prednisone and methylprednisolone) can be associated with weight gain, glucose intolerance, increases in blood pressure, insomnia, mood swings, glaucoma, cataracts, an increase in the risk of infection, skin toxicity (including acne, hirsutism, easy bruisability, skin tears, and striae) and adverse effects on bone mineral density.

Premedications are administered before each elotuzumab infusion. These premedications are:

1. Methylprednisolone 50 mg
2. Diphenhydramine 25-50 mg
3. Acetaminophen 650 mg
4. H2 blocker: famotidine (20 mg intravenously or orally) or equivalent H2 blocker.

Diphenhydramine can be associated with somnolence, drowsiness, impairment of mental functioning, dry mouth, inability to urinate, and constipation.

Acetaminophen can be associated with rash, nausea, headache, hypersensitivity, serious skin reactions, kidney and liver damage.

5.3 Risks of Study Procedures

5.3.1 Risks Specific to Imaging and Contrast Material

Oral or intravenous contrast agents may be used in some radiology studies. The Iodine-based and barium-sulfate compounds may be used for CT scans, with gadolinium the contrast material used for MRI. Risks of contrast include allergic reaction, and rarely anaphylaxis. A careful history regarding risk factors must be assessed. Individuals with history of asthma or allergy to contrast dye, iodine, or shellfish may not be suitable candidates for the procedure. Additionally, impaired renal function may be a contraindication for contrast material. Iodine-based contrast materials pose risk of contrast-induced nephropathy, with worsening of pre-existing renal impairment. Nephrogenic systemic fibrosis, a thickening of the skin, organs, and other tissues, is a rare complication in individuals with renal disease undergoing MRI with contrast material.

The need for contrast agents will be reviewed on an individual basis, consistent with the routine use of these imaging studies and individual risk assessment. Consultation with radiology will be obtained as needed.

5.3.2 Risks Specific to CT Scan

The total amount of radiation for the two CT scans is approximately 12 milliSieverts (mSv). Participants entering the study who have undergone recent CT scan may alternatively have MRI for study baseline establishment. If no abnormalities are detected at Screening/baseline on imaging of the chest/abdomen/pelvis, then the Weeks 24 and 48 imaging study can be an MRI (in the interest of reducing exposure to ionizing radiation from CT).

5.3.3 Risks Specific to MRI

A careful history regarding any of the following contraindications for MRI will be obtained:

- Implanted pacemakers
- Intracranial aneurysm clips
- Cochlear implants
- Certain prosthetic devices
- Implanted drug infusion pumps
- Neurostimulators
- Bone-growth stimulators
- Certain intrauterine contraceptive devices; or
- Any other type of iron-based metal implants.

MRI is also contraindicated in the presence of internal metallic objects such as bullets or shrapnel, as well as surgical clips, pins, plates, screws, metal sutures, or wire mesh. Pregnancy is an exclusion for the procedure and study as a whole.

MRI is contraindicated for individuals with epilepsy. Additionally, a history of claustrophobia and anxiety with previous MRI must be considered as a possible contraindication.

5.3.4 Risks with Peripheral Intravenous Catheters

The placement of peripheral intravenous catheters can be associated with pain, bleeding, ecchymosis, peripheral nerve injury, and infection. Only medical personnel trained and proficient in the placement and management of venous access devices will perform this function in the study.

5.4 Potential Benefits

IgG4-RD is a recently-described disease for which no approved therapy exists. IgG4-RD causes important end-organ damage, including failure of both the exocrine and endocrine pancreas (autoimmune pancreatitis); hepatic failure (cholangitis); kidney failure from intrinsic renal disease (tubulointerstitial nephritis); obstructive nephropathy and chronic pain (retroperitoneal fibrosis); dysfunction of other organs (orbits, lung); and death from a variety of causes (complications of aortitis, pulmonary disease, meningeal involvement, other). Prednisone is an effective therapy in many participants but does not cure the disease, nor does it lead to sustained, treatment-free remissions in most participants. Moreover, the use of glucocorticoids in a disease that affects a middle-aged to elderly population and has a predilection for causing exocrine insufficiency of the pancreas is problematic. Rituximab is a potential alternative therapy to prednisone that has not been studied in detail.

IgG4-RD is an excellent disease model for studying human fibrotic disease. Certain characteristics of IgG4-RD make it an ideal condition through which to explore human immunology and the broad impact of targeting SLAMF7 in human fibrotic disease. First, although recognized only in the past fifteen years, IgG4-RD is in fact relatively common, with an estimated prevalence in the U.S. of approximately 186,000 cases – just barely classifiable as an orphan disease. IgG4-RD has a worldwide disease distribution and is evaluated by medical subspecialists of nearly every type.

Second, IgG4-RD has a clinical phenotype that is now well-recognized. The 2019 Classification Criteria for IgG4-RD have a specificity of 98% and a sensitivity of 83% [30, 31].

Third, and perhaps most importantly, IgG4-RD is typically an indolent disease that causes tissue injury over months or even years due to unbridled inflammation, myofibroblast activation, cytotoxicity, and fibrosis. The indolence of IgG4-RD is crucial to our ability to study disease mechanisms. The upshot of its indolent nature is that clinical trials in IgG4-RD can be designed such that participants are treated with an investigational medication with close monitoring, with little or no additional immunosuppression (e.g., glucocorticoids, mycophenolate mofetil, methotrexate). IgG4-RD therefore offers a favorable disease state in which to investigate the impact of a targeted intervention on the immune system carefully, without the confounding factor of non-specific immunosuppressive therapies used concomitantly.

6 Investigational Regimen

6.1 Elotuzumab and Placebo for Elotuzumab

6.1.1 Product Description

Elotuzumab (BMS-901608) is a humanized recombinant mAb targeted against SLAMF7, a cell surface glycoprotein. Elotuzumab consists of the complementarity determining regions of the mouse antibody, MuLuc63, grafted onto human IgG1 heavy and kappa light chain framework regions.

Elotuzumab for injection is provided in 400 mg single-dose vials for reconstitution, dilution, and IV infusion. The drug product, a nonpyrogenic lyophilized powder, is a white to off-white, whole or fragmented cake contained in a 20 cc Type I glass vial, closed with a 20-mm stopper and sealed with an aluminum seal. Each vial of drug product contains the labeled amount of elotuzumab drug substance, sucrose, sodium citrate dihydrate, citric acid monohydrate, and polysorbate 80. A 0.8-mL overfill is included in each vial to account for vial, needle, and syringe holdup.

6.1.2 Formulation, Packaging, and Labeling

Elotuzumab (Empliciti®) is a marketed drug and will be provided for the conduct of this study by the manufacturer, Bristol-Myers Squibb Co. (BMS). Elotuzumab will be distributed to sites by a designated drug distributor under contract with NIAID.

6.1.3 Storage Conditions

Store elotuzumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light. Do not freeze or shake.

6.1.4 Dosage, Preparation, and Administration

Part 1

Participants receive either a 1-month or twelve-month regimen of elotuzumab, depending on enrollment phase (see Study Design Section 3). Each intravenous dose will be 10 mg/kg, to be determined based on participant's weight. Rounding is permissible within 5% of the nominal dose. The participant's actual weight will be used for dosing. At the Baseline/Day 0 visit, the participant's screening weight will be used for calculation of the Baseline/Day 0 infusion dose. For all subsequent infusions, weight from the previous visit will be used unless weight was obtained more than 42 days previously. If more than 42 days have elapsed since the previous visit, the participant's current weight will be used for calculation.

The 1-month regimen consists of 4 weekly doses of elotuzumab (10 mg/kg) on days 0, 7, 14, and 21. The twelve-month regimen consists of 6 doses at Baseline/Day 0, Week 8, Week 16, Week 24, Week 32, and Week 40.

Part 2

Part 2 is a randomized, double-blind, placebo-controlled phase in with participants receive either elotuzumab or placebo for elotuzumab in a 2:1 ratio. It is anticipated that the twelve-month regimen from Part 1 will be used for the elotuzumab and placebo for elotuzumab dosing schedule, provided there is no safety signal detected. The pharmacist is the only site personnel not blinded to the treatment assignment. Placebo for elotuzumab will be investigational sites' stocked 0.9% normal saline prepared by the site pharmacist.

The oral glucocorticoid regimen for all participants in Part 1 and Part 2 is described in Protocol Section 7.1.1.3.

6.1.4.1 Placebo for Elotuzumab

The placebo for elotuzumab will be 0.9% sterile normal saline for injection. Placebo for elotuzumab will be prepared at each site's investigational pharmacy. Investigational pharmacies will use sterile normal saline that is produced by an FDA registered facility as designated by the presence of a National Drug Code (NDC) number on product labeling. Product information including manufacturer, lot number, and expiration date will be documented on participant-specific accountability log during each preparation and dispensing. Placebo for elotuzumab will be given as intravenous infusion bag, volume matched to elotuzumab. More detailed information will be included in the pharmacy manual.

6.1.4.2 Elotuzumab Administration and Monitoring

6.1.4.2.1 Pre-medication

Pre-medicate approximately 45-90 minutes prior to each elotuzumab/placebo infusion with the following:

- Methylprednisolone 50 mg intravenously
- Diphenhydramine 25-50 mg orally or intravenously
- Acetaminophen 650 mg orally
- H2 blocker: famotidine (20 mg intravenously or orally) or equivalent H2 blocker

6.1.4.2.2 Administration

The infusion is to be administered through a sterile, nonpyrogenic, low protein binding in-line filter (with a pore size of 0.2 µm to 1.2 µm) using an automated infusion pump. Initiate infusion at a rate of 0.5 mL per minute. The infusion may be increased in a stepwise fashion as described in the table below if no infusion reaction. The maximum rate should not exceed 5 mL per minute.

First Dose		Second Dose		Subsequent Doses
Time Interval	**Rate**	**Time Interval**	**Rate**	**Rate**
0-30 min	0.5 mL/min	0-30 min	3 mL/min	5 mL/min
30-60 min	1 mL/min	≥ 30 min	4 mL/min	
≥ 60 min	2 mL/min	---	---	

Elotuzumab must not be administered as an IV push or bolus. Do not mix elotuzumab, or administer as an infusion, with any other medicinal products.

In Part 1A, there must be a minimum of four full days between each weekly infusion. In Part 1B and 2, there must be a minimum of seven full days between each infusion.

If an infusion is missed for reasons other than those requiring premature discontinuation (Section 6.6), a single intermediate delayed infusion may be permitted if it can be administered with the minimum windows before the next scheduled infusion that are noted above. Additional details on toxicity management and criteria for the resolution of specific adverse events before restarting infusions are given in Section 6.4.

In Part 1A, if the infusion schedule has been interrupted, administration of infusions may be adjusted to permit administration of 4 doses prior to the week 11 visit. In Part 1B and 2, no infusions can be administered after Week 44 in order to evaluate the durability of a disease response or complete remission at Week 48.

6.1.4.2.3 Monitoring

Elotuzumab/placebo infusions will occur in a setting with access to advanced cardiovascular life support (ACLS) certified personnel, resuscitative drugs, monitoring devices, and CPR equipment. Vital signs must be assessed prior to the infusion, approximately every 15 minutes during the infusion, at the end of the infusion, and 1 hour after completion of the infusion or per comparable institutional standards.

If an infusion reaction occurs, the infusion should be interrupted and medical management instituted as needed (e.g., glucocorticoids, epinephrine, bronchodilators, or oxygen). See protocol Section 6.4.1 for additional guidelines on managing an infusion reaction.

6.2 Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed. The investigator will ensure that the investigational product is stored as specified in the protocol and pharmacy manual in a secured area within the pharmacy, with access limited to authorized study personnel. For this study, these responsibilities are delegated to each site's Pharmacist of Record (PoR).

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed. All remaining unused investigational product will be returned to the sponsor or sponsor's representative after study termination.

All records regarding the disposition of the investigational product will be available for inspection.

6.3 Assessment of Participant Dosing Compliance

Elotuzumab/placebo will be administered intravenously at sites by trained medical staff. Compliance, therefore, will be monitored by the site and documented on the electronic Case Report Form (eCRF).

Dosing compliance with oral prednisone (see Protocol Section 7.1.1.3) will be assessed by pill count at each visit. Study personnel will calculate compliance in the presence of the participant so that reinforcement/re-education can be conducted as needed. Drug accountability and compliance will be documented on the source visit record and in the electronic data capture system.

6.4 Toxicity Prevention and Management

6.4.1 Infusion Reactions

Infusion reactions in the pivotal studies in multiple myeloma are described in Protocol Section 5.1.1. Pre-medications are described in Protocol Section 6.1.4.2.1**.** In the event of a Grade 2 infusion reaction, suspend the infusion and institute appropriate medical and supportive measures per institutional standards. Upon complete or partial resolution (Grade 1), restart elotuzumab/placebo at 0.5 mL/min. Gradually increase infusion rate by 0.5 mL/min every 30 minutes as tolerated to the rate at which the reaction occurred. Resume rate escalation regimen (Protocol Section 6.1.4.2.2) if there is no recurrence of infusion reaction.

In the event of an infusion reaction, monitor vital signs at least every 30 minutes for 2 hours after completion of the infusion and otherwise as clinically indicated. If the infusion reaction recurs, stop the infusion and do not restart on that day. A Grade 3 or higher infusion reaction including anaphylaxis will require permanent discontinuation of elotuzumab/placebo. If anaphylaxis occurs, immediately and permanently discontinue elotuzumab/placebo and administer emergency medical therapy.

6.4.2 Infection

Elotuzumab should not be given during periods of active infection. Signs and symptoms of infection that warrant investigator consideration to withhold study drug administration include but are not limited to the following:

- Fever > 38° C
- Symptoms of upper/lower respiratory or urinary tract infection
- Vomiting/diarrhea within 24 hours

Discontinue study drug permanently in the event of a Grade 4 infection.

Guidance for proceeding with study drug administration following a Grade 3 infection and resolution includes:

- Allowing at least one month between restarting the study drug and start of the infection
- Full recovery of acute symptoms and effects
- Completion of treatments for the infection
- Clinical determination that participant is deemed fit to resume elotuzumab

Guidance for proceeding with study drug administration following a ≤ Grade 2 infection and resolution includes:

- Improvement/resolution of symptoms
- Resolution of fever for at least 24 hours
- Antibiotic administration for a minimum of 48 hours (as applicable)
- Initial cultures negative at 48 hours (if obtained) unless appropriate antibiotic therapy instituted 48 hours in advance of the infusion

Elotuzumab should not be given if a participant has a positive SARS-CoV-2 (COVID-19) viral test. If a participant develops a SARS-CoV-2 (COVID-19) infection, elotuzumab may be resumed one month after start of the infection, once the participant has recovered from the infection's acute symptoms and effects, stopped treatments for the infection, including supplemental oxygen, and is deemed fit to resume elotuzumab. Instructions for resuming the protocol-specified prednisone taper are detailed in section 7.1.1.3.

Once the infection resolves, elotuzumab/placebo may be restarted at the next scheduled dose. If the infection resolves in time for a delayed infusion to be administered in the minimum window before the next scheduled infusion specified in Section 6.1.4.2.2, a single intermediate administration is permitted. In Part 1A, if the infusion

schedule has been interrupted, administration of infusions may be adjusted to permit administration of 4 doses prior to the week 11 visit. In Part 1B and 2, no infusions can be administered after Week 40 in order to evaluate the durability of a disease response or complete remission at Week 48.

6.4.2.1 Varicella Zoster Infection and Reduced Response to Vaccination

Participants will be informed about the potential for Varicella zoster (herpes zoster) infections. Following a discussion with the investigator as part of the consent process, participants who have not received the recombinant zoster vaccination (Shingrix®) may elect to receive the first dose of the vaccine prior to participating in the study as part of standard of care. In this situation, the second vaccine dose may be administered as recommended 4-6 months later, as standard of care and not part of the study. Participants will be counseled about the potential effects of elotuzumab on responses to immunization and the need to follow up on the status of their immunity with their primary care providers following participation in the trial.

6.4.2.2 General Principles for Protection from COVID-19

The following principles guide the conduct of the trial during the COVID-19 public health emergency:

- The safety of participants is paramount. Any decisions to begin, continue, or stop enrollment in the study will be made with consideration of the potential impact of COVID-19 on the safety of the participants. Trial participants will be kept informed of any changes in the study and any impacts on their participation. The nature of the study intervention, a targeted therapy with immunosuppressive properties, requires careful monitoring of the study participants and the status of the rates of COVID-19 infections at the individual clinical sites.

- The decision to continue or discontinue the experimental intervention will be made with the safety and welfare of the trial participant in mind. This decision will be made jointly between the sponsor, study chair, site investigator, and Institutional Review Board. Due consideration will be given to the fact that elotuzumab/corticosteroids may interfere with the ability of the participant's immune system to produce neutralizing antibodies against SARS-CoV-2 and could significantly increase the susceptibility to and severity of infection.

- Participants should be advised to increase their protection from COVID-19 infection by doing the following: wearing a well-fitting mask indoors in public in areas or when around others who are not up to date on their COVID-19 vaccines or not eligible to receive COVID-19 vaccines, stay 6 feet away from others, avoid poorly ventilated spaces and crowds, and wash hands often. These recommendations are subject to change, but are updated at: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

- In certain cases, the participant may not be able to come to the study site, or local institutional policies or other factors may intervene to limit access to the research site. The sponsor in consultation with site personnel will determine if alternative methods for assessments are necessary and feasible, and will assure the safety of the study participant. For example, in-person visits may be substituted with virtual visits or phone contact, or trial participants may come to an alternative site for completion of their safety assessments (e.g. off-campus laboratory). Changes in modality/timing of study visits, data collection, and/or other protocol deviations will be documented accordingly.

- Urgent or emergent changes in the protocol as a result of COVID-19 infection or the rising rates of COVID infections to protect the safety of participants may be implemented immediately without IRB approval, with concurrent notification of the IRB. The sponsor and the investigators will work closely with IRB to implement any required changes in the protocol or the consent form, as appropriate and submit any revised documents to FDA per current guidance.

- Participants should continue to receive SARS-CoV-2 vaccinations per CDC and FDA recommendations during the course of the study.

- Any participant who has close contact with a SARS-CoV-2 infected individual should be evaluated for post-exposure prophylaxis as soon as possible after exposure.

6.4.2.3 SARS-CoV-2 Prevention

The AIG01 protocol requires specific measures in the interest of preventing SARS-CoV-2 infections. The current and future FDA approval and emergency use authorization of SARS-CoV-2 vaccines and updates to CDC recommendations on vaccinations programs to promote public health may impact the enrollment and monitoring of trial participants. The sponsor in consultation with the investigators will determine if any protocol modifications are necessary as the situation evolves. Vaccine immune response may be blunted by treatment with corticosteroids and elotuzumab.

Specific measures designed to prevent SARS-CoV-2 infections include:

- Participants must be confirmed negative for SARS-CoV-2 by antigen test within 24 hours of each infusion. Participants will be provided antigen tests by the site, test themselves, and provide proof of negativity.

6.4.3 Hepatotoxicity

IgG4-RD seldom affects hepatocytes directly. Abnormalities of the liver noted in IgG4-RD are usually the result of biliary tract disease. We do not anticipate, therefore, an increased propensity to liver injury among the IgG4-RD participants in this trial. Nevertheless, the eligibility criteria have been written conservatively to exclude participants with significant risk-factors for hepatic insult. Liver function tests will be monitored frequently prior to infusions with elotuzumab/placebo and throughout the follow-up period to assess for potential drug-induced liver injury, with particular concern for hepatic transaminase elevation and hyperbilirubinemia. The specific laboratory measures of concern, which correspond to Grade 3 adverse events, are:

- ALT or AST elevation > 5 times ULN,
- Total bilirubin > 3 times ULN. If Gilbert's disease, total bilirubin > 3 times baseline value.

A grade 3 or higher elevation in liver enzymes, defined as ALT or AST > 5 times ULN or a total bilirubin > 3 times the upper limit of normal, that persists longer than 5 days will result in discontinuation of elotuzumab/placebo. For a grade 3 or higher event that resolves in less than 5 days, elotuzumab/placebo may be restarted under the schedule noted in Section 6.4.2.

6.4.4 Primary Malignancy

The eligibility criteria have been written conservatively to exclude individuals with a history of malignancy within 5 years (except for successfully treated in situ cervical cancer, resected squamous cell or basal cell carcinoma of the skin). Given the information on second primary malignancies in the elotuzumab prescribing information, attention will be paid to monitoring for malignancy as consistent with standard of care.

Participants over the age of 50 should have age-appropriate cancer screenings at the investigator's discretion prior to enrollment and throughout the course of the study. For additional information, consult the American Cancer Society (ACS) reference below: http://www.cancer.org/healthy/toolsandcalculators/reminders/screening-recommendationsby-age

6.5 Submandibular Gland Biopsy

During Part 1A, an optional submandibular gland biopsy (MGH participants only) will be performed between screening and Baseline/Day 0 and between Weeks 16 and 24 to evaluate the tissue response to study therapy. During Part 1B and 2, an optional submandibular glad biopsy will be performed prior to the Baseline/Day 0 Visit, following eligibility confirmation, and between Weeks 40 and 44. The participants will be instructed to suspend aspirin or NSAID intake 3-7 days before the procedure. Core needle biopsy of the submandibular gland is generally only slightly painful and rarely associated with significant morbidity. However, it is possible that a biopsy site might become infected, requiring antibiotic treatment or surgical debridement. The biopsy is done through normal appearing overlying skin. After application of a topical anesthetic, local anesthetic with vasoconstrictor is infiltrated into the area around the submandibular gland. An ice pack is then placed on the skin in the area of the biopsy to reduce swelling and bruising (risk management). Part of the submandibular gland biopsy will be placed in normal saline for special studies. Part will be placed in a neutral buffered formalin for studies using paraffin-embedded sections. The remaining gland will be placed on an aluminum foil boat and then transferred into a Nunc vial, which is capped and immersed into liquid nitrogen for snap freezing.

6.6 Premature Discontinuation of Investigational Agent

Study treatment will be discontinued for any participant who experiences any of the following:

- Pregnancy
- Any Grade 4 or higher infection
- For AEs associated with laboratory evaluations, any of the following lab abnormalities that persist longer than 5 days:
  - i. eGFR < 30 ml/minute/1.73m^2
  - ii. WBC ≤ 1.5 x 10^9/L
  - iii. Platelet count < 50 x 10^9/L
  - iv. Hemoglobin < 8 g/dL
  - v. ANC < 1.0 x 10^9/L
  - vi. ALT or AST elevation > 5 times ULN
  - vii. Total bilirubin > 3 times ULN. If Gilbert's disease, total bilirubin > 3 times baseline value.
- For AEs associated with clinical evaluations, any Grade 3 or higher event as defined by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) that is possibly, or definitely related to elotuzumab including anaphylaxis (see **Appendix 7: Clinical Criteria for Diagnosing Anaphylaxis**)[39] or infusion reaction
- Malignancy excluding squamous cell and basal cell carcinoma of the skin
- Disease flare, as defined in Section 3.5.3
- Participants who decide to discontinue the treatment
- The investigator believes that the study treatment is no longer in the best interest of the participant.

Participants will be expected to remain in the study for follow up despite discontinuation of study drug. Participants who discontinue protocol-specified treatment requirements will be treated as medically indicated according to physician discretion.

7 Concomitant Medications

7.1 Required Medications

7.1.1 Prednisone

7.1.1.1 Product Description

Prednisone tablets will be purchased and over-encapsulated by DAIT NIAID's Clinical Product Center under contract, EMINENT Services Corporation (EMINENT), for the conduct of Protocol AIG01. The over-encapsulation is for the purpose of patient's safety and regimen adherence.

7.1.1.2 Formulation, Packaging, and Labeling

EMINENT will over-encapsulate, bottle, label, package and distribute prednisone tablets to the clinical site's investigational pharmacies. The details for the prednisone bottles are as follows:

DOSE	Directions	# of Capsules
40mg	1 pill daily for 2 weeks	30
30mg	1 pill daily for 2 weeks	30
20mg	1 pill daily for 1 week	12
15mg	1 pill daily for 1 week	12
10mg	1 pill daily for 1 week	12
7.5mg	1 pill daily for 1 week	12
5mg	1 pill daily for 1 week	12
2.5mg	1 pill daily for 1 week	12

7.1.1.3 Dosage and Administration

Participants in Part 1 and Part 2 will begin dosing with prednisone on the day of their first elotuzumab/placebo infusion. The ten-week dosing taper is described below:

Study Day	**Prednisone Dose**
Day 0 to Day 13	40 mg/day for two weeks, then
Day 14 to Day 27	30 mg/day for two weeks, then
Day 28 to Day 34	20 mg/day for one week, then
Day 35 to Day 41	15 mg/day for one week, then
Day 42 to Day 48	10 mg/day for one week, then
Day 49 to Day 55	7.5 mg/day for one week, then
Day 56 to Day 62	5 mg/day for one week, then
Day 63 to Day 69	2.5 mg/day for one week, then Discontinue

Based on the investigator's judgement, participants who present with aggressive disease or who require a higher starting dose of prednisone because of a large body mass index may be placed on up to 60 mg prednisone daily during the screening period. The dose will need to be decreased to 40 mg prednisone /day by the baseline visit. Participants who have been on prednisone 40 mg/day for at least two weeks during the screening period will begin Day 0 on 30 mg/day of prednisone and stay on 30 mg/day to Week 4 before continuing to taper prednisone from Week 5 onwards according to the schedule described above.

Participants on less than 40 mg/day for two weeks during the screening period will begin the prednisone taper from Day 0, beginning with 40 mg/day.

It is anticipated that in some participants, an interruption of the protocol-specified prednisone taper may be required (e.g., in the setting of an infection). This will be handled as follows:

- If the participant's protocol-specified prednisone taper is modified in the setting of infection, the protocol-specified prednisone taper will resume at the dose the participant was taking at the time of modification, once medically appropriate.

7.2 Standard of Care Recommended/Permitted Therapies

- Course of glucocorticoids for non-IgG4-RD indications that are discontinued within 2 weeks: only 2 such courses are permitted and must be complete by 8 weeks prior to the Week 48 visit.
- Potential participants are encouraged to obtain vaccines as standard of care per age-specific Center for Disease Control and Prevention (CDC) guidelines before participating in the study. Live vaccines must be avoided within 8 weeks of initiation of study drug. If possible it is suggested participants obtain other immunizations at least 4 weeks prior to initiation of study therapy. Seasonal flu vaccine should be obtained during the course of the study. Other non-live vaccines as needed for standard of care may be administered.
- Concomitant therapies taken for the long term treatment of pre-existing conditions other than IgG4-RD may be continued during the study provided they are in accordance with the exclusion criteria and the list of prohibited medications. During the study, concomitant medications and new medications should be administered at the discretion of the site investigator or treating physician in order to provide the participant with the best possible medical care.
- Medications used for prevention and treatment of COVID-19, approved by the FDA or authorized for emergency use, are permitted.
- Participants should continue to receive SARS-CoV-2 vaccinations per CDC and FDA recommendations and other seasonal vaccinations during the course of the study.

7.3 Prohibited Medications

All participants are to have access to any care deemed medically necessary, but administering the following medications, for the purposes of this study, are prohibited and will be considered protocol deviations unless administered for a disease flare:

- Any systemic glucocorticoids, except for:
  - Prednisone (or equivalent) detailed in Section 7.1.1: Prednisone and in 7.2: Standard of Care Recommended/Permitted Therapies
- Any biologic or non-biologic immunomodulating drug therapy including but not limited to methotrexate, mycophenolate mofetil, 6-mercaptopurine, tacrolimus, cyclophosphamide, azathioprine, rituximab or other CD20 depleting agents.
- Investigational agents or treatments are prohibited during study participation, except for SARS-CoV-2 vaccines as specified in Section 6.4.2.3.
- Live vaccines within 8 weeks prior to initiation of study therapy and during study participation.

8 Study Procedures

8.1 Visit Windows

Appendix 1 presents the Schedule of Events Tables for Part 1 and Part 2. The date for all visits are calculated relative to the date of the Baseline/Day 0 Visit. The visit windows are defined below:

Part 1A:

- Screening until Baseline/Day 0: 28 days from time of obtaining informed consent until randomization and initiation of study treatment
- Weekly infusion visits*: + 3 days / - 1 day
- Every 2-week infusion visits: ± 3 days

Monthly follow-up visits: ±5 days

* Weekly infusion visits must be scheduled to allow for a minimum of four full days between infusions.

Part 1B and 2:

- Screening until Baseline/Day 0: 28 days from time of obtaining informed consent until randomization and initiation of study treatment
- Day 7: ± 2 days
- Safety Visits (Weeks 4, 12, 20, 28, 36, 44, 48): ± 7 days
- Infusion Visits (Weeks 8, 16, 24, 32, 40): ± 7 days

8.2 Unscheduled Visits

Unscheduled visits may be performed if disease activity increases or for other concerns between regularly scheduled visits. In the event of a disease flare, the assessments and procedures outlined for the Week 24 visit should be obtained. For unscheduled visits conducted for a reason other than a disease flare, participants should be evaluated per clinical judgement of the investigator.

8.3 Screening and Enrollment

This study will be explained in lay language to each potential participant. Each participant will sign an informed consent form before committing to study screening procedures.

After obtaining informed consent, all screening assessments and procedures to establish eligibility will be performed. These may be completed during one or more study visits within the 28-day screening window.

The following labs, procedures, and assessments will determine participant eligibility:

8.3.1 Evaluation of Eligibility and Randomization

In Part 1, if the participant meets all eligibility criteria for enrollment, then proceed as follows:

- Schedule Baseline/Day 0 Visit (within 28 days of 1st Screening assessment)

In Part 2, if the participant meets all eligibility criteria for enrollment, then proceed as follows:

- Schedule Baseline/Day 0 Visit (within 28 days of 1st Screening assessment)
- Randomize the participant

Randomization will be accomplished through a password-protected, web-based, randomization system maintained by the Statistical and Clinical Coordinating Center (SCCC).

8.4 General Assessments

See Schedule of Events Tables in Appendix **1: Schedule of Visits and Assessments** for more detailed information.

- Demographics
- Medical History
- Comprehensive physical examination: to include an evaluation of the head, ears, eyes, nose, throat, lymph nodes, heart, lungs, abdomen, skin, extremities, and neurology.
- Targeted physical examination: to include heart, lungs, and abdomen. Additional evaluations to be guided by participant complaints and prior abnormalities.
- Vital Signs
- Weight/Height
- Adverse Events
- Concomitant medications: Any medication related to IgG4-RD taken at any point should be recorded. Other non-IgG4-RD related concomitant medications taken 30 days prior to screening through study completion or termination should be reported.
- SARS-CoV-2 Antigen Testing: Participants must be confirmed negative for SARS-CoV-2 by antigen test within 24 hours of infusion. Participants are provided antigen tests by the site, test themselves, and provide proof of negativity. Participants will otherwise will be monitored for SARS-CoV-2 according to institutional standards.

8.5 Clinical Laboratory Assessments

- Complete Blood Count (CBC) with diff, ANC
- Comprehensive Metabolic Panel: to include total protein, potassium, sodium, calcium, chloride, albumin, glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, direct bilirubin, alkaline phosphatase , aspartate aminotransferase (AST), alanine aminotransferase (ALT).
- Serum amylase and lipase
- eGFR (calculated centrally based on the Chronic Kidney Disease Epidemiology (CKD-EPI) formula [40]).
- Serum Immunoglobulins
- Serum IgG subclasses
- IgE
- Erythrocyte Sedimentation Rate (ESR)
- C-reactive protein (CRP)
- Serum complement levels: C3 and C4
- TB Testing: IGRA
- Other Infectious Disease Testing: HIV, Hepatitis B surface antigen and core antibody, Hepatitis C antibody test
- Urinalysis: macro, microscopic, culture as indicated
- Serum human chorionic gonadotropin (HCG) (women of child-bearing potential)
- Urine HCG (women of child-bearing potential): pre-infusions

8.6 Disease-Specific Assessments

- ACR Classification Criteria
- IgG4 History, including all assessments of serum IgG4 concentration obtained within 6 months of the Baseline visit.
- CT scan or MRI: chest, abdomen, pelvis. Include head and/or orbits if head/neck/intraocular muscle involvement
- IgG4-RD Responder Index
- Physician Global Assessment VAS

- Patient Global Assessment VAS
- SF-36 Health Survey
- Flare Assessment

9 Mechanistic Assays

During Part 1A, PBMCs and plasma will be isolated and frozen from each participant at baseline and then two days after the first elotuzumab infusion. Subsequent samples will also be obtained at 1, 5, 16, 24, and 48 weeks, with corresponding clinical blood draws. During Part 1B and 2, samples will be collected at Screening or Baseline/Day 0 and Weeks 8, 16, 24, 32, 40 and 48, corresponding with clinical blood draws. Samples should not be collected at Screening if the participant is taking glucocorticoids on the day of the Screening Visit. If samples were not collected at the Screening Visit, they must be collected at Baseline/Day 0. Mechanistic samples will be obtained on all participants at all sites at the specified timepoints. PBMCs and plasma will be stored in liquid nitrogen for preservation. The mechanistic studies will be conducted at both the Massachusetts General Hospital/Ragon Institute and Emory University. Further instructions to the site on shipment of biospecimen will be provided in the Lab Manual. The following experiments will be carried out in batches of 10 participant timepoints per experiment:

- Flow cytometric quantification of plasmablasts, activated B cells, terminally differentiated CD4+CTLs, terminally differentiated CD8+CTLs, activated TFH cells, and 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 on the schedule noted above to determine the treatment effect on the absolute numbers and proportions of these cell types.
- Quantified cell populations will be analyzed for correlation with one another, disease activity, plasma IgG4 levels and clinical responsiveness to elotuzumab.
- From 5 of the enrolled participants with known expansions of the respective cell type and clinical responsiveness to elotuzumab, terminally differentiated CD4+CTLs, terminally differentiated CD8+CTLs, and activated B cells will be sorted by FACS at weeks 0, 16, 24, and 48. RNA will be isolated to undergo RT-PCR amplification of the TCR-β/IgH. Next-Generation Sequencing will be used to define the diversity of the TCR/BCR repertoire longitudinally to ascertain how elotuzumab may impact clonality.

9.1 Kinetics of Cell Depletion

We will determine the kinetics of cell depletion induced by elotuzumab on disease-associated, SLAMF7-expressing lymphocyte subpopulations including CD4+ cytotoxic T cells and activated B cells, including plasmablasts. We will use a flow cytometry panel to analyze longitudinal blood samples from participants enrolled in the clinical trial.

9.2 Mechanistic Assessments

Mechanistic studies for this trial will include:

- Plasma assays
- PBMC assays
- Single cell RNA sequencing
- Submandibular gland biopsies (MGH participants only)

9.3 Effect of Elotuzumab at the Tissue Level

We will determine whether elotuzumab achieves tissue-level depletion of SLAMF7-expressing lymphocyte sub-populations by examining pre- and post-treatment submandibular gland biopsies by multi-color immunofluorescence to quantify infiltrating CD4+CTLs, activated B cells, and plasma cells.

During Part 1A, an optional core biopsy of the submandibular gland will be performed at the Baseline visit and again between Weeks 16 and 24 to evaluate the tissue response to study therapy. During Part 1B and 2, an optional submandibular gland biopsy will be performed prior to the Baseline/Day 0 Visit, following eligibility confirmation, and between Weeks 40 and 44. The participants will be instructed to suspend aspirin or NSAID intake 3-7 days before the procedure. Core biopsy of the submandibular gland is generally only slightly painful and rarely associated with significant morbidity. However, it is possible that a biopsy site might become infected, requiring antibiotic treatment or surgical debridement. After application of a topical anesthetic, local anesthetic with vasoconstrictor is infiltrated into the skin and subcutaneous tissues external to the submandibular gland. The biopsy is then performed with a large-gauge biopsy needle. The biopsy obtained will be preserved in saline for additional studies.

We will examine submandibular gland biopsies by multi-color immunofluorescence to quantify infiltrating CD4+CTLs, activated B cells, and plasma cells. We hypothesize that elotuzumab will achieve tissue-level depletion of SLAMF7-expressing lymphocyte subpopulations and this will correspond with clinical improvement. For control salivary gland tissue, we will obtain fresh, disease-free margins from the MGH Surgery Department from participants undergoing salivary gland resection. Tissue samples will be fixed in formalin, embedded in paraffin and sectioned. Sections will be incubated with antibodies specific for CD4, CD8, SLAMF7, TGF-β, GZMA, IFN-γ, CD19, CD27, IgD, CD38, CD138, IgG4 and CD57. Lymphocyte subpopulations will be quantified using TissueQuest Software. In addition to demonstrating the tissue-level effects of elotuzumab in comparing the pre- and post-treatment samples, the pre-treatment samples will also allow accurate quantification of cell-cell interactions by measuring inter-nuclear distances.

9.4 Determine the Utility of Using the Clonally-expanded Effector Subset (CD57+CD28-) of CD4+CTLs as a Biomarker of Disease Activity

We will determine the utility of using the clonally-expanded effector subset (CD57+CD28-) of CD4+CTLs as a biomarker of disease activity by using longitudinally-collected blood samples to quantify these cells by flow cytometry and analyze correlations with the IgG4-RD RI.

9.5 Determine the Utility of Soluble Plasma SLAMF7 Levels as Indicators of Disease Activity

We will determine the utility of soluble plasma SLAMF7 levels as indicators of disease activity and predictors of disease relapse by quantifying soluble SLAMF7 levels in longitudinally-collected plasma samples using sandwich ELISA.

10 Biospecimen Storage

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.

Peripheral blood samples will be obtained for mechanistic studies, as specified in the protocol. Samples will be coded and stored at the Ragon Institute of Harvard, MGH, and MIT. The site investigators and site staff are bound to maintain the strict confidentiality of medical and research information that may be linked to individuals.

Additional aliquots will be stored for future studies, which will be guided by results of the investigations planned. See Appendix 1: Schedule of Visits and Assessments for detailed schedule and type of samples.

11 Criteria for Participant and Study Completion and Premature Study Termination

11.1 Participant Completion

Part 1: All participants will be followed for a total study period of up to 48 weeks, regardless of whether disease flare occurs and the participant begins glucocorticoid or alternative immunosuppressive therapy at the Investigator's discretion unless consent has been withdrawn.

Part 2: All participants will be followed for a total study period of up to 48 weeks, regardless of whether study medication has been discontinued as detailed below unless consent has been withdrawn. Completing the Week 48 visit is the time point at which the primary outcome is assessed.

11.2 Participant Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

- The participant elects to withdraw consent from all future study activities, including follow-up.
- The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
- The participant dies.
- The Investigator no longer believes participation is in the best interest of the participant.
- The study is stopped by the sponsor.

11.3 Participant Replacement

For the primary objective in Part 1 to determine the safety and tolerability of elotuzumab for participants with IgG4-RD, participants who prematurely discontinue elotuzumab may be replaced. Participants who discontinue treatment for reasons related to safety or tolerability of the agent will not be replaced. Participants who discontinue treatment early and withdraw from the study without evidence of toxicity or intolerability of the agent will be replaced such that the regimen in each cohort will be evaluable in 6 participants.

For Part 2, participants may be replaced if they withdraw prior to receiving any investigational product. In this case the participant will not count towards the target accrual of 63.

11.4 Follow-up After Early Study Withdrawal

Participants wishing to withdraw prematurely from the study will be asked to consent to a final study visit focused on collection of safety assessments.

11.5 Safety Stopping Guidance

The following events will trigger an ad hoc DSMB review (Section 12.11.3):

- Any death that is at least possibly related to elotuzumab, IgG4-RD, or a study-mandated procedure;
- Any grade 4 adverse event, including infection, that is a clinical event such as a sign/symptom, diagnosis, or laboratory abnormality with clinical consequence and at least possibly related to use of the investigational study medication. Any life-threatening infusion reactions during infusion of study treatment or within the two-hour observation period after study treatment that lead to permanent discontinuation of the infusion, including anaphylaxis;
- Two or more of the first 6 treated participants within a given cohort (cohorts 1a, 1b or 2) experience a drug-related adverse event resulting in the permanent discontinuation of study treatment; subsequently, if >20% of participants on study or within a cohort experience a drug-related adverse event resulting in the permanent discontinuation of study treatment (as specified in Section 6.6);

- The occurrence of a Grade 3 or higher related and unexpected SAE in three or more of the study participants who have received a study treatment;
- Malignancy;
- Any event which in the opinion of the Protocol Chair or Medical Monitor merits DSMB review.

Events that trigger an ad hoc DSMB review will be cumulative over Parts 1 and 2 of the study.

12 Safety Monitoring and Reporting

12.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5) to the IND sponsor, DAIT/NIAID. Appropriate notifications will also be made to site principal investigators (Pis), IRBs, and the U.S. FDA.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

12.2 Definitions

12.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonisation E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

12.2.2 Adverse Reaction and Suspected Adverse Reaction (SAR)

SAR is any adverse event for which there is a reasonable possibility that the investigational drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a) and ICH E2A).

An adverse reaction (AR) is any adverse event caused by the study drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

12.2.3 Unexpected Adverse Event/Reaction

A SAR is considered "expected" when it is listed in the investigator brochure, the package insert, or the protocol. A SAR is considered "unexpected" when its nature (specificity), severity, or rate of occurrence is not consistent with applicable product information as described in the safety information provided in the investigator brochure, the package insert, or the protocol (21 CFR 312.32(a) and ICH E2A). A serious unexpected suspected adverse reaction is referred to as a SUSAR. For this study, expectedness will be determined by product information provided in the investigator brochure, package insert, and protocol for elotuzumab.

12.2.4 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor (DAIT/NIAID), it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor (DAIT/NIAID), its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations are not to be reported as an SAE unless hospitalization is prolonged due to complications.

12.3 Grading and Attribution of Adverse Events

12.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study participants according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event
Grade 2 = moderate adverse event
Grade 3 = severe or disabling adverse event
Grade 4 = life-threatening or urgent intervention
Grade 5 = death

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events if related to a study-mandated procedure, treatment, or change in treatment (but are not treatment-emergent). If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

Liver function abnormalities will be graded using alternative criteria which are based on CTCAE version 4.0, and are defined relative to the ULN as follows:

- Aspartate aminotransferase [AST] increased
    - Grade 1: > ULN – 3.0x ULN
    - Grade 2: > 3.0x ULN – 5.0x ULN
    - Grade 3: > 5.0x ULN – 20.0x ULN

- Grade 4: > 20.0x ULN

- Alanine aminotransferase [ALT] increased
  - Grade 1: > ULN – 3.0x ULN
  - Grade 2: > 3.0x ULN – 5.0x ULN
  - Grade 3: > 5.0x ULN – 20.0x ULN
  - Grade 4: > 20.0x ULN

- Alkaline phosphatase [ALP] increased
  - Grade 1: > ULN – 2.5x ULN
  - Grade 2: > 2.5x ULN – 5.0x ULN
  - Grade 3: > 5.0x ULN – 20.0x ULN
  - Grade 4: > 20.0x ULN

- Blood bilirubin increased
  - Grade 1: > ULN – 1.5x ULN
  - Grade 2: > 1.5x ULN – 3.0x ULN
  - Grade 3: > 3.0x ULN – 10.0x ULN
  - Grade 4: > 10.0x ULN

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

12.3.2 Attribution Definitions

The relationship, or attribution, of an adverse event to elotuzumab and prednisone will initially be determined by the site investigator and recorded on the appropriate AE electronic case report form (eCRF). Final determination of attribution for safety events that may be eligible for expedited reporting to health authorities will be determined by the sponsor, DAIT/NIAID. The relationship of an adverse event to study therapy regimen will be determined using the descriptors and definitions provided in Table 1. In addition, Investigators will report events as possibly related or related in situations where the evidence is less than a "reasonable possibility" to suggest a causal relationship between elotuzumab and an adverse reaction. AEs whose etiologies may overlap between study product and glucocorticoids will be designated as related or possibly related to elotuzumab.

Table 1. Attribution of Adverse Events

Code	Descriptor	Relationship (to elotuzumab or prednisone)
UNRELATED CATEGORY		
1	Not Related	The adverse event is clearly not related; there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

12.4 Collecting and Recording of Adverse Events

12.4.1 Collection Period

All adverse events, regardless of severity, should be recorded in the study source documentation and will be captured in the database per the following criteria:

- Adverse events of all grades will be collected from the time the participant signs the informed consent until he/she initiates study intervention or until he/she is determined to be ineligible to receive study intervention, if the investigator determines that the adverse event is related to a study-mandated procedure, treatment, or change in concurrent medication.

- Adverse events of all grades will be collected from the initiation of study intervention until completion of the study or until 30 days after the participant is prematurely withdrawn (without withdrawal of consent) or withdraws from the study, whichever occurs first.

12.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant
- Interviewing the participant (e.g., using a checklist, structured questioning, diary, etc.)
- Receiving an unsolicited complaint from the participant
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, Grading and Attribution of Adverse Events

12.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 12.2, Definitions) on the appropriate eCRF regardless of the relationship to study therapy regimen or study procedure. Events will be recorded on the appropriate AE case report form (CRF) for this study.

Once recorded, an AE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

An SAE will be followed until it resolves with or without sequelae OR until 30 days after the end of study participation if consent has not been withdrawn.

If the AE is related to a laboratory or diagnostic evaluation, the evaluation that produced the value or result should be repeated until that value or result returns to normal or can be explained and the participant's safety is not at risk.

12.5 Reporting Adverse Events and Serious Adverse Events to Sponsor: DAIT/NIAID

12.5.1 Reporting Adverse Events

This section describes the responsibilities of site investigators to report adverse events to the study sponsor (DAIT/NIAID) via the SCCC. Timely reporting of all adverse events is required.

Unless otherwise noted below in Section 12.5.2 for serious adverse events and events requiring reporting within 24 hours, AEs must be recorded on the AE eCRF within five (5) days of discovery of the event. Whenever possible, a diagnosis should be provided, rather than compilation of signs/symptoms, with grade of the event dictated by highest grade of the sign/symptom component.

12.5.2 Reporting of Serious Adverse Events

This section describes the responsibilities of the site investigator to report serious adverse events and events that need to be reported within 24 hours to the sponsor via the eCRF. Timely reporting of adverse events is required by 21 CFR Part 312.32 and ICH E6 guidelines.

The adverse events outlined below must be reported by the site investigators to DAIT/NIAID via the SCCC regardless of relationship or expectedness to study intervention within 24 hours of occurrence/discovery, whichever occurs first:

- All SAEs per 21 CFR 312.32 definitions (see Section 12.2.4, Serious Adverse Events).
- In addition, the following events need to be reported within 24 hours:
    - Any lab abnormalities that persist longer than 5 days leading to study drug discontinuation (see Section 6.6).
    - Grade 3 or higher infusion reaction.
    - Anaphylaxis, defined as a serious allergic reaction that is rapid in onset and may cause death (see **Appendix 7: Clinical Criteria for Diagnosing Anaphylaxis**)[39].
    - Grade 3 or greater infection.
    - All disease flares as defined in Section 3.5.3.
- All other Clinical events with a NCI-CTCAE Grade 3 or greater severity deemed possibly or definitely related to elotuzumab.

Note: clinical events include signs/symptoms, diagnoses, and laboratory abnormalities with clinical consequence (defined as the requirement for intervention, correction, increased monitoring, or further evaluation).

When a site investigator identifies a serious adverse event or event specified as a 24 hour reportable event above, he or she must notify DAIT/NIAID via the SCCC within 24 hours. Site investigators are to report these events on the SAE eCRF in Electronic Data Capture (EDC). Sites are encouraged to download a blank SAE eCRF in the beginning of the study in an event EDC becomes unavailable/ inaccessible, the site investigator should complete the paper SAE form and email to Rho_productsafety@rhoworld.com. However, within the next business day or when the EDC system becomes functional, the SAE eCRF must be completed.

All requested information on the SAE eCRF should be provided. Unavailable details of the event at time of initial report should not delay submission of known information. The initial report should include at a minimum: AE term, relationship to study intervention (i.e., elotuzumab, prednisone), and reason why event is serious (per definitions) or requires 24 hour reporting. Supplementary CRF pages including medical history, concomitant medications, demographics, study drug administration, and death must be provided. As additional details become available, the SAE eCRF should be updated and submitted. With each iteration of the form, the investigator (or designated sub-investigator) must sign the form electronically.

For additional information regarding SAE reporting, contact Rho Product Safety (SCCC):

12.6 Reporting to Health Authorities

After an adverse event requiring 24 hour reporting (per Section 12.5.2, Reporting of Serious Adverse Events) is submitted by the site investigator and assessed by DAIT/NIAID, there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities (Annual Reporting and Expedited Reporting).

12.6.1 Annual Reporting

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 12.2.2, Adverse Reaction and Suspected Adverse Reaction, and Section 12.2.3, Unexpected Adverse Event/Reaction).
- Serious and not a suspected adverse reaction (see Section 12.2.2, Adverse Reaction and Suspected Adverse Reaction).
- Pregnancies.

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual IND Report.

12.6.2 Expedited Safety Reporting

This option applies if the adverse event is classified as one of the following:

- Serious and unexpected suspected adverse reaction [SUSAR]:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
    - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug
    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

The sponsor (DAIT/NIAID) will notify the appropriate health authorities (FDA) and all participating investigators of Expedited Safety Reports within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) will be reported as soon as possible or within 7 calendar days.

Final Study Report: A complete summary of safety information (including both Standard and Expedited reports as defined above) is included in the final study report to be submitted to the US FDA at the closure of the protocol.

12.7 Reporting of Adverse Events to IRBs/IECs

All investigators shall report AEs and SAEs, including IND safety reports, in a timely fashion to the IRB in accordance with applicable regulations and guidelines.

12.8 Reporting Pregnancy

The investigator shall be informed immediately if a female study participant becomes pregnant, or if a male participant becomes aware of a pregnancy in a female partner anytime during the year period of participation. A pregnant participant shall be instructed to stop taking study medication. The investigator shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The investigator shall report to the sponsor (DAIT/NIAID) via the SCCC all pregnancies that occur in female study participants within 24 hours of becoming aware of the event according to the procedures specified in Section 12.5.2. The Pregnancy eCRF will be used to submit the information for tracking purposes only, as the pregnancy itself is not

considered an AE or SAE. All female participant pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy information must be updated and submitted to the SCCC via the eCRF form as new information becomes available.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion should be submitted on the SAE eCRF form.

The investigator shall also report to DAIT/NIAID all male participant partner pregnancy outcomes by eCRF when this information can be obtained. Specific information collected will include number of infants; gender, weight, length, and head circumference of each infant; any infant complications, medical problems, or congenital anomalies. Informed consent will be pursued from the pregnant partner to obtain this information for the database.

12.9 Reporting Unanticipated Problems

An investigator must promptly notify the sponsor (DAIT/NIAID) via the SCCC if an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event.

12.10 Review of Safety Information

12.10.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the SCCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate eCRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received from the SCCC.

12.11 Data Safety and Monitoring Board Review

12.11.1 Routine DSMB Reviews

The progress of the study will be monitored by the NIAID DSMB. The NIAID Autoimmune DSMB will be chartered to review safety data and to make recommendations to NIAID regarding continuation, termination, or modification of the study. The DSMB will review the safety data approximately 6 months after the first participant is treated.

Following the initial review, the DSMB will review the safety data twice annually during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs as well as an evaluation for a safety signal by arm by the DAIT Statistical and Coordinating Center.

The DSMB chair will be informed of any IND Safety Reports in a timely manner in order to make a recommendation for an ad hoc full board review and /or protocol suspension. Discontinuation of study treatment will also be periodically reported to the DSMB. In addition, safety data will be reviewed by the DSMB when an event occurs that

is of sufficient concern to the NIAID medical monitor or protocol co-chairs to warrant review, or when an event occurs that could contribute to a stopping rule.

12.11.2 Protocol-Defined Interim Safety Reviews

Interim safety reviews will be undertaken by a SRC comprised of a subgroup of the DSMB. The study design (Section 3.1) specifies an interim safety analysis and review by the SRC of the first dosing cohort occur one month after the last participant enrolled has completed dosing and the week 9 visit has occurred as described in Section 13.5.2. Recommendation to continue by the SRC is required, with enrollment of the second dosing cohort (every 2 months) as specified per Protocol Section 3.1.1. A second interim safety analysis and review by the SRC will take place after the last participant in the Part 1B, twelve-month dosing cohort has completed dosing and the week 48 visit has occurred.

Following the protocol-specified safety review between dosing cohorts, the SRC can recommend actions regarding study conduct, including, but not limited to, the following:

1. Continue the study as planned.
2. Add participants to an existing dosing cohort.
3. Reduce the number of weeks of study drug administration for the next higher dosing cohort.
4. Stop the study.

Recommendation by the SRC is required in order to begin enrollment in Part 2. Unless the safety data suggests otherwise the twelve-month dosing regimen will be used in Part 2.

12.11.3 Ad hoc DSMB Reviews

If any of the events listed in Safety Stopping Guidance, Section 11.5 occur, the chair of the DSMB will be notified and a review of the safety data will be performed. The DSMB will have the discretion to recommend actions regarding study conduct, and will determine if enrollment in the study should be stopped and/or administration of investigational study medication should be halted.

If any of the first 2 events occur, then no new participants will be consented, and no new participants will be enrolled, until after the DSMB completes review of the safety data. Participants in the screening phase of the study may continue to undergo minimal risk procedures.

If any of the remaining events occur, the study will proceed as planned pending DSMB review of the data. However, if two weeks has elapsed and the DSMB has not met, then no new participants will be consented, and no new participants will be enrolled, until after the DSMB completes review of the safety data.

In the event that a temporary halt is placed on consent and enrollment, participants already enrolled in the study will continue to receive study medication if they are not the participant of the DSMB review.

13 Statistical Considerations and Analytical Plan

13.1 Overview

This is a two-part multi-center clinical trial in participants with active IgG4-RD. Part 1 is an open-label phase to determine the safety and tolerability of elotuzumab and to select the duration of treatment for evaluating efficacy of the agent. Part 2 is a randomized, placebo-controlled, double-blinded phase to compare the efficacy of the addition of

elotuzumab versus placebo to prednisone in participants with IgG4-RD. The primary efficacy endpoint is disease response.

13.2 Endpoints

Primary, secondary, and exploratory endpoints are listed in Sections 3.2, 3.3, and 3.4.

13.3 Measures to Minimize Bias

In Part 2, randomization to treatment allocation will be performed to minimize bias in the comparison of the primary and secondary efficacy endpoints. Randomization will be stratified by newly-diagnosed or relapsing disease at entry to minimize confounding with the effects of treatment. In addition, the use of a placebo-controlled design for elotuzumab will minimize the risk of ascertainment bias in the IgG4-RD Responder Index and assessments of efficacy and safety endpoints in Part 2 of the study.

13.4 Analysis Plan

13.4.1 Analysis Populations

In Part 1:

Safety population: will be defined for each treatment regimen as all participants who received any amount of investigational product.

In Part 2:

Modified Intent-to-Treat (mITT) population: will be defined as all participants who undergo random assignment and receive any amount of elotuzumab / elotuzumab-placebo. The primary efficacy analyses will be based on the mITT population according to the groups to which the participants are assigned.

Per Protocol (PP) population: will be defined as the subgroup of participants in the mITT population who (1) receive at least 5 of 6 elotuzumab / elotuzumab-placebo infusions or discontinue treatment due to a disease flare (2) receive at least 80% and no more than 120% of the cumulative dose of prednisone during the 10 week taper defined in Section 7.1.1.3, (3) adhere to the permitted single course of glucocorticoids for non-IgG4-RD indications defined in Section 7.2 and (4) have no major protocol deviations or ineligible entry criteria that would impact efficacy assessments through week 48.

A masked data review will evaluate deviations from the protocol in a blinded manner for impact on the efficacy assessments and exclusion from the PP population. This may include, but is not limited to, violations of entry criteria, departures from assigned treatment regimen, modifications of concurrent therapy, failure to complete study visits, or administration of study procedures outside the specified visit windows.

Safety population: will be defined as all participants who received any amount of at least one elotuzumab / elotuzumab-placebo infusion. Safety analyses will be based on the actual treatment which the participants receive.

13.4.2 Primary Analysis of Primary Endpoint

Part 1

Descriptive statistics will be used to summarize the proportion of participants in each cohort who experience at least one Grade 3 or greater adverse event during study participation for all participants in the safety population. The primary analysis of efficacy and safety endpoints will be conducted after all participants in Cohort 1a and 1b complete the Week 48 assessments or are withdrawn from the study.

Part 2

The primary endpoint for Part 2 is disease response at 48 weeks, defined as the percent improvement in the IgG4-RD RI score over baseline:

$$\%\ Improvement\ in\ IgG4RD\ RI_{Week\ 48} = 100 * (\frac{IgG4RDRI_{Baseline} - IgG4RDRI_{Week\ 48}}{IgG4RDRI_{Baseline}})$$

For participants whose IgG4-RD RI score is worse (e.g. higher) at week 48 than baseline, their % Improvement in IgG4-RD $RI_{Week\ 48}$ will be considered 0%. Additionally, participants who use glucocorticoids or other immunosuppressants beyond that permitted by protocol, or who experience a disease flare as defined in Section 3.5.3 at any time point before 48 weeks will be defined as achieving no disease response (0%).

The observed levels of disease response at 48 weeks will be summarized by arm in the mITT population as the median, interquartile range, and range. A between-group comparison of the assessment of disease response at 48 weeks will be performed using a Wilcoxon-Mann-Whitney test with a two-sided Type I α of 0.05, and will be reported with a two-sided 95% confidence interval for the Mann-Whitney parameter (Section 13.6) derived under the proportional odds assumption [41]. The primary analysis of disease response will treat all participants who drop out of the study prior to reaching week 48 for any reason, including a disease flare, initiation of non-protocol therapy, or any other reason to cause them to be unevaluable using the IgG4 Responder Index, as having no disease response (0% improvement) for the primary endpoint. The primary analysis will be conducted after all participants in Cohort 2 complete the Week 48 assessments or are withdrawn from the study.

13.4.3 Supportive Analyses of the Primary Endpoint

A supportive analysis of the primary endpoint will consider participants who drop out of the study prior to reaching week 48 without evidence of disease flare, initiation of non-protocol therapy, or other indications of increased disease activity as missing-completely-at-random (MCAR). Descriptive statistics and the Wilcoxon-Mann-Whitney test will be repeated in the subgroup of the mITT population excluding participants with data MCAR. A masked data review panel will evaluate participant disposition and all disease activity assessments in a blinded manner to define the types of missing data. In addition, analysis of the primary endpoint will be repeated as a van Elteren test with a covariate for the stratification factor of newly-diagnosed versus relapsing disease at study entry. As an additional supportive analysis which does not assume data are MCAR, a two-dimensional tipping point analysis of missing data will be conducted. Additional details on supportive analysis will be specified in the Statistical Analysis Plan.

Supportive analyses of the primary endpoint will be repeated in the PP populations and as a preplanned subgroup analysis in participants who are identified as having elevated serum IgG4 level prior to initiation of study therapy. The subgroup is defined as any serum IgG4 concentration greater than 1.5 times the upper limit of normal that is obtained within 6 months of the Baseline visit or at the baseline assessment of Serum IgG subclasses.

13.4.4 Analyses of Secondary and Other Endpoints

The key secondary endpoint for Part 2 is complete response at 48 weeks, defined as an IgG4-RD RI Score of 0 and a glucocorticoid dose of 0 mg/day and no flare since beginning treatment. A fixed sequence testing procedure will be conducted with the primary efficacy endpoint, to control the overall Type I error rate at 0.05. Specifically, if the between-group comparison of disease response at 48 weeks reaches statistical significance, a comparison of the rates of complete remission at 48 weeks will be performed using a Fisher's Exact test with a two-sided Type I α of 0.05. If the between-group comparison of disease response at 48 weeks fails to reach statistical significance,

inferences on complete remission will be supportive without overall Type I error control. The proportion in complete remission in each arm will be reported with two-sided 95% Clopper-Pearson confidence intervals. All participants in the mITT population who drop out of the study prior to reaching week 48 for any reason, including a disease flare, initiation of non-protocol therapy, or any other reason to cause them to be unevaluable using the IgG4 Responder Index, will be defined as not achieving complete remission.

All inferential analyses for the additional secondary efficacy endpoints are considered supportive; p-values for test of differences among groups will be presented without adjustment for multiple comparisons. All secondary endpoints will be analyzed in the mITT and PP populations, and in the subgroup with elevated serum IgG4 level prior to initiation of study therapy.

For all dichotomous efficacy endpoints, Fisher's Exact tests will be conducted and two-sided 95% Clopper-Pearson confidence intervals will be reported.

Frequency counts of the number of disease flares and the number of organ sites with disease-related damage will be reported by arm, and between-group comparison will be performed using Fisher's Exact Test.

For secondary continuous efficacy endpoints, including the Physician Global Assessment and Patient Global Assessment, descriptive statistics will be used to summarize the distribution of scores in each arm. The absolute change from baseline will be analyzed using an analysis of covariance model (ANCOVA) with treatment allocation as the independent variable.

Treatment group differences for the safety endpoints will be compared using a Fisher's exact test.

13.4.5 Descriptive Analyses

Summary statistics for baseline and demographic characteristics, disposition, and medication use will be provided for the mITT and PP populations. These data will be presented in the following manner:

- Continuous data (e.g. age, weight, and height) will be summarized by mean, standard deviation, median, and range.
- Categorical data (e.g. sex and race) will be presented as counts and percentages.

All medications taken by or administered to study participants beginning 30 days before the Screening Visit and continuing throughout the study will be collected. All medications used will be coded according to the World Health Organization (WHO) drug dictionary. The number and percentage of participants receiving prior and concomitant medications/therapies will be presented overall and by medication class.

13.5 Interim Analyses

13.5.1 Interim Analysis of Efficacy Data

No early stopping for increased efficacy of the addition of elotuzumab versus placebo to prednisone is planned for this study.

13.5.2 Interim Analysis of Safety Data

In Part 1, an interim analysis of safety will be conducted as described in Sections 3.1.1, 3.1.2 and 12.11.2. To make a determination on the safety of proceeding to Cohort 1b in Part 1 and proceeding to Part 2, the SRC will perform a broad review of all of the safety data in an independent and unbiased fashion. Safety analysis reports to be provided

for review will include tables, listings and figures, including the following within each dosing group using the safety population:

- AE summary tables will report the number of events and the number and percentage of participants having at least one event in the following categories:
  - All AEs (overall and classified by MedDRA system organ class and preferred term)
  - AEs indicated as serious
  - AEs with an outcome of death
  - AEs by severity
  - AEs that lead to study drug discontinuation
  - AEs by relatedness to each study drug
- Clinical laboratory measurements will be summarized and plotted over time, including:
  - Complete Blood Count with differential/ANC
  - Comprehensive Metabolic Panel: total protein, potassium, sodium, calcium, chloride, albumin, glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT).
  - Serum amylase and lipase
  - eGFR
  - Serum Immunoglobulins
  - Erythrocyte Sedimentation Rate (ESR)
  - C-reactive protein (CRP)
  - Serum complement levels: C3 and C4
- All disease flares as defined in Section 3.5.3
- Vital Signs, physical examinations, use of medications, and other observations related to safety

Full details on the content and generation of safety reports will be specified in the Statistical Analysis Plan.

In Part 2, no formal interim analysis of safety data is planned for this study. Routine reviews by the NIAID Autoimmune Data and Safety Board will be conducted as defined in Section 12.11.

13.5.3 Futility Analysis

No early stopping for futility is planned for this study.

13.6 Statistical Hypotheses

In Part 2, the null hypothesis for the Wilcoxon-Mann-Whitney test is defined according to the Mann-Whitney parameter [42], as the probability that a randomly selected individual in the treatment arm will have a better outcome than a randomly selected individual in the control arm, with an adjustment for ties [43]. Specifically, let X_E be a random outcome from a population to receive elotuzumab, and X_P be a random outcome from a population to receive placebo. Then,

$$H_0: \delta = Pr(X_E > X_P) + {}^1/_2 \cdot Pr(X_E = X_P) = 0.5$$

The alternative hypothesis is that there is unequal probability that the addition of elotuzumab treatment is superior to the addition of placebo in achieving disease response at 48 weeks.

$$H_1: \delta = Pr(X_E > X_P) + {}^1/_2 \cdot Pr(X_E = X_P) \neq 0.5$$

13.7 Sample Size Considerations

In Part 1, no formal power analyses were conducted and all safety and tolerability evaluations are considered exploratory. The target sample size for this part of the study is 12 participants with at least 6 participants receiving elotuzumab under each treatment regimen. The ability to detect significant events of certain frequencies was considered. Table A illustrates the probability of observing at least 1 significant event in a dosing cohort of 6 participants.

Table A Probability of Observing at Last One Event

	True Probability of Event		
	0.1	**0.2**	**0.3**
Probability of observing at least 1 event in 6 participants	0.47	0.74	0.88

Additionally, Table B displays the upper and lower limits of the exact 95% Clopper-Pearson confidence interval for a binary outcome.

Table B Confidence Limits for a Binary Outcome

Number with an event	Proportion with event	Lower Limit for Exact 95% CI	Upper Limit for Exact 95% CI
0	0.000	0.000	0.459
1	0.167	0.004	0.641
2	0.333	0.043	0.777
3	0.500	0.118	0.882
4	0.667	0.223	0.957
5	0.833	0.359	0.996
6	1.000	0.541	1.000

In Part 2, a 2:1 allocation ratio was selected to evaluate aspects of treatment, including both safety of the combination of elotuzumab with prednisone and the exploratory objectives of the study. The sample size for Part 2 was determined by specifying the natural parameter to the Wilcoxon-Mann-Whitney test of $\delta = 0.75$ would warrant further investigation of the agent. The probability of 0.75 was selected as a target effect size for this proof-of-concept study using a simulation study based on the scale of the IgG4 RI and variable rates of improvement and achievement of complete remission. Under Gaussian assumptions, the Mann-Whitney parameter is equivalent to a mean difference of 1.0 standardized units. Using the formula from Noether [44], and with the desired allocation ratio of 2:1 to receive elotuzumab versus placebo in addition to the prednisone-taper, N = 63 participants (n_E = 42, n_P = 21) would provide 90% power to detect the target effect-size. For the secondary efficacy endpoint of complete remission at 48 weeks, Yunyun et al. [8] reported a complete remission rate at 6 months of approximately 25% with glucocorticoid treatment alone. With the target sample size of 63 participants, a Fisher exact test using α = 0.05 (two-sided) will have at least at 80% power (exact power = 0.826) to detect an improvement from 25% to 65% in the complete remission rate at 48 weeks with the addition of elotuzumab.

14 Identification and Access to Source Data

14.1 Source Data

Source documents and source data are considered to be the original documentation where participant information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

14.2 Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID, NIAID representatives, agents, employees, contractors, and other persons assisting in conducting, monitoring, or analyzing the study, as well as to relevant health authorities, and Bristol-Myers Squibb Company. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15 Quality Assurance and Quality Control

The principal investigator is required to keep accurate records to ensure that the conduct of the study is fully documented. The principal investigator is required to ensure that all eCRFs are completed for every participant entered in the trial. The period of record retention should be consistent with the record retention policies of the sponsoring agency or applicable regulatory agencies. However, in certain instances, documents should be retained for a longer period if required by the applicable regulatory agency or by the National Institutes of Health.

Data will be obtained from a variety of sources including, but not limited to laboratory notebooks, automated instrument output files, and clinical participant charts. Data from these source materials will be transmitted to the DAIT data center via one of two mechanisms. Data collected electronically at central laboratories will be transferred electronically directly from the laboratory to the DAIT data center using standard secure data transfer procedures. Data collected at the clinical sites will be transmitted to the DAIT data center using an internet-based remote data entry system. Clinical site personnel use an internet browser to key data into eCRFs; each CRF page is submitted to the clinical database electronically as the page is completed. Univariate data validation tests are performed as the data are keyed. The clinical database is backed up nightly; backup tapes are saved in a secure, off-site location. At any time, authorized site personnel may log in to the remote data entry system, review and correct previously entered data, or key additional data. The data will be further validated per the study data validation plan via a series of computerized and manual edit checks, and all relevant data queries will be raised and resolved on an ongoing basis. Complete, clean data will be frozen to prevent further inadvertent modifications. All discrepancies will be reviewed and any resulting queries will be resolved with the investigators and amended in the database. All elements of data entry (i.e., time, date, verbatim text, and the person performing the data entry) will be recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations.

Monitors are responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

Monitors will periodically visit the participating clinical sites and audit the source documents in order to validate the data in the central database. Data will be provided using the participant's screening or enrollment number, the DAIT data center will not collect personally identifying information such as the participant's name or social security number. Participants will provide demographic information such as race, ethnicity, and birth date.

Data collected by the DAIT data center will be held in the strictest confidence, and are protected from access that could reveal personally identifying information about any participant in the trial.

16 Protocol Deviations

16.1 Protocol Deviation Definitions

Protocol Deviation – Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. Protocol deviations occur for a variety of reasons, such as an investigator's intentional or unintentional departure from the protocol, the participant's lack of adherence to the protocol, or external/environmental factors (e.g., severe weather or holidays) that change the performance of a protocol. Some protocol deviations are anticipated and/or intentional; others are not. Some protocol deviations are known or identified before they occur; others are only discovered to have occurred after the fact. The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted or approved beforehand by the study Sponsor.

Major Protocol Deviation (Protocol Violation) – A Protocol Violation is a deviation from the IRB approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation – A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

16.2 Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

When a deviation occurs, corrective actions may be necessary depending on the nature of the deviation. Risk assessment must occur by the PI and study Sponsor. The PI should ensure a procedure for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study. The depth of Corrective Action/Preventive Action (CAPA) required should match the risk and impact on safety of participants and/or the quality of the data.

Upon determination that a protocol deviation has occurred, the PI/designated study staff will report the deviation according to the processes outlined for the study. A major deviation is to be reported within 3 business days and reported by the PI to the IRB per IRB reporting requirements. The study Sponsor will determine reportability of the deviation to the DSMB and FDA as applicable.

17 Ethical Considerations and Compliance with Good Clinical Practice

17.1 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study

initiation, the protocol and the informed consent documents will be reviewed and approved by an Institutional Review Board. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

17.2 Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the FDA 1572 will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

17.3 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study Monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study sites will permit access to such records.

18 Publication Policy

The Autoimmunity Centers of Excellence (ACE) publication policy will apply to publication of study results. Authorized study personnel may find details regarding the policy on the ACE study portal. Site investigators are encouraged to communicate and publish study results with prior notification of and review by DAIT, NIAID, and Bristol-Myers Squibb.

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20 Appendices

20.1 Appendix 1: Schedule of Visits and Assessments

Part 1A (1 Month Open-label Regimen)

Visit Name	Screening	Base-line/ Day 0[1]	Day 2	Day 7	Day 14	Day 21	Week 5	Week 9	Week 13	Week 16	Week 24	Week 36 (phone call)	Week 48	Unscheduled[14]
Visit window	-28 days	N/A	N/A	+3/-1 day	+3/-1 day	+3/-1 day	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	N/A
Clinical Draw (mL)	27.4	28	3	7	7	7	26	7	7	26	28	0	15	28
Research Draw (mL)	0	50	30	30	0	0	30	0	0	30	30	0	30	30
Visit Draw Total (mL)	27.4	78	33	37	7	7	56	7	7	56	58	0	45	58
General Assessments														
Informed Consent	X													
Confirm Eligibility		X												
Demographics	X													
Medical History	X													
ACR Classification Criteria	X													
IgG4 History	X													
Comprehensive Physical Examination	X	X									X			X
Targeted Physical Examination				X	X	X	X	X	X	X			X	
Vital signs/Height/Weight[2]	X	X		X	X	X	X	X	X	X	X		X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SARS-CoV-2 Antigen Test[17]		X		X	X	X								
Disease Activity Assessments														
CT scan w/ or MRI w/o contrast[3, 3a]	X										X			X
IgG4-RD Responder Index (RI)[13]	X	X[16]									X			X
Physician Global Assessment VAS	X	X		X			X	X		X	X		X	X
Patient Global Assessment VAS	X	X		X			X	X		X	X		X	X
Flare Documentation Guide [12]	X	X	X	X	X	X	X	X	X	X	X		X	X
SF-36 Health Survey		X					X			X	X		X	X
Clinical Laboratory Assessments														
CBC with differential/ANC[11, 11a]	X	X	X	X	X	X	X	X	X	X	X		X	X
Comprehensive Metabolic Panel[11, 11a]	X	X		X			X	X	X	X	X		X	X
Serum amylase and lipase	X	X		X	X	X	X	X	X	X	X			X
eGFR[4]	X			X			X	X	X	X	X		X	X
Serum Immunoglobulins[15]		X					X			X	X		X	X
Serum IgG subclasses		X					X			X	X		X	X
ESR		X									X		X	X
CRP		X					X			X	X			X
Serum complement: C3 and C4		X					X			X	X			X

Visit Name	Screening	Base-line/ Day 0[1]	Day 2	Day 7	Day 14	Day 21	Week 5	Week 9	Week 13	Week 16	Week 24	Week 36 (phone call)	Week 48	Unscheduled[14]
Visit window	-28 days	N/A	N/A	+3/-1 day	+3/-1 day	+3/-1 day	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	N/A
ELF score[5]		X					X				X			X
TB Testing[6]	X													
Other infectious disease testing[7]	X													
Clinical Laboratory Assessments (continued)														
Urinalysis and culture[8]	X						X			X	X		X	X
Serum HCG[9]	X													
Urine HCG[9]		X		X	X	X								
Mechanistic Assessments														
Flow Cytometry: PBMC collection		X	X	X			X			X	X		X	X
Plasma Collection		X	X	X			X			X	X		X	X
Submandibular Gland Biopsy[10]		X								X[10a]	X[10a]			
Study Drug Administration														
EVUSHELD/COVID-19 Prophylaxis[18]	X													
Elotuzumab 10 mg/kg IV		X		X	X	X								
Oral steroid		X		X	X	X	X	X						
Steroid compliance check and dispensing				X	X	X	X	X						

[1] Baseline and Day 0 assessments may be split to accommodate salivary gland biopsy so long as first infusion occurs within 28 days of start of screening.

[2] Height at screening. The screening weight may be used for calculation of all doses as long as there is a less than 10% change over the study treatment period (or as consistent with institutional policy).

[3] Imaging required to complete a full IgG4-RD RI assessment will be performed for the Screening visit. Specifically, all participants will undergo either a CT or MRI of the chest, abdomen, and pelvis at Screening. Participants with clinical evidence of orbital disease will also undergo CT or MRI of that area. If abnormalities in a particular area are detected at Screening, the participant will have the same type of study repeated at Week 24. Imaging at week 24 will be performed if there is a clinical reason to suspect disease activity at that site. Imaging may also be repeated at the discretion of the investigator at a visit other than those two time points if required to assess disease activity because of a potential disease flare or to assess an adverse event.

[3a] Oral or intravenous contrast agents may be used in some radiology studies. The need for contrast agents will be reviewed on an individual basis, consistent with the routine use of these imaging studies. Consultation with radiology will be obtained as needed.

[4] eGFR to be calculated centrally per the CKD-EPI formula.

[5] ELF Score serology: TIMP-1, PIIINP, HA.

[6] By Interferon-Gamma Release Assay (IGRA). If indeterminate, repeat (with same or other IGRA per local policy) or obtain PPD (the latter to be read within 48-72 hours and may be read locally with documentation of result by health care provider). If history of BCG vaccine or other complication in interpretation of result, consultation with ID is required for clearance to proceed.

[7] HIV, Hepatitis B surface antigen and Hepatitis B core antibody, Hepatitis C antibody.

[8] U/A macroscopic and microscopic analysis, culture if indicated.

[9] For women of child-bearing potential. Stat urine HCG prior to each infusion may be performed locally with point of care testing.

[10] Submandibular gland biopsy: fine needle aspiration of parotid or submandibular salivary gland. Sub-study to be conducted only at MGH. May use tissue previously acquired if available. Opt-out language to be included in the informed consent document.

[10a] Submandibular gland biopsy may be obtained between Week 16 and 24.

[11] To be obtained stat locally and reviewed before each infusion (or within 48 hours of subsequent infusion).

[11a] Safety labs should be repeated at baseline after screening only as clinically indicated.

[12] To be completed only at visits following a flare occurrence.

[13] Can be completed at screening or baseline per Section 3.5.2 *IgG4-RD Responder Index*.

[14] In the event of a disease flare, the assessments and procedures outlined for the Week 24 visit should be obtained. For unscheduled visits conducted for a reason other than a disease flare, participants should be evaluated per clinical judgement of the investigator.

[15] Serum Immunoglobulins include IgA, IgG, IgM, and IgE.

[16] The IgG4-RD RI will need to be repeated at Baseline if there has been a change in Prednisone or other DMARD or if there has been an apparent change in disease activity between Screening and Baseline.

[17] Participants must be confirmed negative for SARS-CoV-2 by antigen test within 24 hours of infusion. Participants are provided antigen tests by the site, test themselves, and provide proof of negativity.

[18] EVUSHELD or other prophylaxis will be administered as per section 7.1.2.

Part 1B (Twelve Month Open-label Regimen) and Part 2 (Randomized Phase)

Visit Name	Screening	Base-line/ Day 0[1]	Day 7 (phone call)	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Unscheduled[14]
Visit window	-28 days	N/A	±2 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	N/A
Clinical Draw (mL)	27.4	28	0	7	28	7	28	7	28	7	28	7	28	7	28	28
Research Draw (mL)	50[18]	50[18]	0	0	30	0	30	0	30	0	30	0	30	0	30	30
Visit Draw Total (mL)	27.4	78	0	7	58	7	58	7	58	7	58	7	58	7	58	58
General Assessments																
Informed Consent	X															
Confirm Eligibility		X														
Randomization (Part 2 only)		X														
Demographics	X															
Medical History	X															
ACR Classification Criteria	X															
IgG4 History	X															
Comprehensive Physical Examination	X	X							X						X	X
Targeted Physical Examination				X	X	X	X	X		X	X	X	X	X		
Vital signs/Height/Weight[2]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SARS-CoV-2 Antigen Test[17]		X			X		X		X		X		X			
Disease Activity Assessments																
CT scan w/ or MRI w/o contrast[3, 3a]	X														X	X
IgG4-RD Responder Index (RI)[13]	X	X[16]													X	X
Physician Global Assessment VAS	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Global Assessment VAS	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Flare Documentation Guide[12]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36 Health Survey		X			X		X		X		X		X		X	X
Clinical Laboratory Assessments																
CBC with differential/ANC[11, 11a]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic Panel[11, 11a]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum amylase and lipase	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
eGFR[4]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Immunoglobulins[15]		X			X		X		X		X		X		X	X
Serum IgG subclasses		X			X		X		X		X		X		X	X
ESR		X			X		X		X		X		X		X	X
CRP		X			X		X		X		X		X		X	X
Serum complement: C3 and C4		X			X		X		X		X		X		X	X

Visit Name	Screening	Base-line/ Day 0[1]	Day 7 (phone call)	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Unscheduled[14]
Visit window	-28 days	N/A	±2 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	N/A
ELF score[5]		X			X		X		X		X		X			X
TB Testing[6]	X															
Clinical Laboratory Assessments (continued)																
Other infectious disease testing[7]	X															
Urinalysis and culture[8]	X								X						X	X
Serum HCG[9]	X															
Urine HCG[9]		X			X		X		X		X		X			
Mechanistic Assessments																
Flow Cytometry: PBMC collection	X[18]	X[18]			X		X		X		X		X		X	X
Plasma Collection	X[18]	X[18]			X		X		X		X		X		X	X
Submandibular Gland Biopsy[10]	X[19]	X[19]											X[10a]	X[10a]		
Study Drug Administration																
Elotuzumab/placebo 10 mg/kg IV		X			X		X		X		X		X			
Oral steroid		X		X	X											
Steroid compliance check			X	X	X	X										

[1] Baseline/Day 0 assessments may be split to accommodate submandibular gland biopsy so long as first infusion occurs within 28 days of start of screening.

[2] Height at screening. At the Baseline/Day 0 visit, the screening weight will be used for calculation of the baseline infusion dose. For all subsequent infusions, the weight assessed at the previous infusion visit will be used for calculation of dose.

[3] Imaging required to complete a full IgG4-RD RI assessment will be performed for the Screening visit. Specifically, all participants will undergo either a CT or MRI of the chest, abdomen, and pelvis at Screening. Participants with clinical evidence of orbital disease will also undergo CT or MRI of that area. If abnormalities in a particular area are detected at Screening, the participant will have the same type of study repeated at Week 48. Imaging at week 48 will be performed if there is a clinical reason to suspect disease activity at that site. Imaging may also be repeated at the discretion of the investigator at a visit other than those two time points if required to assess disease activity because of a potential disease flare or to assess an adverse event.

[3a] Oral or intravenous contrast agents may be used in some radiology studies. The need for contrast agents will be reviewed on an individual basis, consistent with the routine use of these imaging studies. Consultation with radiology will be obtained as needed.

[4] eGFR to be calculated centrally per the CKD-EPI formula.

[5] ELF Score serology: TIMP-1, PIIINP, HA.

[6] By Interferon-Gamma Release Assay (IGRA) at or within 90 days of the Screening visit. If indeterminate, repeat (with same or other IGRA per local policy) or obtain PPD (the later to be read within 48-72 hours and may be read locally with documentation of result by health care provider). If history of BCG vaccine or other complication in interpretation of result, consultation with ID is required for clearance to proceed.

[7] HIV, Hepatitis B surface antigen and Hepatitis B core antibody, Hepatitis C antibody.

[8] U/A macroscopic and microscopic analysis, culture if indicated.

[9] For women of child-bearing potential. Stat urine HCG prior to each infusion may be performed locally with point of care testing.

[10] Submandibular gland biopsy: fine needle aspiration of parotid or submandibular salivary gland. Sub-study to be conducted only at MGH. May use tissue previously acquired if available. Opt-out language to be included in the informed consent document.

[10a] Submandibular gland biopsy may be obtained between Week 40 and 44.

[11] To be obtained stat locally and reviewed before each infusion (or within 72 hours of subsequent infusion).

[11a] Safety labs should be repeated at Baseline/Day 0 after screening only as clinically indicated.

[12] To be completed only at visits following a flare occurrence.

[13] Can be completed at screening or baseline per Section 3.5.2, *IgG4-RD Responder Index*

[14] In the event of a disease flare, the assessments and procedures outlined for the Week 24 visit should be obtained. For unscheduled visits conducted for a reason other than a disease flare, participants should be evaluated per clinical judgement of the investigator.

[15] Serum Immunoglobulins include IgA, IgG, IgM, and IgE.

[16] The IgG4-RD RI will need to be repeated at Baseline/Day 0 if there has been a change in Prednisone or other DMARD or if there has been an apparent change in disease activity between Screening and Baseline.

[17] Participants must be confirmed negative for SARS-CoV-2 by antigen test within 24 hours of infusion. Participants are provided antigen tests by the site, test themselves, and provide proof of negativity.

[18] Mechanistic assessments should not be collected at screening if the participant is taking glucocorticoids on the day of the Screening Visit. If Mechanistic Assessments were not collected at the Screening Visit, they must be collected at Baseline/Day 0.

[19] Submandibular gland biopsy can be completed during the screening period once eligibility has been confirmed.

20.2 Appendix 2: ACR/EULAR

The 2019 ACR/EULAR Classification Criteria for IgG4-Related Disease

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, or thyroid gland [Riedel's thyroiditis]) OR pathologic evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain etiology in one of these same organs.	**Yes** or No**
2. Exclusion Criteria∞	**Domains and Items**	
	Clinical	Yes or **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	
	Primarily granulomatous inflammation	
	Pathologic features of macrophage/histiocytic disorder	
	Known Diagnosis of the Following:	
	Multicentric Castleman's Disease	
	Crohn's disease or Ulcerative Colitis (if only pancreatobiliary 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**	**Weight‡**
	Histopathology	
	Uninformative biopsy	+ 0
	Dense Lymphoplasmacytic Infiltrate	+ 4
	Dense Lymphoplasmacytic Infiltrate and Obliterative Phlebitis	+ 6
	Dense Lymphoplasmacytic Infiltrate and Storiform Fibrosis with or without Obliterative Phlebitis	+ 13
	Immunostaining† (Table 2b)	**+ 0-16**
	Serum IgG4 Concentration	
	Normal or Not Checked	+ 0
	> Normal but < 2x Upper Limit of Normal	+ 4
	2x to 5x Upper Limit of Normal	+ 6
	≥ 5x Upper Limit of Normal	+ 11

	Bilateral Lacrimal, Parotid, Sublingual, and Submandibular Glands	
	No set of glands is involved	+ 0
	One set of glands is involved	+ 6
	Two or more sets of glands are involved	+ 14
	Chest	
	Not checked or neither of the items listed is present	+ 0
	Peribronchovascular and septal thickening	+ 4
	Paravertebral Band-Like Soft Tissue in the Thorax	+ 10
	Pancreas and Biliary Tree	
	Not checked or none of the items listed is present	+ 0
	Diffuse pancreas enlargement (loss of lobulations)	+ 8
	Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+ 11
	Pancreas (either of above) and biliary tree involvement	+ 19
	Kidney	
	Not checked or none of the items listed is present	+ 0
	Hypocomplementemia	+ 6
	Renal pelvis thickening/soft tissue	+ 8
	Bilateral renal cortex low density areas	+ 10
	Retroperitoneum	
	Not checked or neither of the items listed is present	+ 0
	Diffuse thickening of the abdominal aortic wall	+ 4
	Circumferential or antero-lateral soft tissue around the infra-renal aorta or iliac arteries	+ 8
4. Total Inclusion Points	**A case meets the classification criteria for IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥20**	

*Refers to enlargement or tumor-like mass in an affected organ except in:
- the bile ducts, where narrowing tends to occur

• in the aorta, where wall thickening or aneurysmal dilatation is typical
• and in the lungs, where thickening of the bronchovascular bundles is common

**If Entry Criteria not fulfilled, then the patient cannot be further considered for classification as IgG4-RD

***If Exclusion Criteria are met, then the patient cannot be further considered for classification as IgG4-RD

† Biopsies from lymph nodes, mucosal surfaces of the gastrointestinal tract, and the skin cannot be considered

‡ Only the highest-weighted item in each Domain is scored

ᵒᵒAssessment for the presence of Exclusion Criteria should be individualized depending on a patient's clinical scenario.

20.2.1 Immunostaining for ACR/EULAR Classification

Immunostaining (See Table Below and Enter Appropriate Weight)

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

Immunostaining weight:

Round the weight to the nearest whole integer

20.3 Appendix 3: IgG4-RD RI

Date: ___/___/____ Visit:_____ Patient ID:_____

IgG4-RD Responder Index (Version: July 25, 2016)

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

At the initial assessment, the physician enters a 2 after any active organs/sites and a 0 after uninvolved organs/sites.
At each subsequent assessment, the physician enters a 0-3 score after the organ/site listed.

0 = Normal or resolved
1 = Improved but still present since the previous assessment or improved from initial assessment with no change from previous assessment
2 = Disease activity unchanged from previous assessment
Once an organ or site has improved or worsened, the score of 2 will no longer be used for that organ/site, ie, an improved organ/system will maintain a score of 1 until resolution (score as 0) or worsening (score as 3).
No change from previous assessment will often refer to disease manifestations that require follow-up imaging to assess accurately; ie, a disease manifestation only assessable by imaging will be assumed to be unchanged until such time that repeat imaging demonstrates improvement, worsening, or resolution.
3 = Worsened or new disease manifestation since the last assessment and requirement for additional therapy (intent to treat)

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**	**Symptomatic (Y/N)**	**Urgent (Y/N)**	**Yes/No**	**Symptomatic (Y/N)**
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 (example: tonsillitis, pharyngitis): _____					
Thyroid					
Lungs					

Date: ____/____/_____ Visit:_____ Patient ID:_____

Organ/Site			Activity			Damage	
			organ/site score	Symptomatic (Y/N)	Urgent (Y/N)	Yes/No	Symptomatic (Y/N)
	Lymph node chain	(Check if present):					
Lymph nodes	Submental						
	Submandibular						
	Cervical						
	Axillary						
	Mediastinal						
	Hilar						
	Abdominal/pelvic						
	Inguinal						
	Other lymph node chain: _____						
Aorta/Large Blood Vessels							
Heart/Pericardium							
Retroperitoneal Fibrosis (RPF)							
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. Each "other" item is counted separately)							
Other involvement-specify: _____ (consider prostate, breast, gallbladder involvement. Each "other" item is counted separately)							
Other involvement-specify: _____ (consider prostate, breast, gallbladder involvement. 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: _____

Signature of Investigator:_____ Date: ____/___/_____

20.4 Appendix 4: PhGA and PGA VAS

PATIENT GLOBAL ASSESSMENT:

(100mm)

Patient Instructions: Please answer the question by placing a vertical (|) mark to indicate your response. Please sign and date this form.

Considering all the ways IgG4 Related Disease affects you, mark a vertical line at the spot on the horizontal line to describe your disease activity within the last 24 hours.

YOUR RESPONSE:

0 Not Active

100 Extremely Active

Patient's Signature: _____ **Date:** _____

PHYSICIAN GLOBAL ASSESSMENT:

(100mm)

Subject ID #: _____ **Assessment Date:** _____ / _____ / _____
(dd/mon/yyyy)

YOUR RESPONSE:

Please rate the patient's current IgG4 Related Disease activity on the scale below, with 0 being no disease activity and 100 being extremely active disease activity.

0
Not Active

100
Extremely Active

Initials of individual marking the line: _____ Date: _____
(dd/mon/yyyy)

---------- **For Site Coordinator Use Only** ----------

Site Coordinator Directions: Using the markings provided, measure from the "0" to the vertical line placed by the physician. Enter the distance in millimeters as indicated below, then transfer the pertinent information onto the appropriate eCRF page, and place this document in the subject's research record.

Length of line
(from 0 to vertical assessment line) _____ mm

Initials of site personnel measuring the line: _____ Date: _____
(dd/mon/yyyy)

20.5 Appendix 5: Flare Documentation Guide

AIG01 FLARE DOCUMENTATION GUIDANCE

This document provides guidance with regard to the evaluation of potential disease flares and outlines appropriate work-ups for IgG4-RD activity in each organ.

Investigators will complete a disease activity assessment only in the organs involved in the flare. The suggested laboratory evaluation, radiology studies, and other procedures (e.g., biopsy) as well as the minimum criteria for diagnosis of a disease flare are provided for each organ system.

Following the documentation of evidence supporting a flare in a given organ, the investigator will complete a short narrative justifying the diagnosis of a flare in that organ.

Collection of data during evaluation of a potential disease flare

For each potential flare event, the following will be collected:

1. Observation that led to the initiation of evaluation for a disease flare (mark all that apply)
   - ☐ New/worsening symptoms reported by the patient
   - ☐ New/worsening finding on physical examination
   - ☐ New/worsening laboratory finding
   - ☐ Incidental finding on imaging
2. Investigator Narrative (free text)

   The narrative should be a complete medical account of the event. The narrative should include a description of any symptoms, physical examination findings, laboratory abnormalities, imaging findings, or biopsy data collected for the evaluation of this event.

   The narrative should refer to historical data (e.g., the patient's baseline visit or more recent trial visit) to establish the new/worsening nature of the disease manifestations.

   The descriptions must be sufficiently detailed to understand the findings and the investigator's interpretation of them. The narrative must describe findings in every organ affected by the disease flare. Data supporting the occurrence of a disease flare in each organ are recorded in the organ-specific sections, below.

   After the completion of treatment, the narrative should be updated with response to treatment.
3. Details on the organ-specific flare criteria must be completed for every organ potentially affected by the disease flare.

4. Treatment (mark all that apply)
   - ☐ Glucocorticoids (specify drug, dose, start/stop dates)
   - ☐ Supportive therapy (e.g., pancreatic enzyme replacement, bile acid sequestrant, artificial saliva/lubricant, specifying drug, dose, start/stop dates)
   - ☐ Immunosuppression other than glucocorticoids (specify drug, dose, start/stop dates)
   - ☐ Surgical intervention or other procedural intervention (e.g., stenting), specify procedure and date performed (describe in narrative)
   - ☐ None (provide rationale in the investigator narrative)
5. Outcome of treatment: (Mark all that apply)
   - ☐ Returned to baseline before current flare
   - ☐ Disease activity suppressed but disease damage sustained (resultant organ damage compared to pre-flare baseline)
   - ☐ Ongoing immunosuppressive therapy required at 24-weeks

ORGAN-SPECIFIC FLARE CRITERIA

Pachymeninges

Symptoms and Findings

Symptom(s)	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with pachymeningeal flare:			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Headache			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with pachymeningeal flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Cranial nerve palsy, neurologic abnormalities consistent with radiculomyelopathy			
Other (describe)			
None			
Laboratory findings consistent with pachymeningeal flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Cerebrospinal fluid pleocytosis			
Cerebrospinal fluid increased protein			
Other (describe)			
None			
Imaging (CT, MRI, PET) consistent with pachymeningeal flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Meningeal enhancement ☐ Meningeal thickening			

Symptom(s)	Observed (✓)	New onset or worsening (N/W)	Description
Other (describe)			
None			
Biopsy results consistent with pachymeningeal flare			**Describe tissue and reading**
Biopsy/tissue consistent with pachymeningeal flare			
Biopsy/tissue not done or insufficient			
Not consistent, specify tissue and reading			

Criteria for Pachymeningitis Flare and Investigator Conclusion

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
1. New or worsening symptom or physical examination finding consistent with IgG4-RD pachymeningitis		
2. EITHER:		
a. Cerebrospinal fluid lab finding consistent with IgG4-RD pachymeningitis OR		
b. Imaging finding confirming new or worsening meningeal involvement		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy finding		

Investigator Conclusion – Pachymeningitis Flare

☐ Yes

☐ No

Why do you believe this patient is having an IgG4-RD flare involving the pachymeninges?

Pituitary Gland

Symptoms and Findings

Symptom(s)	Observed (✓)	New onset or worsening (N/W)	Descriptions
Symptoms consistent with pituitary flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Visual field abnormalities, headache, symptoms consistent with anterior or posterior pituitary endocrine failure			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with pituitary flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Visual field deficits			
Other (describe)			
None			
Laboratory findings consistent with pituitary flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Pituitary endocrine dysfunction, documented by abnormalities of one or more of the following: • Thyroid stimulating hormone • Growth hormone • Follicular stimulating hormone • Luteinizing hormone • Cortisol • Prolactin			

Symptom(s)	Observed (✓)	New onset or worsening (N/W)	Descriptions
Anti-diuretic hormone			
Other (describe)			
None			
Other, describe: Imaging (CT, MRI, PET) consistent with pituitary flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Pituitary mass ☐ Pituitary enhancement			
Other (describe)			
None			
Biopsy results consistent with pituitary flare			**Describe tissue and reading**
Biopsy/tissue consistent with pituitary gland flare			
Biopsy/tissue not done or insufficient			
Not consistent, specify tissue and reading			

Criteria for Pituitary Gland Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
EITHER New or worsening anterior/posterior pituitary endocrine dysfunction OR		
Imaging finding confirming new or worsening pituitary involvement		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Flare in Pituitary Gland

☐ Yes

☐ No

Why do you believe this patient is having an IgG4-RD flare involving the pituitary gland?

Orbits

Symptoms and Findings

Symptom(s) or Finding(s)	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with flare in orbits:			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Diplopia, proptosis, eye or retrobulbar discomfort or pain, or other visual symptoms including vision blurring or loss, symptoms consistent with scleritis, symptoms from compression of peripheral nerves in the area of the orbit, such as trigeminal and infra-orbital nerves (pain or numbness)			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with orbital flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Proptosis, supra-orbital swelling or other peri-orbital swelling consistent with enlargement of extra-ocular muscles, field cuts, cranial nerve palsies, extraocular movement abnormality, infra-orbital/supra-orbital nerve enlargement			
Other (describe)			
None			
Imaging (CT, MRI, PET) consistent with orbital flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
CT or MRI compatible with orbital disease ☐ enlargement of extra-ocular muscles ☐ enlargement of optic nerve ☐ abnormalities of retrobulbar space or within cavernous sinus			

Symptom(s) or Finding(s)	Observed (✓)	New onset or worsening (N/W)	Description
Other (describe)			
None			
Biopsy results consistent with orbital flare			**Describe tissue and reading**
Biopsy/tissue consistent with orbital flare			
Biopsy/tissue not done or insufficient			
Not consistent, specify tissue and reading			

Criteria for Orbital Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present, EITHER:		
New or worsening symptom or physical examination finding consistent with orbital flare **OR**		
New or worsening orbital abnormality on imaging consistent with orbital flare		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Flare in the Orbit

☐ Yes

☐ No

Why do you believe this patient is having an IgG4-RD flare involving the orbit(s)?

Lacrimal Glands

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset/ worsening (N/W)	Description
Symptoms consistent with flare in lacrimal glands			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Lacrimal gland discomfort, pain or swelling; redness of the eye, excessive tearing; blurred vision			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with lacrimal gland flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Lacrimal gland swelling/mass			
Other (describe)			
None			
Imaging (CT, MRI, PET) consistent with lacrimal gland flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Lacrimal gland enlargement demonstrated by CT or MRI			
Other (describe)			
None			
Biopsy results consistent with lacrimal gland flare			**Describe tissue and reading**
Biopsy/tissue consistent with lacrimal gland flare			
Biopsy/tissue not done or insufficient			
Not consistent, specify tissue and reading			

Criteria for Lacrimal Gland Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
New or worsening lacrimal gland enlargement/mass on physical examination or observed on imaging		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Lacrimal Gland Flare

☐ Yes

☐ No

Why do you believe this patient is having an IgG4-RD flare involving the lacrimal glands?

Major Salivary Glands

Specific salivary gland(s) involved:

- ☐ Parotid
- ☐ Submandibular
- ☐ Sublingual

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with salivary gland flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Sicca symptoms, pain, swelling of gland(s)			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with salivary gland flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Salivary gland swelling or tenderness			
Other (describe)			
None			
Imaging (CT, MRI, PET) consistent with salivary gland flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Major salivary gland (submandibular, parotid, or sublingual) swelling demonstrated by CT or MRI			
Other (describe)			
None			
Biopsy results consistent with salivary gland flare			**Describe tissue and reading**
Biopsy/tissue consistent with salivary gland flare			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Biopsy/tissue not done or unreadable			
Not consistent, specify tissue and reading			

Criteria for Salivary Gland Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
New or worsening salivary gland enlargement or tenderness on physical examination or new/worse enlargement on imaging		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Flare in Salivary Gland(s)

☐ Yes

☐ No

Why do you believe this patient is having a disease flare in one or more of the major salivary glands?

Lymph node(s)

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with flare in lymph node(s)			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Patient-reported swelling			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with flare in lymph node(s)			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Lymphadenopathy (specify localized or diffuse)			
Other (describe)			
None			
Laboratory findings consistent with flare in lymph node(s): NA			
Imaging (CT, MRI, PET) consistent with lymphadenopathy (localized or diffuse)			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Lymphadenopathy demonstrated by imaging			
Other (describe)			
None			
Biopsy results consistent with lymph node flare			**Describe tissue and reading**
Biopsy/tissue consistent with lymph node flare			
Biopsy/tissue not done or unreadable			
Not consistent, specify tissue and reading			

Criteria for Lymph Node Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present, EITHER:		
In a patient with concurrent IgG4-RD in another organ(s): Multiple enlarged nodes (generally nontender) by physical examination or imaging in an area separate from other current organ with flare **OR**		
In a patient with no other organ with concurrent flare: Multiple enlarged lymph nodes (generally nontender) by physical examination or imaging AND lymph node biopsy to exclude other diagnosis, such as malignancy		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Flare in Lymph Node(s)

☐ Yes

☐ No

Why do you believe this patient is having an IgG4-RD flare manifested as lymphadenopathy?

Lungs, Including Pleura and Parenchyma

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with lung flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Dyspnea at rest or with exertion, cough			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with lung flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Increased respiratory rate, findings suggestive of pleural effusion, dry crackles compatible with pulmonary fibrosis, localized diminished breath sounds, findings consistent with infiltrate			
Other (describe)			
None			
Laboratory findings consistent with lung flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
New or worsening pulmonary function test abnormalities consistent with lung flare			
Other (describe)			
None			
Imaging (CXR, CT, MRI, PET) consistent with lung flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Pulmonary nodules or mass ☐ Pulmonary infiltrate/ground glass opacities consistent with interstitial pneumonia ☐ Pulmonary fibrosis			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
☐ Pleural effusion ☐ Pleural thickening ☐ Peribronchovascular and septal thickening ☐ Paravertebral mass/Paravertebral band-like soft tissue in thorax			
Other (describe)			
None			
Biopsy results consistent with lung flare			**Describe tissue and reading**
Biopsy/tissue consistent with lung flare			
Biopsy/tissue not done or unreadable			
Not consistent, specify tissue and reading			

Criteria for Parenchymal or Pleural Lung Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
New or worsening imaging finding confirming pleuropulmonary involvement		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Lung Flare

☐ Yes

☐ No

Why do you believe this patient is having an IgG4-RD flare in the lungs or pleura?

Aorta & large blood vessels

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with aorta & large blood vessels flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Pain, palpable mass			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with aorta & large blood vessels flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Palpable arterial mass, especially if pulsatile, or bruit			
Other (describe)			
None			
Imaging (CT, MRI, PET) consistent with aorta & large blood vessels flare:			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Aneurysm ☐ Dissection ☐ Thickening/enhancement of vessel wall			
Other (describe)			
None			
Biopsy results consistent with aorta/large blood vessel flare			**Describe tissue and reading**
Biopsy/tissue consistent with aorta/large blood vessel flare			
Biopsy/tissue not done or unreadable			
Not consistent, specify tissue and reading			

Criteria for Aorta & Large Blood Vessel Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present: EITHER		
New or worsening aortic or other vessel wall thickening or other evidence of aortitis (dissection, aneurysm) by imaging		
Demonstration of aortitis, dissection or aneurysm or similar findings for other large artery at surgery or intervention (stenting) of an aneurysm, dissection or other vascular anomaly		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Aorta & Large Blood Vessel Flare

☐ Yes

☐ No

Why do you believe this patient is having an IgG4-RD flare manifested by involvement of the aorta or other large blood vessels?

Retroperitoneum, Mediastinum, & Mesentery

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with retroperitoneum, mediastinum & mesentery flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Pain (e.g., flank, back, thighs, abdominal, other including chronic pain), leg edema, dyspnea, cough			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with retroperitoneum, mediastinum & mesentery flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Palpable mass or findings consistent with superior vena cava syndrome, leg edema, or fibrosing mediastinitis			
Other (describe)			
None			
Laboratory findings consistent with retroperitoneum, mediastinum & mesentery flare			
For retroperitoneal involvement of ureters: elevated creatinine, decreased eGFR			
Other (describe)			
None			
Imaging (CT, MRI, PET) consistent with retroperitoneum, mediastinum & mesentery flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Mass lesion			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
☐ Ureteral stenosis or hydronephrosis ☐ Superior vena cava syndrome ☐ Retroperitoneal enhancement (often infra-renal, peri-aortic distribution extending down to iliac vessels but may involve root of mesentery) ☐ Circumferential/antero-lateral soft tissue around infrarenal aorta or iliac arteries ☐ Other radiologic evidence of inflammation in mesentery or mediastinum			
Other (describe)			
None			
Biopsy results consistent with retroperitoneum, mediastinum & mesentery flare			**Describe tissue and reading**
Biopsy/tissue consistent with retroperitoneum, mediastinum & mesentery flare			
Biopsy/tissue not done or unreadable			
Not consistent, specify tissue and reading			

Criteria for Flare in Retroperitoneum, Mediastinum or Mesentery

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present: EITHER		
New or worsening imaging evidence of involvement of retroperitoneum, mediastinum and/or mesentery		
Tissue confirmation at time of surgery or intervention (stenting) that confirms involvement of retroperitoneum, mediastinum and/or mesentery		
Required to be absent:		

Criteria for Flare	Present (✓)	Absent (✓)
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Flare in Retroperitoneum, Mediastinum or Mesentery

☐ Yes

☐ No

Why do you believe this patient is having an IgG4-RD flare involving the retroperitoneum, mediastinum, or mesentery?

Pancreas and Common Bile Duct

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with flare of pancreatic disease			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Pain (eg, flank, back, abdominal, other)			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with flare of pancreatic disease			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Abdominal tenderness, jaundice, palpable mass, weight loss			
Other (describe)			
None			
Laboratory findings consistent with flare of pancreatic disease			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Elevated bilirubin, alk phos, amylase and/or lipase			
Other, including low fecal elastase, high glucose/HbA1C (describe)			
None			
Imaging findings consistent with flare of pancreatic disease			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Pancreatic mass ☐ Diffuse pancreatic enlargement with loss of lobulations ☐ Diffuse pancreatic enlargement ☐ Pseudocapsule ☐ Pancreatic duct stricture ☐ Common bile duct abnormality			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Other (describe)			
None			
Biopsy results consistent with pancreatic flare			**Describe tissue and reading**
Biopsy/tissue consistent with pancreatic flare			
Biopsy/tissue not done or unreadable			
Not consistent, specify tissue and reading			

Criteria for Pancreatic Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
In a patient with a prior history of IgG4-related autoimmune pancreatitis, EITHER:		
New or worsening symptom and/or physical examination finding AND new or worsening laboratory finding consistent with autoimmune pancreatitis		
Imaging or endoscopic finding that confirms new or worsening involvement of the pancreas		
In a patient with no prior history of IgG4-related autoimmune pancreatitis:		
New symptom, physical examination finding and/or laboratory finding consistent with involvement of the pancreas, AND EITHER		
New imaging or endoscopic (ERCP) finding that confirms involvement of the pancreas, OR		
Biopsy evidence of involvement of the pancreas		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Pancreatic Flare:

☐ Yes
☐ No

Why do you believe this patient is having an IgG4-RD flare involving the pancreas?

Biliary tree (IgG4-RD sclerosing cholangitis)

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with flare of bile duct/biliary tree			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Itching, abdominal pain, RUQ pain			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with flare of bile duct/biliary tree			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Abdominal tenderness, jaundice, RUQ fullness			
Other (describe)			
None			
Laboratory findings consistent with flare of bile duct/biliary tree			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Elevated bilirubin, Alt/AST, alk phos			
Other (describe)			
None			
Imaging consistent with flare of bile duct/biliary tree			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Thickening of the extra-or intra-hepatic bile ducts ☐ Mass ☐ Strictures and/or dilatation			
Other (describe)			
None			
Biopsy results consistent with bile duct/biliary tree flare			**Describe tissue and reading**
Biopsy of liver or biliary tree consistent with bile duct/biliary tree flare			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Biopsy/tissue not done or unreadable			
Not consistent, specify tissue and reading			

Criteria for Flare in Bile Duct/Biliary Tree

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
EITHER:		
New or worsening laboratory finding consistent with biliary tree flare OR		
New or worsening imaging or ERCP finding that confirms worsening involvement of the bile duct/biliary tree		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Flare in Bile Duct/Biliary Tree

☐ Yes
☐ No

Why do you believe this patient is having an IgG4-RD flare involving the biliary tree?

Kidney

Kidney flare is specifically intrinsic renal disease or ureteropelvic junction (UPJ) mass or obstruction. Disease caused by ureteral obstruction below the UPJ should be entered under retroperitoneum.

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with kidney flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Fatigue, mental status changes			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with kidney flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Edema			
Other (describe)			
None			
Laboratory findings consistent with kidney flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Elevated creatinine, decreased eGFR, hematuria or proteinuria			
Other, including hypocomplementemia (describe)			
None			
Imaging (CT, MRI, PET) consistent with kidney flare			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Hypodense lesions in the renal cortex ☐ Renal atrophy ☐ Renal pelvis thickening			
Other (describe)			
None			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Biopsy results consistent with kidney disease flare			**Describe tissue and reading**
Biopsy/tissue consistent with kidney disease flare			
Biopsy/tissue not done or unreadable			
Not consistent, specify tissue and reading			

Criteria for Kidney Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
In a patient with a prior history of IgG4-related kidney disease EITHER:		
Worsening renal function or proteinuria, OR		
Any imaging finding or biopsy that confirms worsened involvement of the kidney		
In a patient with no prior history of IgG4-related renal disease, EITHER		
Worsening renal function, or proteinuria AND either biopsy or imaging finding consistent with renal flare, OR		
Worsening renal function in the setting of active IgG4-RD in other organs with worsened hypocomplementemia and increased IgG4		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Kidney Flare

☐ Yes
☐ No

Why do you believe this patient is having an IgG4-RD flare involving the kidneys?

Skin

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with flare of skin disease			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Rash			
Systemic/constitutional			
Other (describe)			
None			
Physical examination findings consistent with flare of skin disease			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Erythematous papules or nodules, hyperpigmented lesions or other skin lesions			
Other (describe)			
None			
Biopsy results consistent with skin disease flare			**Describe tissue and reading**
Biopsy/tissue consistent with skin disease flare			
Biopsy/tissue not done or unreadable			
Not consistent, specify tissue and reading			

Criteria for Skin Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
New or worsening IgG4-RD skin lesions from symptoms or physical examination **AND EITHER**		
Prior biopsy-proven IgG4 skin disease, **OR**		
Current biopsy consistent with diagnosis		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Skin Flare

☐ Yes
☐ No

Why do you believe this patient is having an IgG4-RD flare involving the skin?

Other sclerosis/mass formation in thyroid (Riedel's thyroiditis), liver, breast, prostate, maxillary sinus, nasal septum, pericardium, peripheral nerves, other

Specify site of sclerosis/mass formation:

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with flare of other sclerotic/mass forming disease			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Site dependent, describe			
Systemic/constitutional			
None			
Physical examination findings consistent with flare of sclerotic/mass forming disease			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Site dependent, describe			
None			
Laboratory findings consistent with flare of sclerotic/mass forming disease			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
Site dependent, describe			
None			
Imaging (CT, MRI, PET) consistent with flare of sclerotic/mass forming disease			**Describe the finding and indicate why it represents IgG4-RD activity worsening from recent baseline**
☐ Radiology findings consistent with sclerotic/mass forming disease			
Other (describe)			
None			
Biopsy results consistent with sclerotic/mass forming disease			**Describe tissue and reading**
Biopsy/tissue consistent with sclerotic/mass forming disease flare			
Biopsy/tissue not done or unreadable			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Not consistent, specify tissue and reading			

Criteria for Sclerotic/Mass Forming Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present, EITHER:		
EITHER:		
New or worsening imaging result that confirms involvement (specify):		
Any new biopsy evidence of involvement		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Sclerotic/Mass Forming Flare

☐ Yes
☐ No

Why do you believe this patient is having a disease flare?

20.6 Appendix 6: SF-36 Health Survey

RAND HEALTH

RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

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?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

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**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

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)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

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**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

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.

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

ABOUT

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.

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20.7 Appendix 7: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

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

PEF, Peak expiratory flow; *BP*, blood pressure.
* Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Adapted from the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network [39]

20.8 Appendix 8: Acceptable Contraception Methods for Females of Reproductive Potential

<table>
<tr><th colspan="4">Acceptable Contraception Methods for Females of Reproductive Potential*</th></tr>
<tr><td>Option 1
Methods to Use Alone</td><td colspan="3">• Intrauterine devices (IUDs)
• Tubal sterilization
• Patient’s partner had a vasectomy
• Implant</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td rowspan="2">Option 2
Choose One Hormone Method AND One Barrier Method</td><td>Hormone Methods
choose 1</td><td></td><td>Barrier Methods
choose 1</td></tr>
<tr><td>Estrogen and Progesterone
• Oral contraceptive pill
• Transdermal patch
• Vaginal ring
• Injection</td><td>AND</td><td>• Diaphragm with spermicide
• Cervical cap with spermicide
• Contraceptive sponge
• Male condom
• Female condom</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td rowspan="2">Option 3

Choose One Barrier Method from each column (must chose two methods)</td><td>Barrier Methods
choose 1</td><td></td><td>Barrier Methods
choose 1</td></tr>
<tr><td>• Diaphragm with spermicide
• Cervical cap with spermicide
• Contraceptive sponge</td><td>AND</td><td>• Male condom
• Female condom</td></tr>
</table>

* Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause.

Adapted from the Mycophenolate REMS (Risk Evaluation and Mitigation Strategy): https://www.mycophenolaterems.com/