A PHASE 3, RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED STUDY OF INEBILIZUMAB EFFICACY AND SAFETY IN IGG4-RELATED DISEASE

SHORT TITLE: MITIGATE

Investigational Product	Inebilizumab
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SPONSORS SIGNATURE PAGE

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Biostatistics Representative		
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[redacted] PhD	Senior Director, Biostatistics	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 08-Aug-2023 | 08:46 CDT E759BA2A8AF94B7A8CB3949D8FB22D6E

SUMMARY OF CHANGES TO THE PROTOCOL

The following table summarizes the key changes to the protocol made in Amendment 1:

Protocol Amendment 1 (25Feb2020)

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 1, Synopsis Section 9.3, Determination of Sample Size	The maximum sample size and process for re-estimation were clarified.	Clarifications were in response to scientific advice from the European Medicines Agency (EMA).
Section 1, Synopsis Section 3.2, Secondary Objectives and Endpoints	The secondary safety objective and endpoint were updated to clarify that adverse event data collected during both the 52-week randomized-controlled period (RCP) and the open-label period (OLP) will be used to evaluate the safety and tolerability of inebilizumab.	To clarify the objectives of the OLP, in response to scientific advice from EMA.
Section 1, Synopsis Section 3.3, Exploratory Objectives and Endpoints	[redacted]	
Section 1, Synopsis Section 3.3, Exploratory Objectives and Endpoints Section 6.2.2, Schedule of RCP Assessments and Procedures, Table 4		
[redacted]		
Section 1, Synopsis Section 3.3, Exploratory Objectives and Endpoints Section 4.1, Study Design		
Section 2.1.1, IgG4-Related Disease Section 13, References	The description of IgG4-RD pathogenesis was updated to include recent concepts and publications.	To provide investigators with the most recent understanding of the pathophysiology of IgG4-RD.
Section 2.1.5, Supportive Clinical Data Section 13, References	References to published data from the first 2 studies of inebilizumab were added.	To provide investigators with additional data on the safety of inebilizumab.
Section 4.1, Study Design Section 6.4.2, Withdrawal from Study	In Section 4.1, the description of the RCP was revised to emphasize that any subject who withdraws from the study should be asked to complete a final visit (early discontinuation visit [EDV]). Similar edits were made to the text in Section 6.4.2.	Clarification.

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 4.1, Study Design	Language added to clarify the intent to follow all subjects in the OLP to the end of the OLP for safety and efficacy; at least 6 months after the last dose.	Clarification added in response to EMA scientific advice.
Section 5.1, Inclusion Criteria	Amended inclusion criterion 4 to clarify that both inclusion and exclusion criteria for the ACR/EULAR classification criteria must be met.	Clarification added in response to EMA scientific advice.
Section 6.2.1, Schedule of Screening Assessments and Procedures, Table 3	The following was added to the list of laboratory tests at screening: B cell count in patients who received B cell depleting therapy in the 6-12 months prior to screening.	To clarify and ensure that the required B cell counts are obtained to address exclusion criterion 5.
Section 6.2.1, Schedule of Screening Assessments and Procedures, Table 3 Section 6.2.2, Schedule of RCP Assessments and Procedures, Table 4 Section 6.1.1, Order of Assessments	[redacted]	[redacted]
Section 6.2.1, Schedule of Screening Assessments and Procedures, Table 3 Section 6.3.1.2, Demographics and Baseline Characteristics		
Section 6.2.2, Schedule of RCP Assessments and Procedures, Table 4		
Section 6.2.2, Schedule of RCP Assessments and Procedures, Table 4 Section 6.2.3, Schedule of OLP Assessments and Procedures, Table 5	A footnote was added to both the RCP and OLP schedule of assessments to emphasize that premedication will be administered prior to each IP infusion.	To add additional guidance to help ensure adherence to required protocol procedures for administration of IP.
Section 6.2.2, Schedule of RCP Assessments and Procedures, Table 4	Added rows to the RCP assessment table for providing oral GCs (Day 1 [Visit 2]) and assessing oral GC compliance (Days 15, 29, and 57 [Visits 3, 4, and 5]).	Added to the assessment table to ensure adherence to the protocol procedures for the additional study medication.
Section 6.2.3, Schedule of OLP Assessments and Procedures, Table 5	The schedule of assessments during the OLP was revised as follows: • In addition to the symptom-driven physical exams, full physical exams will be performed on Days 1 and 365 (Visits 1 and 14 [or EDV]). [redacted]	• To add a full physical exam at the start and end of the OLP. [redacted]

Protocol Section(s) Impacted by Change	Change	Reason for Change
	[redacted]	
Section 6.3.1.3, Safety Assessments at Screening	The description of the tuberculosis (TB) testing at screening was updated to remove "as per local standard-of-care guidelines".	This text was removed because initial TB testing will be performed by the central laboratory.
Section 6.2.3.1, Eligibility for OLP	Some specific B-cell agents that would be exclusionary were added to the eligibility criteria for the OLP.	Additions were in response to EMA scientific advice.
Section 6.4.1, Discontinuation of Investigational Product	Amended events requiring discontinuation of investigational product (IP): • Added "Any AE of immune complex disease" • Replaced "Any Grade 4 SAE" and "Any Grade 4 infection" with "Any life-threatening (Grade 4) adverse event" • Removed "Any Grade 3 infusion-related reaction" • Added "Any Grade 3 adverse event" with listed exceptions	The list of events requiring discontinuation of IP was revised in response to advice from the US FDA.
Section 9.5.1, Analysis of the Primary Efficacy Endpoint Section 9.5.2, Analysis of the Secondary Efficacy Endpoints	To clarify the subgroup who will be censored for the additional analysis. Similar language was removed from Section 9.5.2 to reduce redundancy.	Text was revised in response to EMA scientific advice.
Section 9.5.4, Subgroup Analyses	Specified subgroup analysis by stratification factors: first or subsequent treatment course for IgG4-RD.	Text was revised in response to EMA scientific advice.
Section 10.7, Biological Specimens and Data	Added clarification that storage of leftover samples for future research will be with patient consent.	Clarification.
Appendix C	Updated version of the IgG4-related disease Responder Index was attached and the version from a previous paper was deleted.	Updated to include the correct scoring table.

The following table summarizes the key changes to the protocol made in Amendment 2:

Protocol Amendment 2 (30Mar2020)

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 14, Appendices, and references to appendices	• Former Appendix A (2019 ACR/EULAR Classification Criteria), Appendix B (Flare Criteria), and former Appendix C (IgG4-RD Responder Index) were removed from the protocol and will be provided via other means to the Investigators. • The remaining appendices were re-lettered to reflect the change. • References to the appendices were updated throughout the document to reflect the change.	Appendices were removed that will be best provided to Investigators via means other than the protocol.
Section 4.1, Study Plan Section 7.4.1, Treatment Allocation for RCP	The description of stratification was clarified to be by IgG4-RD manifestation (ie, newly-diagnosed vs recurrent).	Further clarification following Amendment 1.
Section 5.1, Inclusion Criteria	Added "Females of childbearing potential must have a negative serum pregnancy test at screening" to the text of inclusion criterion no 8.	Clarification.
Section 5.4, Replacement of Subjects	Clarified that subjects who have been randomized but not dosed will not be followed to completion of the RCP.	Clarification.
Section 6.3.1.3, Safety Assessments at Screening	• The description of TB testing at screening was further updated to remove the option of "other interferon gamma release assay test" • A clarification was added that serum will be frozen for possible testing for JCV antibodies "in case of suspected PML".	Clarifications.
[redacted]		
Section 6.4.1, Discontinuation of Investigational Product	Text revised to clarify that subjects who discontinue IP should remain in the study and complete procedures, except IP administration and [redacted] sampling.	• Clarification requested by US FDA.
Section 8.4, Adverse Events of Special Interest	Replaced a reference to the Safety Handling Plan with specific instructions for adverse event of special interest (AESI) reporting.	• Instructions in the protocol are more accessible to sites.

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 9.5.5, Safety Analysis	• The definition of the rate of AEs per 100 person-years at risk was updated to: (total number of AEs)/(total person years) × 100. • Stratification factor was added to the list of subgroup analyses.	• Corrections.

The following table summarizes the key changes to the protocol made in Amendment 3:

Protocol Amendment 3 (16Apr2020)

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 2.1.4, Risk Assessment for Inebilizumab	Updated identified risks to include neutropenia, arthralgia, and reduced immunoglobulin levels.	Changes reflect planned updates to the safety information in the Investigator's Brochure, which is currently in revision.

Protocol Amendment 4 (Japan) (06May2020) (Previously reviewed and approved in Japan only)

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 1, Synopsis Section 5.1, Inclusion Criteria	Updated the age requirement to ≥ 20 years.	In Japan, adults are defined as 20 years of age or older.
Section 5.1, Inclusion Criteria	Revised the text describing any locally required authorization from the subject in inclusion criterion 2.	Removed content that does not apply to Japan.
Section 5.2, Exclusion Criteria Section 6.2.1, Schedule of Screening Assessments and Procedures, Table 3 Section 6.3.1.3, Safety Assessments at Screening	Added "(3) hepatitis B surface antibody (HBsAb)" to exclusion criterion 12. Added HBsAb to the list of tests that require blood collection.	Added a third method to hepatitis B testing.
Section 7.1.1.4, Investigational Product Dosing and Administration	Added text to clarify the administration procedure for the initial randomized-controlled period dose for Japanese subjects.	Added text specific for sites in Japan.
Section 10.1, Good Clinical Practice	Added applicable regulatory requirements in Japan.	Added text specific for sites in Japan.
Section 10.2.1, Ethics and Regulatory Review in Japan	Added details for the ethics and regulatory review in Japan.	Added text specific for sites in Japan.

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 10.4, Deviation from the Clinical Study Protocol	Added a description of the procedures required in the event of a protocol deviation.	Clarification.

Protocol Amendment 5 (Japan) (22Jun2020) (Previously reviewed and approved in Japan, only)

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 7.1.1.4, Investigational Product Dosing and Administration	Removed text requiring inpatient administration of IP for the initial randomized-controlled period dose for Japanese subjects.	Hospitalization for dose administration is not required but is permitted.

Protocol Amendment 6 (China) (19Nov2020) (Previously reviewed and approved in China, only)

Protocol Section(s) Impacted by Change	Change	Reason for Change
[redacted]		

Protocol Amendment 7 (Global) (16Aug2021)

Amendments 4, 5, and 6 are incorporated into this global amendment but were previously only reviewed locally (Amendments 4 and 5 for Japan; Amendment 6 for China).

Protocol Section(s) Impacted by Change	Change	Reason for Change
All sections	"Viela Bio" changed to "Sponsor".	Clarification as Viela Bio, Inc. was acquired by Horizon Therapeutics.
All sections	Minor corrections and clarifications throughout the document.	To correct typographical and other minor errors.

Protocol Section(s) Impacted by Change	Change	Reason for Change
Cover Page	Responsible Medical Officer was changed to [redacted] MD FACS	Responsible Medical Officer has been updated to reflect staff change.
Section 1, Synopsis Section 5.1, Inclusion Criterion 1	Updated to "Male or female adults who have reached the age of consent in the applicable region (eg, ≥ 18 years in the US, ≥ 20 years in Japan)".	As in Protocol Amendment 4 (Japan), the age of consent is ≥ 20 years. Incorporated the age of consent in all global regions.
Section 1, Synopsis Section 9.3, Determination of Sample Size	Updated to "approximately 160 subjects will be randomized and dosed".	To keep the number of subjects consistent with the number of subjects needed for the primary analysis, which is based on the Full Analysis Set and defined as "all subjects randomized and who received any dose of IP in the study".
Section 4.1, Study Design	Updated to allow for remote visits in exceptional circumstances (due to COVID-19 restrictions or other reasons).	To minimize data loss for subjects who cannot attend in-person visits.
Section 5.1, Inclusion Criterion 2	Changed to "any locally required authorization (eg, data privacy) obtained from the subject prior to performing any protocol related procedures, including screening evaluations".	Changes were made in Protocol Amendment 4 (Japan) to remove content that did not apply to Japan. To address local requirements without specifying for each region.
Section 5.1, Inclusion Criterion 5	Added text "Total duration of GC treatment must be at least 3 weeks and not exceed 8 weeks prior to randomization".	Clarification.
Section 5.1, Inclusion Criterion 6	Added text "One organ must meet the requirements for the ACR/EULAR classification criteria (inclusion 4); the second organ is as defined by the Investigator".	Clarification that only one organ must meet ACR/EULAR classification organ list.
Section 5.1, Inclusion Criterion 8	Updated text to "A condom with spermicide (where spermicide is available)".	To account for country-specific availability of spermicide.
Section 5.2, Exclusion Criteria 5 and 19	Exclusion 5 is amended to delete requirement to have B cell counts ≥LLN in subjects who received a B cell depleting agent in the period 6-12 months prior to screening. Exclusion 19 excludes subjects with CD19+ B cells at screen < 40 cells/μL; an exclusionary value may be repeated.	To require a minimal detectable B cell count in all enrolled subjects to permit assessment of B cell decline in response to inebilizumab.

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 5.2, Exclusion Criterion 9	Added text specifying that required GC taper 8 weeks post randomization is for GCs other than ≤ 2.5 mg/day prednisone or equivalent for treatment of adrenal insufficiency or intolerance of taper.	Clarification.
Section 5.2, Exclusion Criterion 12 Section 6.2.1, Schedule of Screening Assessments and Procedures, Table 3 Section 6.3.1.3, Safety Assessments at Screening	Added "(3) hepatitis B surface antibody (HBsAb)" to exclusion criterion 12 for Japan only. Added HBsAb to the list of tests that require blood collection in Japan (no additional blood sample required).	Changes were made in Protocol Amendment 4 (Japan) to add HbsAb to exclusion criterion 12. Incorporates Japanese requirement.
Section 5.2, Exclusion Criterion 13	Updated to clarify that HCV viral load testing must be completed at site or central lab.	Clarification.
Section 5.2, Exclusion Criterion 19	Prothrombin time exclusion criteria updated to > 1.2 x ULN and added that subjects who are anticoagulated due to atrial fibrillation and who have aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 2 x ULN are not excluded.	Updated to account for laboratory variability and to permit enrollment of subjects whose prothrombin time abnormality is related to anticoagulation for atrial fibrillation but is not suggestive of significant hepatic disease.
Section 5.2, Exclusion Criterion 19 Section 6.2.1, Schedule of Screening Assessments and Procedures, Table 3	Subjects are excluded for total immunoglobulins <600 mg/dL. [redacted]	For subject safety as post-dose immunoglobulin levels is not provided to site or Sponsor, although they are available to the SDMC.
Section 5.2, Exclusion Criterion 21 Section 6.2.1, Schedule of Screening Assessments and Procedures, Table 3	Updated to clarify that subjects are excluded for known positive anti-neutrophil cytoplasmic antibodies (ANCA) targeted against proteinase 3 or myeloperoxidase based on patient records ANCA is deleted from laboratory tests obtained at screen, and other references to ANCA testing are deleted.	ANCA is not required for ACR/EULAR classification criteria, but a known positive is exclusionary per classification criteria. ANCA testing can be deleted at screening without affecting assessment of safety.
Section 5.3, Rescreening Procedures	[redacted]	
Section 5.4, Replacement of Subjects	Updated to "Subjects will not be replaced".	All randomized subjects will be included in the clinical database regardless of whether the subject was dosed or not.
Section 6.1.2, Availability of Laboratory Results	[redacted]	

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 6.2.1, Schedule of Screening Assessments and Procedures, Table 3	For legend c: liver functions may be repeated during screening if subject enrolls with hepatobiliary flare, changed to exclusion 20.	Correction of typographical error.
[redacted]		
Section 6.2.3, Schedule of OLP Assessments and Procedures, Table 5	Updated to state "All procedures and blood sampling must be collected before IP administration on days when IP is administered".	Clarification.
Section 6.2.3.1, Eligibility for OLP, Eligibility Criterion 2	Removed "non" and added "open-label commercial inebilizumab" for the criteria "Subjects eligible for the OLP must not have had IP discontinued for any safety reason other than the use of non B cell depleting immunosuppressive agents (eg, rituximab, ocrelizumab, obinutuzumab, ofatumumab, inebilizumab) during the RCP".	Correction of error.
Section 6.2.3.1, Eligibility for OLP , Eligibility Criterion 2	Modified to state that subjects "must not have had IP discontinued for any of the following reasons". Updated to exclude subjects who were in "Receipt of any B cell-depleting therapy (eg, rituximab, ocrelizumab, obinutuzumab, ofatumumab, commercially available inebilizumab) in the 6 months prior to enrollment in the OLP. Receipt of such a B cell-depleting agent in the period 6 to 12 months prior to enrollment in OLP is exclusionary unless B cell counts have returned to ≥ 40 cells/µL by central laboratory".	Correction of error and clarification of eligibility for OLP if subject receives B cell-depleting therapy during RCP.
Section 6.2.3.1, Eligibility for OLP, Eligibility Criterion 3	Removed "specified" from the 28-day washout period" after discontinuation of non-B cell depleting, non-GC immunosuppressive therapy initiated during RCP.	Correction of error.
Section 6.2.3 Schedule of OLP assessments and Procedures, Table 5	• Removal of Physical exam from assessment on V1 OLP	Correction of errors.

Protocol Section(s) Impacted by Change	Change	Reason for Change
	• Removal of Symptom-driven physical exam on V14 OLP	
Section 6.3.1.2, Demographics and Baseline Characteristics	Updated to collect year of birth, sex, and where permitted, race, and ethnicity.	In response to limitations on collections of these data in some regions.
Section 6.3.4,. Clinical Laboratory Assessments	Updated text to specify that in certain instances, safety laboratory tests may be run in a licensed local laboratory with approval of the Sponsor even where the exclusion criterion specifies use of the central laboratory. Instances of use of local laboratory with approval of the sponsor will not be considered protocol deviations.	The effect of COVID-19 on availability of tubes and kits for central lab testing risks loss of data, and it is preferable to use local laboratories than to have loss of safety data; therefore, in some circumstances, use of local laboratories will be permitted.
Section 6.4.1, Discontinuation of Investigational Product	Added text "Subjects who discontinue IP during the RCP may be eligible to enroll in the OLP, if they meet criteria outlined in Section 6.2.3.1".	Clarification.
Section 7.1, Description of Investigational Product, Table 7	IP manufacture legal entity name changed from MedImmune Pharma, BV to AstraZeneca Nijmegen, B.V. Alternate placebo manufacturer Berkshire Sterile Manufacturing, Inc. was added.	Change of manufacturer legal entity name. An alternate placebo manufacturer has been added.
Section 7.5.2, Permitted Glucocorticoid Uses	Updated text to "Oral GC treatment for ≤ 2 weeks (for any purpose)". Updated text to "GCs at a dose of ≤ 2.5 mg of prednisone or equivalent for treatment of adrenal insufficiency (mineralocorticoids are permitted) or intolerance of steroid taper (in this case, continued tapering of steroids should be performed as tolerated). GCs at any dose should not be continued for the purpose of prevention of IgG4-RD related flare". Updated text to "Inhaled, intranasal, or topical corticosteroids".	Clarification.
Section 8.1, Definitions	Updated the Serious Adverse Event definition to include "A hospitalization for elective or pre-planned treatment of a pre-existing condition that did not worsen from baseline will not be considered an SAE".	Clarification.
Section 8.1, Definitions	Updated the Severity or Intensity definition to include "The determination of severity for events not listed in the CTCAE should be made by the Investigator based upon medical judgment and the severity categories of Grade 1 to Grade 5 as	Clarification.

Protocol Section(s) Impacted by Change	Change	Reason for Change
	defined here, with the maximum severity recorded".	
Section 9.1, General Considerations	Replaced "after randomization" with "from Day 1 (Dosing)	For consistency of the definition of RCP
Section 10.1, Good Clinical Practice	Added text regarding applicable local and regional regulatory requirements, which includes Japanese-specific requirements.	Changes were originally made in Protocol Amendment 4 (Japan) to include text specific to regulatory requirements in Japan. Incorporates local and regional regulatory requirements within a single protocol used globally.
Section 10.2, Ethics Review	Updated to state "In Japan the head of the study site should submit a notification of direction/determination, as well as IRB written approval, to the Sponsor and the Principal Investigator before enrollment of any subject into the study".	Changes were originally made in Protocol Amendment 4 (Japan) to Section 10.2.1, Ethics and Regulatory Review in Japan. Incorporates Japanese requirement.
Section 10.4, Deviation from the Clinical Study Protocol	Added a description of the procedures required in the event of a protocol deviation.	Changes were originally made in Protocol Amendment 4 (Japan) Includes additional changes applicable to all regions within a single protocol used globally.
Section 10.7, Biological Specimens and Data	Added "Samples collected in China will be destroyed upon publication of the Clinical Study Report".	Changes were originally made in Protocol Amendment 6 (China). Includes changes applicable to all regions within a single protocol used globally.
Section 11.5.3, Records Retention	Updated to "Investigators must maintain all documentation related to the study for a period of 25 years. Retention may be shorter in accordance with local regulations, as long as records are maintained for a minimum of 2 years following the last marketing application approval, if marketing applications are filed. Added "Sites must obtain sponsor approval prior to destroying any records.".	Clarification.

Protocol Section(s) Impacted by Change	Change	Reason for Change
Appendix D	IgG4-RD Flare Evaluation and Criteria document added to protocol.	To include the flare criteria as part of the protocol, because the definition of flare is an important component of the primary endpoint.

Protocol Amendment 8 (Global) (30JUN2022)

Protocol Section(s) Impacted by Change	Change	Reason for Change
Title page	Updated name and contact information for responsible medical officer	Change in personnel
Sponsors Signature Page	Added sponsors signature page	Change in signature collection process
Summary of Changes, Amendment 6 and Amendment 7	Dates of amendments updated in summary of change table	Error correction
Section 1 Synopsis: Length of Participation; Synopsis: Study Duration; Section 4.1 Study Design; Figure 1	OLP lengthened from 365 days to 1,095 days; follow-up for 730 days after IP discontinuation; total maximum duration now is equal to 2,273 days	Collection of long-term safety and efficacy data, and data on B cell/immunoglobulin recovery after IP discontinuation
Section 1 Synopsis: Interventions; Section 4.1 Study Design	OLP treatments clarified and expanded to include lengthened OLP	Change of OLP duration
Section 2.1.5 Supportive Clinical Data	Deleted text indicating that Study 1155 is ongoing	Study has been completed
Section 2.1.5.3 Phase 2/3 Efficacy and Safety Study in NMOSD	Updated duration of Study 1155 OLP from 52 weeks to 2 years. Added information on study closure and exposure. Removed reference to subjects ongoing in the study	Error correction, updated status of the study
Section 5.1 Inclusion Criteria	Removed age of consent example ≥ 20 years in Japan for Criterion 1	Decision to cite a single example of age of consent
Section 5.2 Exclusion Criteria	Added criterion allowing for patients with thyroid cancer for which surgery has been performed and there is no evidence of active disease for Criterion 4	To accommodate this relatively common condition in study participants at the request of investigators
Section 6.2.1, Table 3 Screening Assessment and Procedures	Removed “in patients who have received B cell depleting therapy in the 6-12 months prior to screening (see exclusion criterion no 5, Section 5.2)”	B cell count at screening is required for all participants, not just those who had recent/prior B cell depletion therapy
Section 6.2.2 Schedule of RCP Assessments and Procedures	Added language that Visit 9 (D183, a dosing visit) may be delayed in certain circumstances, with prior approval of sponsor, and added instructions for subjects who discontinue IP during the RCP.	Allow subjects (particularly in China) with temporary COVID-related travel restrictions to continue receiving IP

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 6.2.3.1 Eligibility for OLP	Removed language allowing participants who received prohibited B cell-depleting therapy during the RCP to participate in the OLP, with some conditions.	Due to potential safety risks, receipt of B cell depleting agent during the RCP is always exclusionary for OLP participation
Section 6.2.3.1 Eligibility for OLP	Removed text regarding follow-up after IP discontinuation, as this paragraph has been replaced by Section 6.2.4 and language added to 6.4.1.	Redundant text
Section 6.2.3, Table 5 Open-Label Period Assessments and Procedures	Added columns for visits during years 2 and 3 of the OLP; Removed EDV designation from the Week 52 OLP visit and made the Week 156 OLP visit the EDV; changed physical exam at Week 52 visit to symptom-driven physical exam; removed footnote related to 90-day follow up, as this has been replaced by the 2-year follow up described in Section 6.2.4.	Accommodate the less-frequent visit schedule during years 2 and 3 of the OLP, reflects desired changes to the physical exam assessments during this period, removes reference to 90 day follow up
Section 6.2.4 Safety Follow-Up Period	Added new section to describe the assessments that take place during the 2-year safety follow-up period after IP discontinuation (was previously a 90-day follow-up with EDV assessments taking place)	Extended SFUP to 2 years (from 90 days) after IP discontinuation
Section 6.3.1.3 Safety Assessments at Screening	Added language that permits, in exceptional circumstances, the use of local lab results for screening purposes with prior approval by the Sponsor	Mitigate risk of screen fails due to travel restrictions in the context of a failed central lab test(for example)
Section 6.3.2.2 IgG4-RD Responder Index	Provided language to clarify data entry timelines (up to 15 days after the visit) for the IgG4-RD RI, given that some results needed to complete the RI will not be available on the data of the study visit	Guidance to investigator
Section 6.3.4 Clinical Laboratory Assessments	Added text that a local lab used for safety assessments must be qualified as well as licensed, and that prior approval from the sponsor is required.	Conditions for the use of local labs
Section 6.4.1 Discontinuation of IP	Added language to describe the 2-year follow-up for patients who discontinue IP (was previously a 90-day follow-up), with reference to details in Section 6.2.4.	Extended follow-up after IP discontinuation for certain labs and safety events
Section 6.4.2 Withdrawal from Study	Removed a redundant sentence	Clarification
Section 6.6 End of Study	Removed completion of OLP as the time point for study completion and specified that the study will end when the last subject has completed all protocol-specified visits.	Need to accommodate SFUP visits before study closure
Section 7.4.2 Treatment Allocation for OLP	Added text to clarify dosing interval after OLP D15	OLP lengthened to 3 years

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 7.5.1 Prohibited Medications	Added "RCP" to clarify which study period was referenced by Week 52	Clarification
Section 8.4 Adverse Events of Special Interest	Added text that AESIs must be reported within 24 hours of awareness regardless of seriousness or relationship to IP	Clarification to avoid protocol deviations and enhance safety reporting
Section 9.3 Determination of Sample Size	Added text to clarify the rationale for the blinded event rate assessment and to indicate that this analysis "may" take place rather that "will" take place	Clarification of the purpose of the blinded event assessment, and description as optional.
Section 9.5.5 Safety Analysis	Added summary for SFUP	To be consistent to the change of the safety follow up period

Protocol Amendment 9 (Global) (15JUN2023)

Protocol Section(s) Impacted by Change	Change	Reason for Change
Title page	Updated name and address of Sponsor	Acquisition of Viela Bio by Horizon Therapeutics
Synopsis; Section 3.2 Secondary Objectives and Endpoints; Section 9.5.2.3 Flare-free Complete Remission; Section 9.5.3 Control of Type I Error	Updated definition of flare-free complete remission to include either a Responder Index score of 0, or determination by the investigator that there is no active disease, at the Week 52 visit	Expanded definition avoids subjects without active disease failing to meet this endpoint due to requirement for a Responder Index score of 2 in the absence of imaging
Section 6.1.2. Availability of Laboratory Results	Specified that serum Ig results will be made available beginning at OLP Week 26	Numerous requests from investigators for access to this data to monitor patient safety (e.g., risk of infection). At this point in the OLP, the risk of serum Ig results unmasking treatment assignment in the preceding RCP is very low.
Section 6.2.2 Schedule of RCP Assessments and Procedures	Footnote 'd' to Table 4 was updated	Clarification due to elimination of 90 day follow-up at the last protocol amendment (replaced by 2 year Safety Follow-Up)
Section 6.2.3 Schedule of OLP Assessments	Vital sign assessments for dosing visits in years 2-3 of the OLP denoted with superscript 'd'	Unintentionally omitted in previous amendment
Section 6.2.4 Safety Follow-Up Period	Visit windows added to Table 6	Unintentionally omitted in previous amendment
Section 6.3.3.3 Pregnancy; Section 8.3 Reporting Adverse Events; Section 8.4 Adverse Events of Special Interest; Section 8.5.1 Pregnancy; Section 8.5.2 Overdose or Misuse	Updated "ICON" to "Sponsor"; updated safety reporting email and fax numbers	Change from ICON to internal safety reporting process

Protocol Amendment 9.1 (Global) (08AUG2023)

Protocol Section(s) Impacted by Change	Change	Reason for Change
All	Typographical and formatting corrections	n/a
Synopsis; Section 3.2 Secondary Objectives and Endpoints; Section 9.5.2.3 Flare-free Complete Remission; Section 9.5.3 Control of Type I Error	For the secondary endpoint "The proportion of subjects achieving flare-free complete remission at Week 52," added the phrase "treatment-free.".	Distinguish this endpoint from the new key secondary (below).
Synopsis; Section 3.2 Secondary Objectives and Endpoints	Added a new key secondary endpoint, "The proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace et al, 2018) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence."	This new key secondary endpoint reflects the importance of glucocorticoids as frontline treatment in many areas of the world where alternative treatments may not be readily available.
Synopsis; Section 3.2 Secondary Objectives and Endpoints;	Reordered the list of secondary endpoints so that the three key secondary endpoints are listed first.	Clarity
Section 9.5.2.3.	Changed the analyses for the flare-free complete remission related endpoints	To be consistent to the updated flare-free complete remission related endpoints in Section 3.2.
Section 9.5.3 Control of Type I Error	Redesignated a key secondary endpoint (time to treatment for new or worsening disease activity by the Investigator regardless of AC determination of flare) as a non-key secondary. A new secondary (flare-free, corticosteroid-free complete remission) was made a key secondary endpoint in its place.	Study aims to have only three key secondary endpoints, and the endpoints were reordered based on clinical importance.

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by International Council for Harmonisation E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

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LIST OF ABBREVIATIONS

Abbreviation or special term	Definition
AC	Adjudication Committee
ACR	American College of Rheumatology
ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCA	anti-neutrophil cytoplasmic antibodies
anti-HBc	hepatitis B core antibody
AST	aspartate aminotransferase
AQP4-IgG	antibodies against aquaporin-4
[redacted]	
β-hCG	serum human chorionic gonadotropin
CD	cluster of differentiation
CDM	Clinical Data Management
CI	confidence interval
[redacted]	
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMARD	disease-modifying anti-rheumatic drug
DMP	Data Management Plan
EC	Eligibility Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDV	early discontinuation visit
eGFR	estimated glomerular filtration rate
[redacted]	
EU	European Union
EULAR	European League Against Rheumatism
[redacted]	
FDA	Food and Drug Administration
GC	glucocorticoid
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation

Abbreviation or special term	Definition
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HPF	high power field
HR	hazard ratio
huCD19 Tg	human CD19 transgenic
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4-RD	immunoglobulin G4-related disease
IP	investigational product
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous(ly)
IXRS	interactive voice/web response system
JCV	John Cunningham virus
LLN	lower limit of normal
LSMEANS	least square means
mAb	monoclonal antibody(ies)
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse-effect level
NMOSD	neuromyelitis optica spectrum disorder
OLP	open-label period
[redacted]	
PET	positron emission tomography
[redacted]	
PI	Principal Investigator
PML	progressive multifocal leukoencephalopathy
[redacted]	
RCP	randomized-controlled period
RI	Responder Index
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SC	subcutaneous
SDMC	Safety Data Monitoring Committee

Abbreviation or special term	Definition
[redacted]	
SID	subject identification number
SFUP	Safety Follow-Up Period
[redacted]	
TB	tuberculosis
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
US	United States
[redacted]	
WBC	white blood cell count

1 SYNOPSIS

Title	A Phase 3, Randomized, Double-blind, Multicenter, Placebo-Controlled Study of Inebilizumab Efficacy and Safety in IgG4 Related Disease
Short Title	MITIGATE
Phase	3
Study Design	Randomized, double-blind, placebo-controlled, parallel-cohort study
Rationale	There are currently no medicinal products approved for the treatment of immunoglobulin G4-related disease (IgG4-RD), a rare disease. The majority of cases follow a relapsing course that can lead to permanent tissue damage with attendant morbidity and potential mortality. Glucocorticoids (GCs) are widely and effectively used for acute treatment of initial disease activity and of recurrent episodes (flares), but GCs do not prevent recurrence of active disease during their taper or after their discontinuation. Moreover, GCs are associated with substantial toxicity. Thus, there is a high unmet medical need for therapies that prevent disease recurrence and limit GC exposure. The pathogenesis of IgG4-RD suggests that B-cell depletion may be an effective avenue for therapeutic intervention. An important role for B cells, particularly plasmablasts and plasma cells, in the pathogenesis of the disease appears likely. The anti-CD19 B cell-depleting activity of inebilizumab suggests that it may provide benefit as treatment for IgG4-RD. This study aims to define the efficacy and safety of inebilizumab for the prevention of flare of IgG4-RD.
Target Population	Male or female adults, who have reached the age of consent in the applicable region, who have recently active IgG4-RD (initial diagnosis or flare) that requires new or ongoing treatment, are at high risk of future flare (as evidenced by multi-organ disease involvement), and meet the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) IgG4-RD classification criteria.
Number of Subjects	Approximately 160 subjects will be randomized and dosed in a 1:1 ratio to 2 treatment groups; approximately 80 subjects to each treatment group. Enrollment may be increased to a maximum of 200 subjects total based on blinded event-rate analysis.
Length of Participation	Screening period: Up to 28 days Randomized-control period (RCP): 365 (± 7) days Optional open-label period (OLP): 1,095 (+ 10) days Safety Follow-Up period (SFUP) after investigational product (IP) discontinuation: 730 days Total maximum duration of study participation: 2,273 days
Interventions	**RCP**: Blinded treatment on Day 1, Day 15, and Week 26: • Inebilizumab group: Inebilizumab 300 mg intravenous (IV) • Placebo group: IV placebo Both groups: Oral prednisone (or equivalent) tablets from Day 1 to the end of Week 8 (tapering dose regimen: 2 weeks each at 20, 15, 10, and 5 mg/day of prednisone or equivalent, open-label, from commercial supply). **Optional OLP**: Open-label inebilizumab 300 mg IV on Day 1, blinded inebilizumab 300 mg or matching placebo on Day 15 (depending on assigned RCP treatment), and then a single inebilizumab 300 mg IV infusion every 6 months for the duration of the OLP.
Primary Objectives and Primary Endpoints	**Primary objective**: To evaluate the efficacy of inebilizumab in reducing the risk of a disease flare in patients with IgG4-RD.

	Primary endpoint: Time to disease flare, defined as the time in days from Day 1 (dosing) to the date of the first treated and Adjudication Committee (AC)-determined IgG4-RD flare within the 52-week RCP. The date of disease flare is defined as the date of initiation of any flare treatment (new or increased GC treatment, other immunotherapy, or interventional procedure) deemed necessary by the Investigator for the flare.
Secondary Objectives and Corresponding Endpoints	**Secondary objectives**: • To evaluate the safety and tolerability of inebilizumab in patients with IgG4-RD. • To evaluate the effect of inebilizumab on other measures of disease activity. **Secondary endpoints:** • Annualized flare rate for treated and AC-determined flares during the RCP. • The proportion of subjects achieving flare-free, treatment-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no treatment for flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace et al, 2018) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence. • The proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace et al, 2018) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence. • Time to initiation of first treatment (medication or procedure) for new or worsening disease activity by the Investigator within the RCP, regardless of AC determination of flare. • Annualized flare rate for AC-determined flares, whether or not treated, during the RCP. • Glucocorticoid use, calculated as the cumulative GC dose taken for the purpose of IgG4-RD disease control during the RCP. • Incidence of treatment emergent adverse events (TEAEs), serious TESAEs, and TEAEs of special interest (AESIs) during the 52-week RCP and during the OLP. • The incidence of ADAs directed against inebilizumab during the RCP.
Exploratory Objectives and Corresponding Endpoints	[redacted]

	[redacted]
Number of Sites	Approximately 60-80 sites in approximately 20 countries
Study Duration	Estimated total study duration is approximately • 1,526 days (4.2 years) for screening, randomized controlled period, and open-label period • Up to an additional 730 days (2 years) for safety follow-up in patients who do not participate in the OLP or who discontinue treatment during the OLP
Data Monitoring Committee	An external, independent Safety Data Monitoring Committee will evaluate safety data at regular intervals throughout the study and make recommendations to the Sponsor as needed. The Committee will not perform a futility analysis or consider early study completion for efficacy.

2 INTRODUCTION

2.1 Background

2.1.1 IgG4-Related Disease

Clinical Presentation and Flares

Immunoglobulin G4-related disease (IgG4-RD) is a recently described chronic, relapsing -remitting, immune-mediated fibroinflammatory disorder that can affect virtually every organ system, with a predilection for salivary glands, orbits, lacrimal glands, pancreas, biliary tree, lungs, kidneys, aorta and retroperitoneum, meninges, and thyroid gland (Stone et al, 2012; Kamisawa et al, 2015). Pancreato-hepatobiliary disease is present in approximately half of cases, and disease is present in at least 2 organs in approximately three-fourths of patients (Wallace et al, 2019a).

Organ involvement generally manifests as swelling, presence of a mass, or organ-specific consequences of tissue damage. The clinical presentation is generally subacute, and most patients are neither acutely ill nor febrile; however, weight loss can be significant, particularly in the setting of exocrine pancreatic failure in IgG4-related autoimmune pancreatitis. Multi-organ involvement is common either at baseline or after progression over time (Umehara et al, 2017). The course depends in part on the predominant organ affected. For example, IgG4-RD-related cholangitis can lead to hepatic failure within months; autoimmune pancreatitis leads to diabetes mellitus, exocrine insufficiency, or both; tubulointerstitial nephritis can lead to renal failure; and aortitis can lead to aneurysms and dissections.

Symptomatic patients with IgG4-RD require treatment. Glucocorticoids (GCs) are the cornerstone of therapy, and rapid GC responsiveness, particularly for the proliferative subtype, is a hallmark of the disease (Stone et al, 2012; Abraham and Khosroshahi 2017; Zhang and Stone, 2019). Treatment has not been fully standardized, but international consensus guidelines recommend 2-4 weeks of induction with 0.6 mg/kg of prednisone equivalent (~30-40 mg/day) tapering over 8-12 weeks (Khosroshahi et al, 2015). Despite remission occurring in the majority of patients, disease flares requiring re-institution of therapy are typical. Patients with more fibrosis in the affected organ tend to have worse clinical responses to treatment; in contrast to proliferative disease, fibrotic disease tends not to improve with treatment.

Steroid-sparing drugs such as disease-modifying anti-rheumatic drugs (DMARDs) generally are not used alone for the induction of remission, and their efficacy in IgG4-RD has not been established (Zhang and Stone, 2019). B-cell depletion with the cluster of differentiation (CD)20-targeted agent rituximab has demonstrated effectiveness in case series and in a small, open-label study in which 97% of 30 subjects had some disease response, and almost half were in complete remission at 6 months, with 86% of these in complete remission at one year (Carruthers et al, 2015). Reponses were rapid, and serum IgG4 decline was observed.

Histopathology and Pathogenesis

Manifestations of IgG4-RD are linked by a common histopathology: a dense lymphoplasmacytic infiltrate containing IgG4-positive (IgG4+) plasma cells, storiform fibrosis, and obliterative phlebitis, often accompanied by tissue eosinophilia (Deshpande et al, 2012). The inflammatory

infiltrate is a mixture of T and B lymphocytes, with B cells typically organized in germinal centers. Although all Ig subclasses may be present, IgG4 predominates, and the IgG4+:IgG+ plasma cell ratio is an important feature.

There has been recent progress in understanding the pathophysiological mechanisms responsible for IgG4-RD. Limited genetic studies suggest predisposition based on human leukocyte antigen serotype and polymorphisms in some genes involved in immunity (Stone et al, 2012; Terao et al, 2019). Dysregulated follicular helper T cells and cytotoxic $CD4^+$ T cells may play a role in disease initiation, through secretion of profibrotic cytokines and other proteins, as well as the induction of IgG4 class switching and plasmablast expansion (Abraham and Khosroshahi, 2017; Kamekura et al, 2019; Mattoo et al, 2017; Perugino et al, 2017). In addition, B cells are important drivers of the disease via antibody-independent (eg, secretion of pro-inflammatory and pro-fibrotic factors) and antibody-dependent (eg, T cell interactions) mechanisms (Della-Torre et al, 2019; Pillai et al, 2020, Lanzillotta et al, 2016). A critical role for B cells in the pathogenesis of IgG4-RD is supported by data from small clinical trials and observational studies that show reduced disease flares in response to rituximab, an anti-CD20 antibody that depletes B cells (Carruthers et al, 2015; Lanzillotta et al, 2016).

The IgG4 antibody produced by plasmablasts and plasma cells in IgG4-RD is probably not pathogenic. However, there is a general correlation between IgG4 serum concentration and disease severity/extent; most patients have elevated IgG4 levels that decline with clinical response to GC treatment (Huggett et al, 2014). Recently, IgG reactivity against self-antigens, including laminin 511 and galectin-3 of the extracellular matrix, were reported to be involved in the pathogenesis of IgG4-RD. Although these antibodies may not be specific to IgG4-RD, patients with IgG4 antibodies against at least 2 autoantigens were reported to have had more severe disease (Liu et al, 2019; Umehara et al, 2019).

Epidemiology

The epidemiology of IgG4-RD, given its recent categorization and variable presentation, remains uncertain. The majority of patients are men, and most are older than 50 years of age. In a study from Japan, the incidence of IgG4-RD was estimated to be 2.8-10.8/million population, with a median age of onset of 58 years (Umehara et al, 2012).

Unmet Need

To date, no randomized prospective controlled studies have been performed for this disease, and no approved therapy is available. IgG4-RD is associated with substantial morbidity and mortality, but there is no established therapy other than GCs for an acute flare (Huggett et al, 2014; Evans et al, 2018; Zhang and Stone, 2019). Although GCs are widely and effectively used for treatment of initial disease and of flare, they are associated with substantial toxicity that limits their use as long-term therapy. Disease flares also occur in many patients either during the GC taper or after GC discontinuation. Patients also continue to relapse on the off-label steroid-sparing immunosuppressive medications used by some physicians to manage patients with IgG4-RD (Omar et al, 2019); thus, there is a high unmet medical need for more effective therapies for prevention of flare in this patient population. Patients need a treatment that will more effectively control their disease and avoid GC toxicity (Omar et al, 2019).

2.1.2 Inebilizumab

Inebilizumab (formerly MEDI-551) is a humanized, affinity-optimized, afucosylated IgG1 kappa monoclonal antibody (mAb) known as 16C-aFuc that binds to the B-cell specific surface antigen CD19, resulting in depletion of CD19+ B cells. Inebilizumab is glycoengineered by expression of mAb 16C4 in a fucosyltransferase-deficient Chinese hamster ovary producer cell line (BioWa Potelligent® Technology), which generates a homogenously afucosylated antibody with enhanced antibody-dependent cellular cytotoxicity. In contrast to the anti-CD20 mAb rituximab, inebilizumab does not mediate complement-dependent cytotoxicity but eliminates B cells via antibody-dependent cellular cytotoxicity and antibody-medicated cellular phagocytosis mechanisms (Herbst et al, 2010).

2.1.3 Supportive Nonclinical Data

As inebilizumab specifically recognizes human CD19 and has poor or no cross-reactivity to CD19 from nonhuman primates, rabbits, or rodents, the human CD19 transgenic (huCD19 Tg) mouse was selected as the relevant animal model. In huCD19 Tg mice, inebilizumab selectively targeted and depleted B cells (Study ONC551-0010). Also in the huCD9 Tg mouse, 2 single and 3 repeated dose intravenous (IV) toxicology studies (one month, 3 months, and 6 months), and a repeated dose subcutaneous (SC) toxicology study found the highest doses tested, 50 mg/kg as a single dose and 30-36.6 mg/kg/week, to be the no-observed-adverse-effect level (NOAEL).

An embryo-fetal development study (Study AAO00141) demonstrated a reduction in fertility index and the number of pregnant mice per cohabitating mice; however, there was no inebilizumab impact on embryo/fetal development. In fetal livers, the site of B-cell development in mice, there was a difference in huCD19+ B cells between progeny of dosed and undosed mice, suggesting inebilizumab crossed the placenta and depleted fetal B cells. In a pre- and post-natal development study (Study 62509), the NOAEL for F0 maternal, F1 systemic and reproductive, and F2 embryo/fetal developmental toxicity was the highest tested dose, 30 mg/kg. F1 pups had a diminished response to antigen challenge after B cells repopulated and the NOAEL for F1 development and immunotoxicity could not be determined.

For details, refer to the inebilizumab Investigator's Brochure (IB).

2.1.4 Risk Assessment for Inebilizumab

The identified risks of inebilizumab are infusion-related reaction (IRR), arthralgia, neutropenia, and reduced immunoglobulin levels.

- Infusion reactions can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash, or other symptoms. Most observed infusion reactions were mild to moderate in severity; however, rare, serious infusion reactions were observed. Potential risks associated with administration of inebilizumab are infection, redness, swelling, pain, and induration at the administration site. Prior to each IV infusion (inebilizumab or placebo) subjects will receive prophylaxis with IV methylprednisolone, oral diphenhydramine, and oral acetaminophen, or equivalent(s) to reduce the risk or severity of IRR.
- The proportion of subjects with arthralgia was numerically higher in the inebilizumab group than the placebo group during the RCP of Study CD-IA-MEDI-551-1155. There is

no known biological mechanism for a potentially higher rate of arthralgia with inebilizumab.
- Neutropenia was reported at low frequency and was generally transient. Neutropenia has been observed with other B cell depleting monoclonal antibodies (rituximab, ocrelizumab).
- Immunoglobulin levels have been observed to decrease with inebilizumab use, most significantly for IgM. Reduction in Ig levels has been observed with other B cell depleting monoclonal antibodies (rituximab, ocrelizumab) and may be a class effect.

Other important potential risks for inebilizumab are based on mechanism of action, nonclinical data, and clinical data. They include:

- Serious infections
- Progressive multifocal leukoencephalopathy (PML)
- Cytopenia
- Hypersensitivity (including anaphylaxis and serious skin reactions)
- Immune complex disease

The safety of use of inebilizumab during pregnancy is unknown; however, inebilizumab is a mAb, and immunoglobulins are known to cross the placental barrier. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B cell-depleting antibodies during pregnancy. One uncomplicated pregnancy occurred in an inebilizumab-exposed subject who discontinued treatment. There were no birth defects in the baby. There are no data on the presence of inebilizumab in human breast milk, but lactating women should be advised not to breastfeed during treatment and for at least 6 months after the last dose.

For a complete summary of risks for inebilizumab, refer to the IB.

2.1.5 Supportive Clinical Data

Inebilizumab has been investigated in both non-oncology and oncology clinical studies. In non-oncology studies, inebilizumab has been investigated in subjects with systemic sclerosis (Study MI-CP200), multiple sclerosis (Study CD-IA-MEDI-551-1102), and neuromyelitis optica spectrum disorder (NMOSD; Study CD-IA-MEDI-551-1155 [Study 1155]).

2.1.5.1 Phase 1 Dose-escalation Study in Systemic Sclerosis

The first clinical study of inebilizumab in subjects with systemic sclerosis was MI-CP200, a phase 1, randomized, double-blind, placebo-controlled study evaluating the safety and tolerability of escalating single IV doses of inebilizumab (0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg) in 28 adult subjects with systemic sclerosis who had at least moderate skin thickening in an area suitable for repeat biopsy. This study is complete; 4 subjects received placebo and 24 subjects received inebilizumab (Schiopu et al, 2016).

In Study MI-CP200, one subject in the 3.0 mg/kg inebilizumab dose group died during the course of the study following renal crisis; the underlying cause of the terminal renal insufficiency was assessed as related to progression of systemic sclerosis. The most frequent (incidence > 15% of subjects) treatment-emergent adverse events (TEAEs) in the total inebilizumab group were

nausea, arthralgia, pain in extremity, fatigue, and IRR, with the majority of TEAEs being Grade 1 (mild) or Grade 2 (moderate) in severity. Treatment-emergent serious adverse events (TESAEs) occurred in 6 of 24 subjects (25.0%) in the inebilizumab group, with no events occurring in more than one subject. Two TESAEs (supraventricular tachycardia and subclavian vein thrombosis) were assessed by the Investigator as being possibly related to inebilizumab.

2.1.5.2 Phase 1 Dose-escalation Study in Multiple Sclerosis

Study CD-IA-MEDI-551-1102 was a phase 1, multicenter, multinational, randomized, masked, placebo-controlled, dose-escalation study evaluating the safety and tolerability of IV or SC doses of inebilizumab in 28 adult subjects with relapsing forms of multiple sclerosis. A total of 28 subjects were enrolled in the study to receive 2 IV administrations of inebilizumab (30, 100, or 600 mg) or placebo on Day 1 and Day 15, or a single SC dose of inebilizumab (60 or 300 mg) or placebo over a 24-week period (Days 1-169) with long-term follow-up for all subjects for B-cell recovery starting after Day 169 (Agius et al, 2019). This study has been completed, with 7 subjects receiving placebo and 21 subjects receiving inebilizumab. Dosing continued through the highest doses tested (600 mg IV and 300 mg SC), and inebilizumab was reasonably tolerated at all doses tested. The most frequent TEAEs (incidence ≥ 14% of subjects) in the total inebilizumab group were IRR, nasopharyngitis, upper respiratory infection, blood pressure increased, pyrexia, urinary tract infection, and urinary tract inflammation, with the majority of TEAEs being Grade 1 or Grade 2 in severity. Injection-related reactions occurred in 2 of 5 subjects (40.0%) in the IV placebo group and 6 of 15 subjects (40.0%) in the total IV inebilizumab group, which all were Grade 1 or 2 in severity and assessed as related to the investigational product (IP). IRRs occurred in none of the subjects in the SC placebo group and in 1 of 6 subjects (16.7%) in the total SC inebilizumab group. One of 7 subjects (14.3%) in the placebo group and 3 of 21 subjects (14.3%) in the inebilizumab groups had at least one TESAE. One subject in the 300 mg SC cohort had a TESAE of pyrexia that was related to IP.

The mean number of cumulative new gadolinium-enhancing magnetic resonance imaging (MRI) lesions by Week 24 was lower in the inebilizumab group than in the placebo group as was the mean number of new or newly enlarged T2 MRI lesions.

2.1.5.3 Phase 2/3 Efficacy and Safety Study in NMOSD

Study 1155 is a randomized, double-masked, placebo-controlled study with an open-label extension, evaluating the efficacy and safety of IV inebilizumab in adult subjects with NMOSD who are seropositive and seronegative for autoantibodies against aquaporin-4 (AQP4-IgG) (Cree et al, 2019). In this study, inebilizumab (300 mg) or placebo was administered as a fixed IV dose on Days 1 and 15 (ie, 300 mg on Day 1 and 300 mg on Day 15) of a 28-week randomized-controlled period (RCP). Thereafter, 300 mg IV inebilizumab was administered every 26 weeks in an open-label extension for at least 2 years. Enrollment into the study was stopped in September 2018 following a recommendation from the Independent Data Monitoring Committee. The Sponsor accepted the recommendation, closed study enrollment, and offered all remaining RCP subjects the option to enroll in the OLP. The primary endpoint of the study was the time (days) from Day 1 to onset of an Adjudication Committee (AC)-determined NMOSD attack on or before Day 197. The study was closed in November 2020, with a total of 225

subjects having received inebilizumab for a median duration of 3.2 years (maximum duration 5.4 years; 730.4 person-years total exposure).

In total, 231 subjects were randomized in Study 1155, including 18 AQP4-IgG seronegative subjects (7.8%) and 213 AQP4-IgG seropositive subjects (92.2%); 230 subjects overall were included in the intent-to-treat population. A total of 223 subjects (97.0%) completed the RCP.

The primary endpoint of this study was met. In both the AQP4-IgG seropositive and total intent-to-treat populations, treatment with inebilizumab statistically significantly reduced the risk of an AC-determined NMOSD attack as compared to treatment with placebo. During the RCP, the hazard ratio (HR) of AC-determined attacks with inebilizumab treatment relative to placebo was 0.227 (95% confidence interval [CI]: 0.1214, 0.4232) for the AQP4-IgG seropositive population and was 0.272 (95% CI: 0.1496, 0.4691) for the total intent-to-treat population; p-value: < 0.0001 for each comparison). Additionally, a statistically significant improvement with inebilizumab compared with placebo was demonstrated for 3 of 4 key secondary endpoints: worsening from baseline in Expanded Disability Severity Scale, cumulative number of total active MRI lesions, and cumulative number of inpatient hospitalizations. One key secondary endpoint, low-contrast visual acuity, did not demonstrate a significant treatment effect with inebilizumab.

In Study 1155, repeated doses of inebilizumab in the RCP and OLP were well-tolerated. The incidence of TEAEs was balanced across the treatment groups during randomized treatment (71.8% in the inebilizumab group and 73.2% in the placebo group). Among subjects treated with inebilizumab across both the randomized and open-label portions of the study, the most common TEAEs by preferred term were urinary tract infection (19.6%), nasopharyngitis (12.9%), IRRs (11.6%), and arthralgia (10.2%). During the RCP, arthralgia incidence was higher in the inebilizumab group than the placebo group (9.8% vs 3.6%) but was lower in the OLP than in the RCP (4.3% for inebilizumab/inebilizumab subjects and 5.9% for placebo/inebilizumab subjects). No events of anaphylaxis or hypersensitivity were observed.

During the RCP, the proportion of subjects with IRR was similar in the inebilizumab and placebo groups (9.2% and 10.7%, respectively). All IRRs were Grade 1 or Grade 2, and the most common symptoms were headache and nausea. Infusion reactions were most common with the first infusion but were observed during subsequent infusions.

The proportion of subjects with a TEAE in the Infections and Infestations System Organ Class was similar in the 2 groups during the RCP (37.9% and 41.1% in the inebilizumab and placebo groups, respectively); serious infections occurred in 3 subjects (1.7%) in the inebilizumab group and 2 subjects (3.6%) in the placebo group. The most common infections reported by inebilizumab-treated subjects in the RCP and OLP included urinary tract infection (19.6%), nasopharyngitis (12.9%), upper respiratory tract infection (7.6%), and influenza (6.2%).

Laboratory changes observed included cytopenias: leukopenia, lymphopenia, and neutropenia were observed more frequently in the inebilizumab group than in the placebo group. Neutropenia (counts between 0.5-1.0 $\times 10^9$/L) occurred in 2.3% vs 0% of subjects who received inebilizumab or placebo, respectively, during the RCP. Consistent with the mechanism of action of the drug, lymphocyte counts were lower in the inebilizumab group than the placebo group during the RCP: 1.7% of inebilizumab-treated subjects had lymphopenia vs 0% in the placebo group.

Immunoglobulin levels decreased with inebilizumab use, most significantly for IgM. At the end of the 6.5-month randomized period, the proportions of subjects with levels < lower limit of normal (LLN) were greater in placebo than in inebilizumab-treated subjects for IgE (13% placebo and 11% inebilizumab) and IgG (9.4% placebo and 3.8% inebilizumab), and greater in inebilizumab than in placebo for IgA (3.1% in placebo and 9.8% in inebilizumab), and IgM (16% placebo and 29% inebilizumab).

During the RCP, TESAEs were reported in 4.6% and 8.9% of subjects in the inebilizumab and placebo groups, respectively. There were no deaths during the RCP of the study. There were 2 deaths during the OLP: one subject died from complications of NMOSD and another died of pneumonia in the context of new brain lesions considered to be probably due to PML; however, a definitive diagnosis was not established, and the differential diagnosis included PML, acute disseminated encephalomyelitis, or an atypical NMOSD attack.

2.1.5.5 Immunogenicity

In Study MI-CP200, ADA to inebilizumab were detected in 4/24 subjects (16.7%) treated with inebilizumab (1 each in 0.3, 1.0, 3.0, and 10.0 mg/kg dose cohort). None of the subjects treated with placebo (N = 4) tested positive for the presence of ADA at any time throughout the study.

No apparent impact on B-cell depletion was observed in ADA-positive subjects following a single dose of inebilizumab.

In Study 1102, none of the 28 subjects in the study (21 inebilizumab-treated and 7 placebo) tested positive for the presence of ADA.

In the RCP of Study 1155, the prevalence of ADA-positive subjects (ADA positive at baseline or at any time during the RCP) was 9.8% of the inebilizumab group and 14.3% of the placebo group. Treatment-emergent ADA (post-baseline positive only) were observed in 2.9% and 7.1% of inebilizumab and placebo-treated subjects, respectively. Overall, there was no marked difference in the mean PK profiles of inebilizumab in ADA-positive and ADA-negative subjects. Additionally, there was no apparent effect of ADA on the efficacy of inebilizumab.

2.2 Study Rationale

This study will establish the safety and tolerability of inebilizumab monotherapy in IgG4-RD and its ability to reduce the risk of disease flares. There are currently no medicinal products approved for the treatment of IgG4-RD. The majority of cases follow a relapsing course that can lead to permanent tissue damage with attendant morbidity and potential mortality (Huggett et al, 2014). Glucocorticoids are widely and effectively used for treatment of initial disease and of flare, but they do not prevent recurrence of active disease after their discontinuation and are associated with substantial toxicity. Patients also continue to relapse on the off-label steroid-sparing immunosuppressive medications used by some physicians to manage patients with IgG4-RD (Omar et al, 2019); thus, there is a high unmet medical need for more effective therapies in this patient population.

The pathogenesis of IgG4-RD suggests that B-cell depletion may be an effective avenue for therapeutic intervention. An important role for B cells, particularly plasmablasts and plasma cells, in the pathogenesis of the disease appears likely (Mattoo et al, 2014; Wallace et al, 2015; Cassione et al, 2017; Lin et al, 2017; Perugino et al, 2017; Lanzillotta et al, 2018), and therapeutic depletion of B cells with rituximab reduces disease-relevant biomarkers (Della-Torre et al, 2015) and appears to have clinical benefit in uncontrolled, retrospective and prospective clinical studies (Carruthers et al, 2015; Ebbo et al, 2017; Majumder et al, 2018). The anti-CD19 B cell-depleting activity of inebilizumab suggests that it may provide benefit as treatment for IgG4-RD. This study aims to define the efficacy and safety of inebilizumab for the prevention of flares of this rare disease.

In addition, the potential of inebilizumab for minimizing GC exposure could limit the well-known adverse effects of GCs on bone, skin, muscle, adrenal gland, and eyes, and GC association with weight gain, diabetes, hypertension, and neuropsychiatric effects (Miloslavsky et al, 2017).

Existing [redacted] safety data from the development of inebilizumab in non-oncology indications are relevant to the IgG4-RD population, providing a pharmacologically active dose regimen with an acceptable safety profile for use in this phase 3 study.

2.3 Study Hypotheses

Primary Hypothesis:

By depleting CD19+ B cells, including plasmablasts and some plasma cells, inebilizumab will reduce IgG4-RD activity by preventing disease flares.

Secondary Hypotheses:

- Inebilizumab will reduce disease activity in patients with IgG4-RD as assessed by additional measures of efficacy.
- Inebilizumab will be well-tolerated and have an acceptable safety profile in patients with IgG4-RD.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives and Endpoints

Primary Objective

To evaluate the efficacy of inebilizumab in reducing the risk of a disease flare in patients with IgG4-RD.

Primary Endpoint

Time to disease flare, defined as the time in days from Day 1 (dosing) to the date of the first treated and AC-determined IgG4 RD flare within the 52-week RCP. The date of disease flare is defined as the date of initiation of any flare treatment (new or increased GC treatment, other immunotherapy, or interventional procedure) deemed necessary by the Investigator for the flare.

3.2 Secondary Objectives and Endpoints

Secondary Objectives

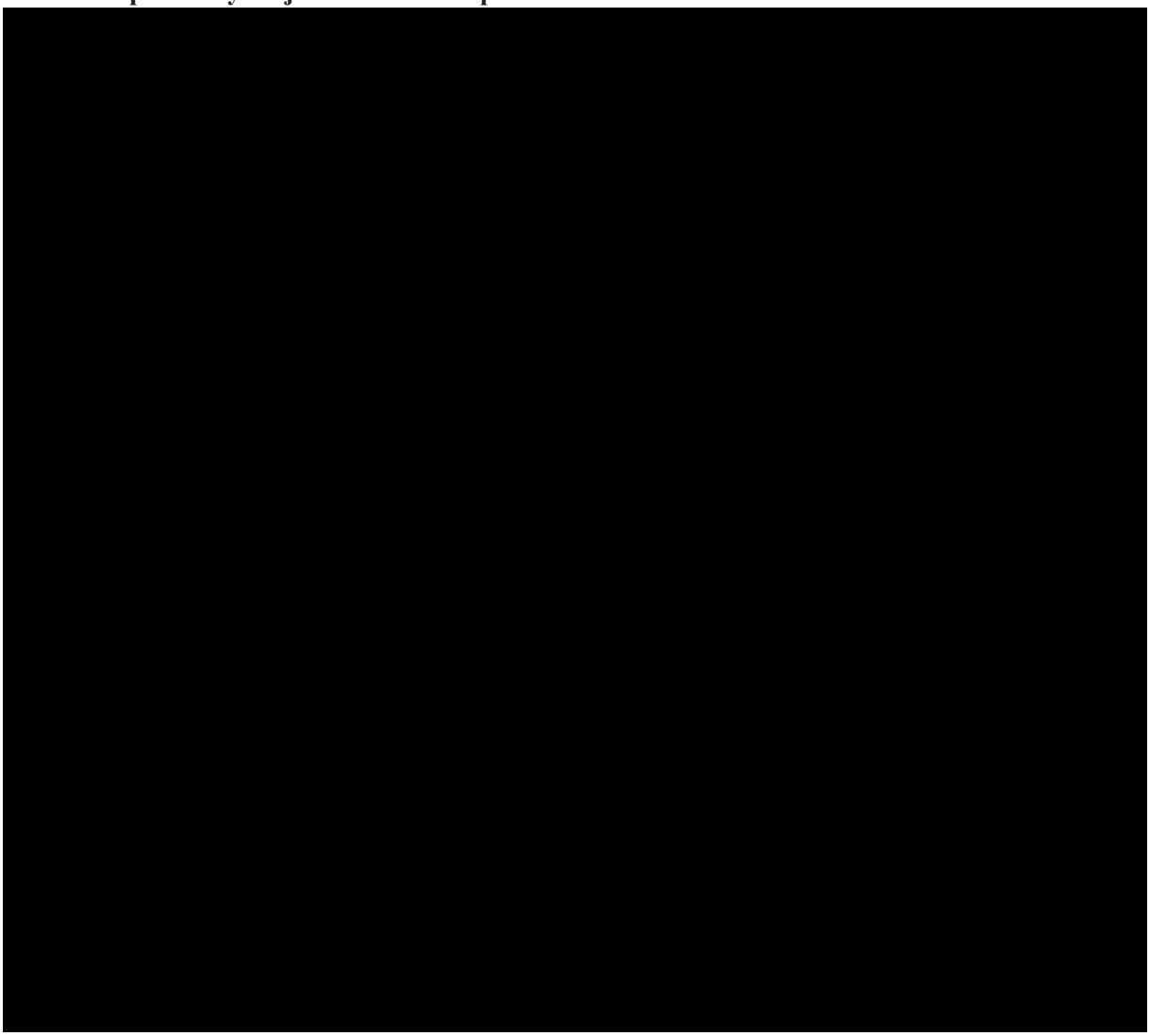
- To evaluate the safety and tolerability of inebilizumab in patients with IgG4-RD.
- To evaluate the effect of inebilizumab on other measures of disease activity.

Secondary Endpoints

- Annualized flare rate for treated and AC-determined flares during the RCP.
- The proportion of subjects achieving flare-free, treatment-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no treatment for flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence.
- The proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence.

- Time to initiation of first treatment (medication or procedure) for new or worsening disease activity by the Investigator within the RCP, regardless of AC determination of flare.
- Annualized flare rate for AC-determined flares, whether or not treated, during the RCP.
- Glucocorticoid use, calculated as the cumulative GC dose taken for the purpose of IgG4-RD disease control during the RCP.
- Incidence of TEAEs, TESAEs, and treatment-emergent adverse events of special interest (AESIs) during the 52-week RCP and during the OLP.
- The incidence of ADAs directed against inebilizumab during the RCP.

3.3 Exploratory Objectives and Endpoints



[redacted]

4 STUDY PLAN

4.1 Study Design

This is a multicenter, randomized, double-blind (Investigator, subject, and Sponsor will be blinded to treatment assignment), placebo-controlled, parallel-cohort study to evaluate the efficacy and safety of inebilizumab for prevention of disease flare in adults with active IgG4-RD who are at high risk of recurrent flare.

Figure 1 presents the overall study design. The study aims to enroll 160 subjects and will be conducted at approximately 60-80 sites in 20 countries. The expected duration of each subject's participation in this study is up to 400 days (screening and RCP) or, for eligible subjects who enroll in the optional OLP, up to 2,273 days (screening, RCP, interval between RCP and OLP, OLP. A safety follow-up of 2 years after the last IP dose will take place for subjects who do not enter the OLP or who discontinue IP during the OLP.

Eligible patients must have a diagnosis of IgG4-RD and meet the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) IgG4-RD classification criteria (Wallace et al, 2019b), have recent or ongoing active disease (new onset or relapse) requiring GC treatment, and be at high risk of further disease flare based on a history of disease in at least 2 organ systems/sites (see Section 5.1).

An Eligibility Committee (EC) will review patient data to confirm eligibility with reference to the 2019 ACR/EULAR IgG4-RD classification criteria prior to randomization (Section 6.3.1.4).

During the screening period (up to 28 days), all subjects must receive at least 3 weeks of GC treatment for their recent flare. The exact GC dose and taper schedule prior to randomization will be determined by the Investigator, but subjects must be at a dose of 20 mg/day prednisone or equivalent on the day prior to randomization. This GC treatment can either be newly initiated or be increased from a prior maintenance dose of ≤ 10 mg/day of prednisone or equivalent. The GC treatment for recent flare must not have exceeded 60 mg/day prednisone or equivalent at any point. Patients who are receiving GCs for treatment of recent flare at the time of consent are not eligible if this treatment has exceeded 4 weeks in duration.

Subjects will be stratified by first or subsequent IgG4-RD manifestation (ie, newly-diagnosed vs recurrent) and randomized 1:1 by an interactive voice/web response system (IXRS) to one of two blinded treatment groups:

- Inebilizumab group: Subjects will receive an infusion of inebilizumab 300 mg IV on Day 1, Day 15, and at Week 26.

- Placebo group: Subjects will receive an infusion of placebo on Day 1, Day 15, and at Week 26.

Both treatment groups will receive open-label IV methylprednisolone 100 mg (or equivalent), diphenhydramine 25-50 mg or equivalent, and paracetamol/acetaminophen 500-650 mg or equivalent, 30-60 minutes prior to each IV infusion for prophylaxis of infusion reactions.

Both treatment groups will continue to receive open-label GCs, from local commercial supply, during an 8-week taper regimen (2 weeks each at 20, 15, 10, and 5 mg/day of prednisone or equivalent), representing completion of the GC taper regimen following treatment for their recent flare (Section 7.2.1).

During the 52-week RCP, subjects will attend monthly visits for study assessments and procedures (Section 546.2.2. Suspicion of flare will trigger diagnostic assessments by the Investigator (Section 6.3.2.1). The Investigator will determine if the event meets protocol -defined criteria for flare, and, independent of the flare determination, will decide if the event requires treatment. The same data reviewed by the Investigator will also be evaluated by a central, independent, and blinded AC that will determine whether protocol-defined flare criteria are met (Section 6.3.2.1).

The end of the RCP is defined, per subject, as the date of completion of the Week 52 RCP visit. All subjects should be followed through the end of the RCP. In exceptional circumstances and with agreement of the medical monitor, particular study visits or procedures may be performed remotely (via teleconference, video conference, or similar) if the subject is not able to physically attend the clinic for that visit or procedure (eg, due to COVID-19 restrictions or for other reasons). Such instances will not be considered protocol deviations. If virtual visits must occur, subjects should obtain safety laboratory testing locally when feasible.

A subject who decides to withdraw from the RCP should be asked to complete the final RCP visit (early discontinuation visit [EDV], Table 4) for safety follow-up whether or not they will permit phlebotomy.

In an optional three-year OLP, all eligible subjects who choose to participate will receive inebilizumab (Section 7.4.2). Flare data collection will continue during this period, and the flare rate will be calculated. The OLP will also contribute to the safety database of inebilizumab in patients with IgG4-RD by increasing the number of patients exposed (those who originally received placebo and who then receive inebilizumab in the OLP) as well as the duration of exposure (in subjects who received inebilizumab in the RCP and then continue in the OLP).

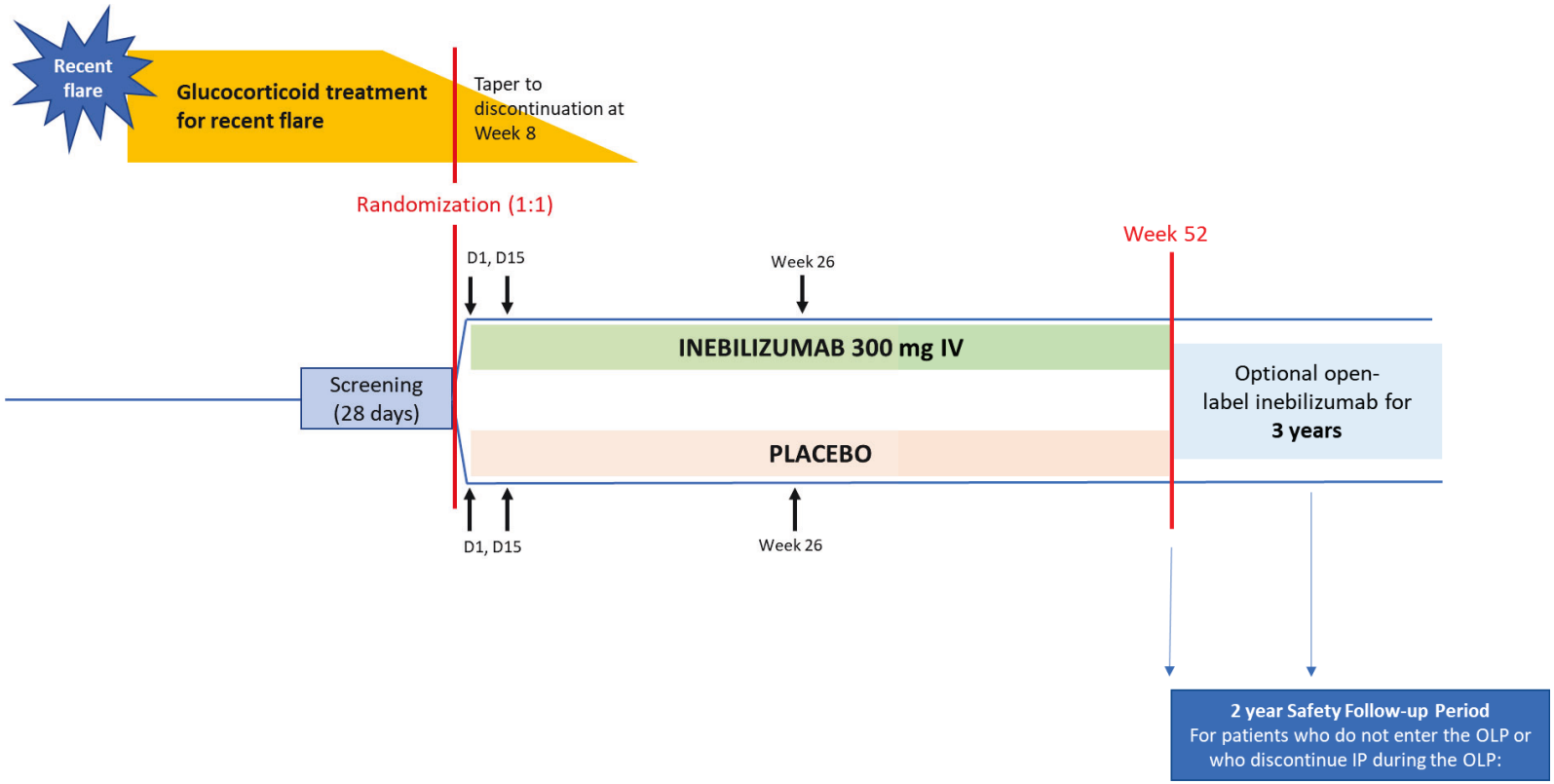
In the OLP, subjects who were assigned to the placebo group during the preceding RCP will receive inebilizumab infusions on OLP Day 1 and Day 15, while those assigned to the inebilizumab group in the RCP will receive IV inebilizumab on OLP Day 1 and a matching placebo infusion on Day 15 to maintaining blinding of sites and subjects to the RCP treatment assignment. Both groups will then receive inebilizumab infusions every 6 months for the duration of the OLP.

Subjects who discontinue IP during the RCP will remain in the RCP for its duration and complete the Day 365 visit.

In addition, all subjects who discontinue IP during the OLP, or who do not participate in the OLP, will be asked to return to the clinic for a series of follow-up visits with limited assessments, occurring every six months for a total of two years after their last IP administration (see Section 6.4.1). This safety follow-up period (SFUP) will provide data on recovery of B cell counts and immunoglobulin levels and monitor for safety events after IP discontinuation.

An independent Safety Data Monitoring Committee (SDMC) charged with monitoring subject safety and ethical conduct of the study will periodically review study data and make recommendations regarding continued conduct of the study.

Figure 1 Study Design



D = day; IV = intravenous.

4.2 Dose and Treatment Regimen Rationale

The regimen of inebilizumab selected for this study, 300 mg administered as an IV infusion on Day 1, Day 15, and every 6 months thereafter, is supported by data from the phase 1 studies in multiple sclerosis and scleroderma in which B-cell depletion at lower dose levels was less complete and/or less durable than at the 300 mg dosage level, and is further supported by data from Study 1155 in which the 300 mg dose level was associated with [redacted] effect, efficacy, and acceptable safety. In Study 1155, the dosing regimen of 300 mg IV on Day 1 and Day 15, and then a single 300 mg infusion approximately every 6 months thereafter, was sufficient to achieve the rapid, profound, and durable depletion of B cells in the vast majority of subjects. The 300 mg dose resides at the efficacy plateau, minimizing the impact of [redacted] variability. The second dose of inebilizumab on Day 15 is timed to deplete newly circulating B cells mobilized out of lymphoid and other tissues. Subsequent doses administered at 6-month intervals are timed to maintain the [redacted] effect based on observations in Study 1155 in which CD20+ B cell counts were significantly reduced 8 days after the initial infusion and remained below the LLN in 100% of subjects at 4 weeks and 94% of subjects at 28 weeks.

Both efficacy and safety outcomes in NMOSD subjects support this dose regimen. In Study1155, inebilizumab reduced the risk of NMOSD attack by 77% relative to placebo in AQP4-IgG seropositive subjects. At the 300 mg dose level, the safety profile was acceptable for further development.

The requirement for prednisone (or equivalent) treatment for 3-8 weeks prior to randomization and a subsequent 8-week taper of prednisone (or equivalent) during the RCP reflect the standard of care for the treatment of active IgG4-RD (Khosroshahi et al, 2015).

The use of IV placebo is justified by the need to assess inebilizumab monotherapy and to maintain blinding (subject, site, Investigator, Sponsor) to assigned treatment during the RCP, limiting bias.

4.3 Rationale for Study Population

The study population will be adults with a diagnosis of IgG4-RD who meet the 2019 ACR/EULAR classification criteria (Wallace et al, 2019b); who have had recent active disease (initial diagnosis or flare) requiring treatment; and who are at high risk of recurrent flare. The classification criteria have been demonstrated to have high specificity for the disease. The inclusion of patients at a high risk of disease recurrence, based on the number of involved organs, represents the population with the greatest medical need and permits a reasonable rate of accrual of events contributing to the efficacy endpoints (Khosroshahi et al, 2015; Omar et al, 2019; Abraham and Khosroshahi, 2017; Zhang and Stone, 2019). Active disease responds well and rapidly to GC therapy; however, recurrence of flare, with its attendant risk of progression of disease and of GC toxicity, requires an approach to the prevention, not just treatment, of disease flares.

The inclusion of subjects with recent active disease (either due to flare or initial diagnosis), serves to enroll patients at risk and to partially harmonize their treatment regimen at study entry. Because subjects have had a recent flare, they need to be appropriately treated but also, for purposes of study, be able to be safely taper and discontinue GCs. Thus, the protocol provides

limits to their GC therapy. To permit an 8-week completion of active disease treatment after randomization, patients must be able to tolerate 20 mg/day of prednisone or equivalent at randomization.

Patients are excluded for risks related to potential immunosuppression and for advanced renal disease or other serious illness that could alter the potential benefit-risk assessment. To avoid confounding interpretation of safety and efficacy data based on the use of prior immunosuppressive drugs, especially B-cell depletive agents, exclusion criteria provide limitations on prior therapy. Patients must have had baseline scans to permit assessment of disease activity and on-study comparisons. [redacted]

4.4 Rationale for the Primary Endpoint

The primary endpoint for this study is time to a treated and AC-determined flare. Flares requiring medical intervention are the most clinically significant events in patients with IgG4-RD, based on the severity of manifestations, the potential for durable morbidity and even mortality, and the toxicity of the GC therapy that is the standard of care for flares. Flares that do not require treatment are not included in the primary endpoint.

Although most (but not all) flares respond rapidly to GC therapy, there are medical consequences of flare, including debilitation during flare, adverse consequences of GC therapy, potential need for medical procedures such as stenting, and the potential for irreversible progression of disease or, less commonly, mortality (Huggett et al, 2014).

The use of time to first flare as the primary endpoint is not affected by standard of care treatments for flare that may be used in enrolled patients after the first flare in accordance with the judgment of their treating physician(s). Such treatments may include steroid-sparing immunosuppressive agents or chronic GC dosing intended to prevent further flares, which would confound interpretation of flare risk after their initiation.

Furthermore, the use of time to first on-study, treated, and AC-determined flare as the primary endpoint does not require all subjects to have achieved complete remission at the time of randomization. The proposed flare definitions accommodate significant worsening of disease activity from a low baseline level (patients must be at 20 mg of prednisone or equivalent to be randomized), which could meet criteria for flare (Section 6.3.2.1).

5 POPULATION

5.1 Inclusion Criteria

To be included in the study, each individual must satisfy all of the following criteria:

1. Male or female adults who have reached the age of consent in the applicable region (eg, ≥ 18 years in the US)
2. Written informed consent and any locally required authorization (eg, data privacy) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
3. Clinical diagnosis of IgG4-RD.
4. Fulfillment of the 2019 ACR/EULAR classification criteria as determined by the Eligibility Committee. Specifically, subjects must meet the classification criteria entry requirements (including involvement of one of the following organs: pancreas, bile ducts/biliary tree, orbits, lungs, kidneys, lacrimal glands, major salivary glands, retroperitoneum, aorta, pachymeninges, or thyroid gland [Riedel's thyroiditis]), must not meet any of the classification criteria exclusions, and must achieve at least 20 classification criteria inclusion points.
5. Experiencing (or recently experienced) an IgG4-RD flare that requires initiation or continuation of GC treatment at the time of informed consent. This criterion may be met in two ways:

   – On GC therapy for recent IgG4-RD flare, having received a maximum of 4 weeks of treatment prior to informed consent at a dose no higher than 60 mg/day prednisone or equivalent, and at 20 mg/day prednisone or equivalent on the day prior to randomization, or

   – Experiencing active disease not currently being treated at the time of informed consent, with planned initiation of treatment for flare with GC at a maximum dose of 60 mg/day prednisone (or equivalent) and with a plan to be treated at a dose of 20 mg/day of prednisone (or equivalent) on the day prior to randomization, for a total duration of GC treatment during screening period of at least 3 weeks at the time of randomization.

     This GC therapy can either be newly initiated or be increased from a maintenance dose of ≤ 10 mg/day of prednisone or equivalent.

     Subjects unable to be tapered to 20 mg/day of prednisone or equivalent by Visit 2 may not be randomized.

     Total duration of GC treatment must be at least 3 weeks and not exceed 8 weeks prior to randomization.

6. IgG4-RD affecting at least 2 organs/sites at any time in the course of IgG4-RD with documentation to confirm. One organ must meet the requirements for the ACR/EULAR classification criteria (inclusion 4); the second organ is as defined by the investigator.
7. Willing and able to comply with the protocol, complete study assessments, and complete the study period.
8. Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use a condom with spermicide (where spermicide is available) from Day 1 through to the end of the study and must agree to continue using such precautions for at least 6 months after the final dose of IP.

Females of childbearing potential must have a negative serum pregnancy test at screening. Females of childbearing potential who are sexually active with a non-sterilized male partner must use a highly effective method of contraception (Table 2) from signing informed consent and must agree to continue using such precautions through the end of the follow-up of the study and at least 180 days after the last dose of IP; cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. A recommendation will be made that the female partners (of childbearing potential) of male study participants should use a highly effective method of contraception other than a barrier method.

Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause and a follicle-stimulating hormone within the postmenopausal range as established by the clinical laboratory).

Table 2 Highly Effective Methods of Contraception for Females of Childbearing Potential

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

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

5.2 Exclusion Criteria

Any of the following excludes an individual from participation in the study:

1. Severe cardiovascular, respiratory, endocrine, gastrointestinal, hematological, neurological, psychiatric, or systemic disorder, or any other condition that, in the opinion of the Investigator, would place the patient at unacceptable risk of complications, interfere with evaluation of the IP, or confound the interpretation of patient safety or study results.
2. History of solid organ or cell-based transplantation.
3. Known immunodeficiency disorder.

4. Active malignancy or history of malignancy that was active within the last 10 years, except as follows:
   - In situ carcinoma of the cervix following apparently curative therapy > 12 months prior to screening,
   - Cutaneous basal cell or squamous cell carcinoma following apparently curative therapy,
   - Prostate cancer treated with radical prostatectomy or radiation therapy with curative intent > 3 years prior to screening and without known recurrence or current treatment, or
   - Thyroid cancer for which surgery has been performed and there is no evidence of active disease.
5. Receipt of any biologic B cell-depleting therapy (eg, rituximab, ocrelizumab, obinutuzumab, ofatumumab, inebilizumab) in the 6 months prior to screening.
6. Receipt of non-depleting B-cell-directed therapy (eg, belimumab), abatacept, or other biologic immunomodulatory agent within 6 months prior screening.
7. Receipt of non-biologic DMARD or immunosuppressive agent other than GCs (eg, azathioprine, mycophenolate mofetil, methotrexate, others) within 4 weeks prior to screening.
8. Receipt of any investigational agent < 12 weeks or < 5 half-lives of the drug (whichever is longer) prior to screening.
9. Inability to be tapered off of GC therapy by 8 weeks post-randomization (other than ≤ 2.5 mg/day prednisone or equivalent for treatment of adrenal insufficiency or intolerance of taper) in the opinion of the Investigator.
10. Receipt of live vaccine or live therapeutic infectious agent within the 2 weeks prior to screening.
11. Pregnancy, lactation, or planning to become pregnant within 6 months of the last dose of IP.
12. Positive test for, or prior treatment for, hepatitis B or HIV infection. A positive test for hepatitis B is detection of either (1) hepatitis B surface antigen (HBsAg); or (2) hepatitis B core antibody (anti-HBc); and in Japan only (3) hepatitis B surface antibody (HBsAb)
13. History of untreated hepatitis C infection, or positive antibody test for hepatitis C virus (HCV) unless patient is considered to be cured following antiviral therapy and has a HCV viral load below the limit of detection at least 24 weeks after completion of treatment at site or central lab.
14. Evidence of active tuberculosis (TB) or being at high risk for TB based on:
   - History of active TB or untreated/incompletely treated latent TB. Patients with a history of active or latent TB who have documentation of completion of treatment according to local guidelines may be enrolled.
   - History of recent (≤ 12 weeks of screening) close contact with someone with active TB (close contact is defined as ≥ 4 hours/week OR living in the same household OR in a house where a person with active TB is a frequent visitor).
   - Signs or symptoms that could represent active TB by medical history or physical examination.

- Positive, indeterminate, or invalid interferon-gamma release assay test result at screening, unless previously treated for TB. Patients with an indeterminate test result can repeat the test once, but if the repeat test is also indeterminate, the patient is excluded.
- Chest radiograph, chest computed tomography (CT) or MRI scan that suggests a possible diagnosis of TB or suggests that a work-up for TB should be considered; all patients must have had lung imaging with an acceptable reading within 6 months prior to consent, or during screening.

15. History of > 1 episode of herpes zoster (any grade) and/or any other definite or probable opportunistic infection in the 12 months prior to screening (see Appendix A) for details on opportunistic infections that require exclusion).
16. Known history of allergy or reaction to any component of inebilizumab formulation or history of anaphylaxis to any human gamma globulin therapy.
17. Allergy to or intolerance of protocol-required treatment, including medications for prophylaxis of infusion reactions (antipyretic such as paracetamol/acetaminophen or equivalent, diphenhydramine or equivalent, and methylprednisolone or equivalent).
18. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 by Modification of Diet in Renal Disease Study (MDRD) equation (NIDDK).
19. Blood tests at screening that meet any of the following criteria:

    - Hemoglobin < 7.5 g/dL
    - Neutrophils < 1200/mm3
    - Platelets < 110 × 109/L
    - Eosinophil count > 3000/mm3
    - Prothrombin time > 1.2 x upper limit of normal (ULN); however, subjects who are anticoagulated due to atrial fibrillation and who have aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 2 x ULN are not excluded
    - Total immunoglobulins < 600 mg/dL
    - CD19+ B cells at screen < 40 cells/µL; an exclusionary value may be repeated.

20. Subjects with the following abnormal liver function tests in the absence of hepatobiliary IgG4-RD activity:

    - Aspartate aminotransferase (AST) > 2 × ULN
    - Alanine aminotransferase (ALT) > 2 × ULN
    - Total bilirubin (TBL) > 2 × ULN unless AST, ALT, and hemoglobin are within central laboratory normal range and the patient has a known history of Gilbert syndrome

    OR

    Subjects with the following abnormal liver function tests in the presence of hepatobiliary IgG4-RD activity:

    - AST > 10 × ULN
    - ALT > 10 × ULN

- TBL > 5 × ULN
- Screening liver function tests may be repeated prior to randomization to permit abnormal values due to hepatobiliary IgG4-RD activity to respond to GC treatment.

21. Known positive anti-neutrophil cytoplasmic antibodies (ANCA) targeted against proteinase 3 or myeloperoxidase based on patient records.
22. History of alcohol or drug abuse that, in the opinion of the Investigator, might affect patient safety or compliance with visits or interfere with safety or other study assessments.
23. Active, clinically significant infection at the time of randomization (IP administration may be delayed until recovery, if within screening window, otherwise subject may be rescreened).
24. Participation in any clinical trial that includes use of any pharmacologic intervention.

5.3 Rescreening Procedures

Patients may be rescreened once if, in the Investigator's judgment, the reason for ineligibility is likely to have resolved at the time of rescreen. Subjects who rescreen within 8 weeks of their original screen do not have to repeat hepatitis testing, HIV testing, interferon-gamma release assay (IGRA) testing, IgG4 levels or, if relevant, B cells and follicle-stimulating hormone testing. A repeat blood sample to freeze for possible John Cunningham virus (JCV) antibody testing is not required.

5.4 Replacement of Subjects

Subjects will not be replaced.

6 STUDY CONDUCT

6.1 General Instructions

6.1.1 Order of Assessments

Subjects should be asked to complete [redacted] prior to other procedures.

Whenever vital signs, 12-lead electrocardiograms (ECGs), and blood draws are scheduled for the same nominal time, blood draws should occur after ECGs and vital signs (temperature, pulse, respiratory rate, and blood pressure). If these investigations did not occur in this order, at least 15 minutes must elapse between blood draw and either ECG or vital signs.

All laboratory sample collections and assessments that are scheduled for a dosing day must be performed prior to dosing, except [redacted] Safety laboratory results from the day of dosing will not be available prior to dosing, because a central laboratory will perform those analyses. Any ECG performed on the day of dosing should be examined by the Investigator prior to dosing to assess the safety of dosing.

6.1.2 Availability of Laboratory Results

All safety laboratory results will be made available to Investigators by the central laboratory. This includes serum IgG4 levels, which will be provided to Investigators per standard management practices for patients with IgG4-RD.

Due to the inebilizumab mechanism of action, results of B cell testing and serum Ig levels post dose could be potentially unblinding. Post-randomization B cell results will not be available to blinded staff or Investigators until the study is unblinded. Serum Ig results will be made available to Investigators only from OLP Week 26 onwards. Research laboratory values, [redacted] and ADA results will also not be available until the study is unblinded.

6.1.3 Repeating Procedures After Randomization

Abnormal laboratory or ECG results obtained after randomization that, in the Investigator's opinion, represent a clinically significant finding or clinically significant change from baseline should be repeated as soon as possible, preferably within 48 hours. If urgent results are needed, testing can be sent to a local laboratory, but blood for the same tests should be sent to the central laboratory as well.

6.2 Schedules of Study Assessments

6.2.1 Schedule of Screening Assessments and Procedures

Table 3 summarizes the screening procedures for the study. All screening assessments must be completed within 28 days prior to randomization. In some cases, more than one screening visit may be required to complete all procedures. Safety laboratory tests may be repeated once during screening.

Table 3 Screening Assessments and Procedures

Study Period	**Screening**
Visit Number	**V1**
Study Day	**Up to Day -28** [a]
Written informed consent and IXRS assignment of SID number	X
Demographics	X
Medical history	X
Assessment of AEs and SAEs	X
Review of vaccination history [b]	X
Assessment of prior and concomitant medications	X
Vital signs (temperature, pulse, respiration rate, and blood pressure)	X
Height and weight	X
Full physical examination excluding pelvic and rectal exam	X
[redacted]	
12-lead ECG	X

Table 3 Screening Assessments and Procedures

Study Period	**Screening**
Visit Number	**V1**
Study Day	**Up to Day -28 [a]**
CT or MRI scan (or equivalent) of chest, abdomen and pelvis at screen or during most recent active disease (ie, within prior 3 months), and, if head and neck disease, MRI (or equivalent) of affected area at screen or within prior 3 months. If clinically indicated, repeat imaging can be performed prior to randomization to assess response to glucocorticoids and to ensure exclusion of malignancy.	X
IgG4-RD RI score	X
Blood collection for: • Safety laboratory testing (serum chemistry [c] , hematology, and coagulation) • Serum β-hCG pregnancy test (all females) • Follicle-stimulating hormone (potentially postmenopausal females) • Hepatitis B surface antigen, anti-HBc, and in Japan only HBsAb • Hepatitis C testing: a) Hepatitis C Ab in patients not known to have had HCV b) HCV load in patients known to have completed curative HCV treatment at least 24 weeks prior to screening • HIV-1 and HIV-2 testing • IGRA testing for TB • IgG4 level • Serum to be frozen for possible testing for JCV antibodies or other safety testing [redacted]	X
Urine collection for urinalysis (dipstick and, for abnormal dipstick, microscopic) and for urine protein/creatinine ratio	X
[redacted]	
Verify preliminary eligibility based on data from Screening Visit prior to scheduling Visit 2	X

Ab = antibody; AE = adverse event; β-hCG = serum human chorionic gonadotropin; CT = computed tomography; ECG = electrocardiogram; [redacted] HCV = hepatitis C virus; Ig = immunoglobulin; IgG4-RD RI = IgG4-RD Responder Index; IGRA = interferon-gamma release assay; IXRS = interactive voice/web response system; JCV = John Cunningham virus; MRI = magnetic resonance imaging; [redacted] SAE = serious adverse event; [redacted] SID = subject identification; TB = tuberculosis; V1 = visit 1.

a Screening may be conducted over multiple visits.

b Subjects should be advised to be up to date on vaccines in accordance with local recommendations prior to enrollment. Vaccines are optimally administered at least 4 weeks prior to dosing to permit development of immune response. Subjects who, on the advice of their physician, should delay Dose 1 for > 28 days to permit a 4-week post vaccine interval to occur should be screen-failed and may be rescreened.

c In patients who enroll with a hepatobiliary flare whose screening liver function test values do not meet eligibility criteria, liver function tests may be repeated (Exclusion 20). Subjects whose values do not fall below the exclusionary values upon repeat may not be randomized.

[redacted]

6.2.2 Schedule of RCP Assessments and Procedures

Table 4 summarizes the schedule of procedures for the RCP.

Table 4 Randomized-Controlled Period Assessments and Procedures

Study Period	**Randomized-Controlled Period**													
Visit Number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**26**	**30**	**34**	**38**	**42**	**46**	**52 or EDV [d]**
Nominal Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**183**	**211**	**239**	**267**	**295**	**323**	**365**
Window	**--**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**
Assessment of AEs/SAEs/AESIs	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
[redacted]														
ECG (prior to IP administration)	X							X						X
Vital Signs	X [b]	X [b]	X	X	X	X	X	X [b]	X	X	X	X	X	X
Weight	X							X						X
Full physical examination	X							X						X
Symptom-driven physical exam		X	X	X	X	X	X		X	X	X	X	X	
IgG4-RD RI	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test in women capable of pregnancy	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4 Randomized-Controlled Period Assessments and Procedures

Study Period	**Randomized-Controlled Period**													
Visit Number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**26**	**30**	**34**	**38**	**42**	**46**	**52 or EDV [d]**
Nominal Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**183**	**211**	**239**	**267**	**295**	**323**	**365**
Window	**--**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**
Urinalysis (microscopic if abnormal) and urine protein/creatinine ratio	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety labs (chemistry, hematology, coagulation)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
ADA	X		X		X			X			X			X
[redacted]														
IgG4 [redacted] levels	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														

Table 4 Randomized-Controlled Period Assessments and Procedures

Study Period	Randomized-Controlled Period													
Visit Number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**26**	**30**	**34**	**38**	**42**	**46**	**52 or EDV [d]**
Nominal Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**183**	**211**	**239**	**267**	**295**	**323**	**365**
Window	**--**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**
[redacted]														
Verify eligibility	X													
Randomization	X													
IP administration [e]	X	X						X						
Provide oral GCs	X													
Assess GC compliance		X	X	X										

AE = adverse event; ADA = anti-drug antibodies; AESI = adverse event of special interest; ECG = electrocardiogram; EDV = early discontinuation visit; [redacted] GC = glucocorticoid; Ig = immunoglobulin(s); IgG4-RD RI = IgG4-RD Responder Index; IP = investigational product; [redacted] SAE = serious adverse event; [redacted] V = visit.

Note: On days of IP administration, all procedures and blood sampling, except for [redacted] must be collected before IP administration. [redacted]

b Vital signs obtained as per Section 7.1.1.5.

[redacted]

d Subjects who have indicated their intent to withdraw consent during the RCP should be asked to complete an EDV visit.

e Premedication will be administered approximately 30-60 minutes prior to each IP infusion (see Section 7.1.1.4). If IP administration at Visit 9 (Day 183) is unavoidably delayed, for example due to COVID travel restrictions, the dosing visit may be delayed upon discussion and agreement with the Sponsor. Adjustment of the timing of the subsequent OLP IP doses will be discussed on a case-by-case with the Sponsor. If a subject discontinues IP during the RCP, they should complete all RCP visits. If they do not subsequently enter the OLP, they should then enter the SFUP (Section 6.2.4).

6.2.3 Schedule of OLP Assessments and Procedures

6.2.3.1 Eligibility for OLP

Subjects eligible for the OLP must:

1. Have completed the RCP Week 52 visit (end of RCP).
2. Must not have had IP discontinued for any of the following safety reasons:
   - Anaphylaxis or a serious hypersensitivity reaction that occurred within 7 days after IV dosing and cannot be attributed to another known allergen exposure (see Appendix B).
   - Any adverse event (AE) or significant laboratory abnormality that, in the opinion of the Investigator, Sponsor, or SDMC, warrants discontinuation of dosing.
   - Any life-threatening (Grade 4) infection.
   - Any event of sepsis or febrile neutropenia.
   - Any infection listed as either a definite or probable opportunistic infection in Appendix A.
   - Any Grade 3 IRR.
   - Any Grade 4 serious adverse event (SAE).
   - Pregnancy or a decision to become pregnant.
   - Malignancy.
   - Absolute neutrophil count < 800 cells/μL confirmed by repeat testing.
   - Determination that the subject was ineligible for study participation and continuation of IP could pose a safety risk to the subject in the judgment of the Investigator or Sponsor.
   - Significant noncompliance with the study protocol, as judged by the Investigator or Sponsor.
   - Receipt of any B cell-depleting therapy (eg, rituximab, ocrelizumab, obinutuzumab, ofatumumab, commercially available inebilizumab).
3. Have completed a 28-day washout period after discontinuation of non-B cell-depleting, non-GC immunosuppressive therapy initiated during the RCP, if relevant.
4. Receive Dose 1 in the OLP within the window of 1-38 days after the RCP Week 52 visit (the final visit for the RCP and the first visit for the OLP cannot occur on the same day).
5. Have a planned taper of GCs to discontinuation by 8 weeks after OLP Dose 1, if receiving GC at the time of OLP entry.

To maintain the every-6-month dosing of IP, subjects should enroll in the OLP and be dosed as soon as is feasible after completion of the RCP. All SAEs and AEs that occur between the end of the RCP and start of the OLP must be collected at OLP Visit 1. Investigational product discontinuation rules apply during the OLP (Section 6.4.1).

Table 5 summarizes the schedule of procedures for the OLP.

Table 5 Open-Label Period Assessments and Procedures

Study Period	**Open-Label Period**												
OLP Visit Number	**OLP V1**	**OLP V2**	**OLP V3, V4**	**OLP V5**	**OLP V6, V7**	**OLP V8**	**OLP V9, V10**	**OLP V11**	**OLP V12, V13**	**OLP V14**	**OLP V15, 17, 19, 21**	**OLP V16, 18, 20,**	**OLP V22/EDV**
OLP Week(s)	**0**	**2**	**4, 8**	**12**	**16, 20**	**26**	**30, 34**	**38**	**42, 46**	**52**	**61, 87, 113, 139**	**78, 104, 130**	**156**
Window	**1-38 days after last RCP visit**	**± 2 days**	**Phone contact ±10 days [b]**	**±10 days**	**Phone contact ±10 days [b]**	**± 10 days**	**Phone contact ±10 days [b]**	**±10 days**	**Phone contact ±10 days [b]**	**+10 days**	**Phone contact ±20 days [b]**	**±20 days**	**±20 days**
Assessment of AEs/SAEs/AESIs	X [c]	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
[redacted]													
Vital signs	X [d]	X [d]		X		X [d]		X		X [d]		X [d]	X
Physical exam													X
Symptom-driven physical exam	X	X		X		X		X		X		X	
IgG4-RD RI	X	X		X		X		X		X		X	X
Urine pregnancy test in women capable of pregnancy [e]	X	X		X		X		X		X		X	X
Safety labs [f]	X	X		X		X		X		X		X	X

Table 5 Open-Label Period Assessments and Procedures

Study Period	**Open-Label Period**												
OLP Visit Number	**OLP V1**	**OLP V2**	**OLP V3, V4**	**OLP V5**	**OLP V6, V7**	**OLP V8**	**OLP V9, V10**	**OLP V11**	**OLP V12, V13**	**OLP V14**	**OLP V15, 17, 19, 21**	**OLP V16, 18, 20,**	**OLP V22/EDV**
OLP Week(s)	**0**	**2**	**4, 8**	**12**	**16, 20**	**26**	**30, 34**	**38**	**42, 46**	**52**	**61, 87, 113, 139**	**78, 104, 130**	**156**
Window	**1-38 days after last RCP visit**	**± 2 days**	**Phone contact ±10 days [b]**	**±10 days**	**Phone contact ±10 days [b]**	**± 10 days**	**Phone contact ±10 days [b]**	**±10 days**	**Phone contact ±10 days [b]**	**+10 days**	**Phone contact ±20 days [b]**	**±20 days**	**±20 days**
[redacted]													
Urinalysis [g]	X	X		X		X		X		X		X	X
ADA	X	X		X		X		X		X		X	X
IgG4 [redacted]	X	X		X		X		X		X		X	X
[redacted]													
Assessment of eligibility for OLP	X												
IP administration [h]	X	X				X				X		X	

AE = adverse event; ADA = anti-drug antibodies; AESI = adverse event of special interest; EDV = early discontinuation visit; [redacted] score; Ig = immunoglobulin; IgG4-RD RI = IgG4-RD Responder Index; IP = investigational product, OLP = open-label period; RCP = randomized-controlled period; SAE = serious adverse event; [redacted]V = visit.

Note: All procedures and blood sampling must be collected before IP administration on days when IP is administered.

a Subjects who have received immunosuppressive therapy other than glucocorticoid treatments must have a washout period of at least 28 days prior to Dose 1 of inebilizumab in the OLP.

b Monthly telephone calls in months without in-person visits. If, during the telephone contact, a safety event or possible flare that requires further follow-up is identified, the subject should be evaluated in the clinic as an unscheduled visit.

c AEs and SAEs occurring after completion of the RCP must be collected at OLP Visit 1.

d Vital signs obtained as per Section 7.1.1.5.

e Perform on days of dosing; confirm negative prior to dose.

f Safety labs include chemistry, hematology, and coagulation; [redacted] will not be performed during the OLP.

g Microscopic if abnormal

h Premedication will be administered approximately 30-60 minutes prior to each IP infusion (see Section 7.1.1.4). If a subject discontinues IP during the OLP, they should enter the SFUP (Section 6.2.4).

6.2.4 Safety Follow-Up Period

Subjects who do not enter the OLP, or who discontinue IP during the OLP, will be followed for an additional two years from the date of last IP infusion. During this time subjects will be seen every six months in-clinic for blood draws and other limited assessments.

Assessments and procedures during the SFUP are detailed in Table 6.

Table 6 Safety Follow Up Period Assessment and Procedures

Study Period	**SFUP**
Visit Number	**V1, 2, 3, 4**
SFUP Weeks	**26, 52, 78, 104**
Window	**±4 weeks**
Assessment of AEs and SAEs	X
Assessment of concomitant medications	X
[redacted]	

AE = adverse event; SAE = serious adverse event; SFUP = safety follow-up period; V = visit

6.3 Description of Study Assessments and Procedures

6.3.1 Screening Procedures

6.3.1.1 Informed Consent

Subjects officially enter the screening period following provision of informed consent.

All candidates for enrollment will sign an informed consent form (ICF) prior to any protocol-related procedures, including screening activities. Informed consent must be obtained by the Principal Investigator (PI) or a designee, such as an Investigator, with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved qualifications. See Section 10.3 for additional details.

After signing the ICF, each subject will be assigned a subject identification (SID) number that will be used on all subject documentation. Numbers will be assigned in ascending, sequential order. This number will also correspond to the subject number entered on test materials. Rescreened patients will receive a new SID number. See Section 5.3 for limitations on rescreening.

6.3.1.2 Demographics and Baseline Characteristics

Demographic information to be collected includes year of birth, sex, and where permitted, race, and ethnicity. Medical history information to be collected includes all ongoing conditions and relevant/significant medical history (including all major hospitalizations and surgeries), as determined by the Investigator. Prior and concomitant medications will be recorded. A complete

physical examination (with the exception of rectal and pelvic examinations) will be conducted at baseline, including vital signs, height, and weight.

Blood will be collected for IgG4 levels.

Examinations needed for the IgG4-RD RI score will also be performed at screening [redacted]

6.3.1.3 Safety Assessments at Screening

Safety-related screening assessments will include AEs, safety laboratory tests (serum chemistry, hematology, and urinalysis), coagulation parameters, ECG, and serum human chorionic gonadotropin (β-hCG) pregnancy test for females.

All screening labs should be performed by the central lab. In exceptional circumstances, for example travel restrictions due to COVID or failure of a central lab test during the screening period without sufficient time for central lab repeat, a local lab with appropriate qualifications and certifications may be used with prior approval by the Sponsor.

Baseline imaging will be performed unless recent readings are available from within the prior 3 months: CT or MRI scan (or equivalent) of chest, abdomen, and pelvis; and if subject has head or neck disease, an MRI (or equivalent) of the affected area. If clinically indicated, repeat imaging can be performed prior to randomization to assess response to GCs and confirm eligibility.

Blood will be collected at screening for the following tests:

- Hepatitis B testing: HBsAg, anti-HBc, and in Japan only HBsAb
- Hepatitis C antibody (HCV load in patients at least 24 weeks after curative treatment for HCV)
- HIV testing: HIV-1 antibody, HIV-2 antibody
- TB testing (eg, QuantiFERON®-TB Gold Test)
- Serum will be frozen for possible testing for JCV antibodies in case of suspected PML

For additional details on safety assessments, see Sections 6.3.3 and 8.

6.3.1.4 Eligibility Committee

Data related to subjects' IgG4-RD disease history and current disease manifestations will be provided to an EC composed of physicians with expertise in the diagnosis and care of patients with IgG4-RD. EC members will independently review these data, including any available biopsy reports, to determine whether a subject fulfills the ACR/EULAR IgG4-RD classification criteria (Wallace et al, 2019b) per Inclusion Criteria 4. These classification criteria were developed to ensure that studies in IgG4-RD avoid enrollment of subjects who do not have a clear diagnosis of IgG4-RD. Accordingly, these criteria are highly specific (99.2% in the first validation cohort and 97.8% in the second) and appropriately sensitive (85.5% in the first validation cohort and 82.0% in the second).

6.3.2 Efficacy Assessments

Over the course of the study, Investigator assessments for a given subject should be completed by the same Investigator, designated physician, or qualified site personnel whenever possible.

6.3.2.1 Flare Assessment, Diagnosis, and Adjudication

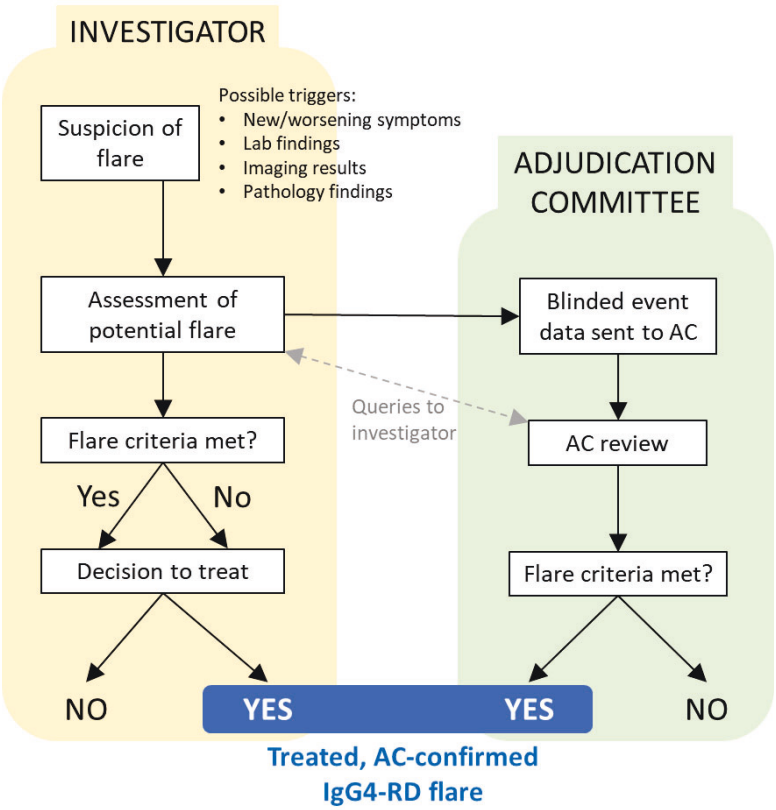
The Investigator is responsible for identifying, diagnosing, and treating IgG4-RD flares during the RCP and OLP. As outlined in Figure 2, this process and the Investigator's specific responsibilities are as follows:

- Investigator **suspects** flare based on symptoms or clinical findings
- Investigator **assesses** the appropriate sites/organs
- Investigator determines whether protocol-defined **flare criteria** are met
- Investigator decides whether flare **treatment** is warranted and initiates treatment

Data collected by the Investigator in this process will be sent to the AC for independent, blinded determination of whether the event meets protocol-defined flare criteria.

These processes are each described in detail in the following sections.

Figure 2 Flare Assessment and Adjudication Process



AC = Adjudication committee; IgG4-RD = immunoglobulin G4-related disease.
Note: This diagram outlines the assessment and adjudication process for suspected flares and highlights the events that contribute to the primary endpoint.

Investigator Assessment of Flare

If a subject's symptoms, physical examination, laboratory parameters, or other clinical finding suggests the possibility that a disease flare may be occurring, the Investigator should evaluate the subject, conduct any medically indicated assessments, and review any relevant data collected at facilities other than the investigational site. Assessments should be per local standard of care and at the discretion of the Investigator. Flare assessments should be conducted prior to the initiation of treatment for flare, if possible.

Data to be evaluated when considering a potential flare may include:

- Symptoms
- Physical examination findings
- Laboratory results
- Imaging results
- Biopsy results

Flare Diagnosis

To promote uniformity and objectivity in the diagnosis of flare, the Investigator will use the flare criteria to determine whether the event meets the definition of flare for this study.

Flare Treatment

For detailed information on flare management, and which flare treatments require discontinuation of IP, refer to Section 7.6.

Briefly, flare treatment is at the discretion of the Investigator and should be initiated after completion of assessments and flare diagnosis, if possible. Flare treatment is not dependent on protocol-specified flare criteria being met.

Investigators will record on the electronic case report form (eCRF) when a subject starts treatment or interventional procedure for IgG4-RD disease activity. Treatment start date for flare will be recorded whether or not the treatment is a prohibited concomitant medication (Section 7.5.1). The indication for use of medications and procedures will be collected to document if the intervention was to control disease activity.

Treatment initiated by a facility or provider other than the Investigator may be used when determining the start of treatment for the purposes of this study, provided that the Investigator reviews all subject data and agrees that initiation of treatment at that time was warranted.

Flare Adjudication

An independent AC, composed of experts in the field, will review the data available to the Investigator or used by the Investigator for decision-making (including any available and relevant imaging reports, laboratory testing, biopsy reports, description of patient symptoms, and a narrative) and will use the same study-specific definition of flare that will be used by the

Investigator. The AC will be blinded and independent, and will be composed of physicians with expertise in the care of patients with IgG4-RD. AC members will review and adjudicate cases individually but will be permitted to discuss cases as a committee as needed. A majority vote is required for AC decisions. Additional details of the process will be provided in the AC Charter.

The AC, in a similar process, is also charged with determining whether sequential IgG4-RD activity events represent a single or more than one flare for the purpose of secondary efficacy endpoints. In general, for treated flares, disease manifestations present prior to flare diagnosis or treatment initiation represent a single flare. New or worsening disease activity that presents during treatment for a flare represents a separate flare. If the flare was not treated, new or worsening of IgG4-RD activity occurring prior to resolution of the presenting flare manifestations does not constitute a new flare.

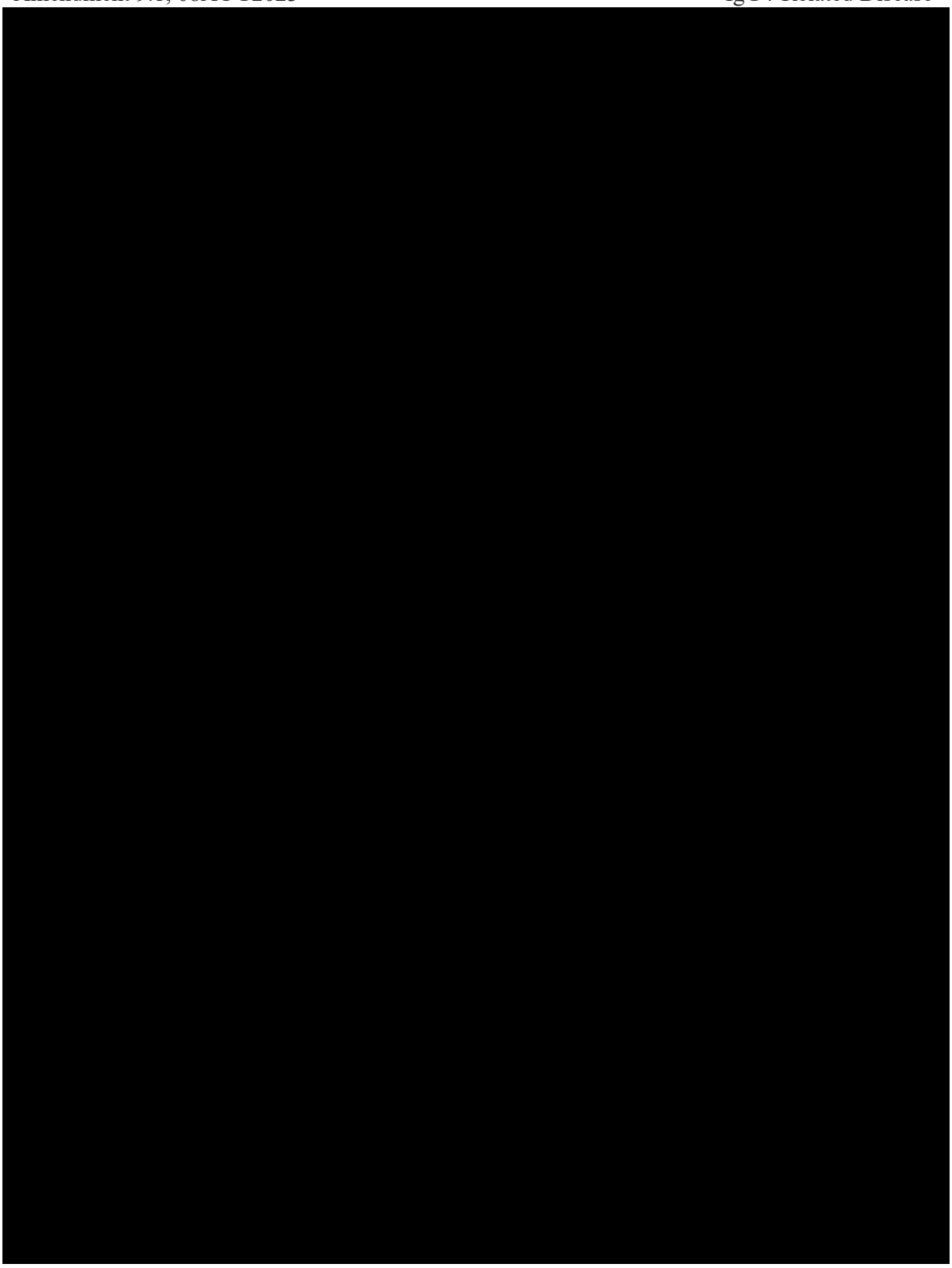
6.3.2.2 IgG4-RD Responder Index

The IgG4-RD RI is a validated instrument for longitudinal assessment of IgG4-RD disease activity, developed and refined by an international team of IgG4-RD experts specifically to permit structured assessment of response to treatment by clinical investigators (Carruthers et al, 2012; Wallace et al, 2018). The RI captures disease activity and damage in 25 domains, with higher weights for disease manifestations that require urgent treatment or that worsen despite treatment. The RI incorporates an activity score for each organ/site of disease, a score for symptomatic disease at each of these sites, and a score amendment for a need for urgent treatment. Serum IgG4 concentration and presence of organ-specific damage are collected but are not part of the overall RI. Because visit-to-visit consistency is important, whenever possible, the same Investigator should complete the IgG4-RD RI for the same subject across all visits.

Not all results needed to complete the IgG4-RD RI (in particular, labs and imaging) will be available at the time of the subject's visit. Therefore, the investigator may delay completion of the IgG4-RD RI for up to 15 business days of the visit date to permit all results to be considered. All other assessments related to the IgG4-RD RI should be completed on the day of the visit.

6.3.2.3 Cumulative Glucocorticoid Use

Cumulative GC use will be calculated as the total GC dose in mg of prednisone or prednisone equivalent taken for the purpose of IgG4-RD disease control during the RCP.



6.3.3 Safety Assessments

Clinically important abnormalities in vital signs, body weight, physical examination, laboratory parameters, and ECGs will be recorded as AEs or SAEs.

6.3.3.1 Vital Signs, Body Weight, and Physical Examinations

Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), body temperature (ºC), and body weight (kg), will be measured using clinically acceptable methods and devices as defined in the schedules of assessments and the IP Administration Manual. Subjects should be seated or supine when vital signs are obtained.

Depending on the visit, physical examinations will be either a full examination (excluding rectal and pelvic examinations) or a symptom-driven examination. Examination of the head and neck, including orbits, salivary glands, and lymph nodes, are to be included in both the complete and the symptom-driven physical examinations.

6.3.3.2 Electrocardiogram

A 12-lead ECG will be performed according to the schedule of assessments and procedures. All ECG recordings will be made with the subject in a supine position, having rested in this position for at least 5 minutes before the start of the ECG.

Each ECG will include ventricular heart rate and intervals (PR, RR, QRS, QT, QTc). The Investigator will be responsible for providing an interpretation of the ECG. Clinically significant abnormalities will be recorded as AEs.

6.3.3.3 Pregnancy

Serum β-hCG pregnancy test(s) will be completed for all females during the screening period and urine pregnancy tests will be completed in females of childbearing potential at all subsequent study visits. At visits where an IP infusion will be administered, a negative urine pregnancy test result must be obtained prior to administration of IV IP in female patients capable of pregnancy. Urine pregnancy tests will be performed at the site. Pregnancy in a female subject who has received IP must be reported to the Sponsor within 24 hours of Investigator awareness (Section 8.5.1).

6.3.3.4 Assessment of Adverse Events

For instructions on collecting and reporting AEs, refer to Section 8.

6.3.3.5 Safety Laboratory Assessments

For descriptions of all laboratory assessments, refer to Section 6.3.4.

6.3.3.6 Anti-drug Antibody Assessments

For descriptions of ADA assessments, refer to Section 6.3.7.

6.3.4 Clinical Laboratory Assessments

Blood and urine samples will be collected for laboratory safety tests as specified in the schedules of assessments (Section 6.2). Laboratory testing is described below. For further details regarding laboratory assessments, see the Study Laboratory Manual.

In certain instances, safety laboratory tests may be run in a qualified and licensed local laboratory with prior approval of the sponsor, even where the exclusion criterion specifies use of the central laboratory. Such instances will not be considered protocol deviations.

6.3.4.1 Hematology

The hematology panel will include a complete blood count, with white blood cell count (WBC) and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), hemoglobin, hematocrit, and platelet count.

6.3.4.2 Serum Chemistry

Serum chemistry assessments will include:

- Albumin
- Alkaline phosphatase (ALP)
- Alanine transaminase (ALT)
- Amylase
- Aspartate transaminase (AST)
- Bicarbonate
- Blood urea nitrogen (BUN)
- Calcium
- Chloride
- Creatinine
- Gamma-glutamyl transferase (GGT)
- Glucose (random)
- Hemoglobin A1C (HbA1C)
- [redacted]
- Lipase
- Magnesium
- Phosphorus
- Potassium
- [redacted]
- Serum to be frozen for possible future safety testing
- Sodium
- Total bilirubin (TBL): (if > 1.5 ULN, indirect and direct bilirubin will be measured)
- Total protein
- Uric acid

Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

6.3.4.3 Coagulation Parameters

Coagulation parameters will include prothrombin time, international normalized ratio, and activated partial thromboplastin time.

6.3.4.4 Urinalysis

Urinalysis will evaluate color, appearance, and specific gravity. Standard dipstick analysis, including pH, protein, glucose, blood, and bilirubin, will be performed. Samples with abnormal dipstick will have microscopy performed. Microscopy will include WBC/high power field (HPF) and red blood cell count/HPF.

Urine protein/creatinine ratio calculates the protein/creatinine ratio from a random urine sample to estimate the 24-hour protein excretion as a marker of renal disease.

6.3.4.5 Progressive Multifocal Leukoencephalopathy

PML is a rare, life-threatening CNS infection caused by the JCV (Berger et al, 2013). Although no confirmed cases of PML have been reported following inebilizumab exposure, PML remains a potential risk based on the inebilizumab mechanism of action. In a case of suspected PML, a cerebrospinal fluid sample should be collected to test for JCV by polymerase chain reaction testing using a validated assay in a clinical testing laboratory.

[redacted]

6.3.6 Imaging

All subjects will have had chest, abdomen, and pelvis imaging (CT scans, unless a CT scan is contraindicated) at baseline unless a CT scan or other appropriate imaging (such as, but not limited to, positron emission tomography [PET] scan or MRI) had been performed within the 3 months prior to screening visit and the reading is available. If clinically indicated, imaging (PET scan excluded) may be repeated prior to randomization, to clarify illness, to assess response to GCs, or to ensure exclusion of malignancy. Other imaging is at the discretion of the Investigator.

6.3.7 Immunogenicity Assessments

Blood samples for immunogenicity (ADA to inebilizumab) will be obtained prior to IP administration according to the visits specified in Section 6.2 and will be assessed using a validated immunoassay.

[redacted]

[redacted]

6.4 Discontinuation of Investigational Product, Withdrawal from Study, and Loss to Follow-up

6.4.1 Discontinuation of Investigational Product

IP must be discontinued if the Investigator determines that continuing it would result in a significant safety risk for that subject. The following events require discontinuation of IP:

1. Anaphylaxis or a serious hypersensitivity reaction that occurred within 7 days after IV dosing and cannot be attributed to another known allergen exposure (see Appendix B).
2. Any AE or significant laboratory abnormality that, in the opinion of the Investigator, Sponsor, or SDMC, warrants discontinuation of dosing.
3. Any AE of immune complex disease.
4. Any life-threatening (Grade 4) AE.
5. Any event of sepsis or febrile neutropenia.
6. Any infection listed as either a definite or probable opportunistic infection in Appendix A.
7. Any Grade 3 AE with the following exceptions:
   - A Grade 3 AE of flare or exacerbation of IgG4-RD (per protocol, these events are not reported as SAEs as they may represent the primary endpoint of the study)
   - A Grade 3 event that is not an IRR or infection, does not meet any other discontinuation criterion, and for which the SDMC has agreed that IP dosing can continue
8. Pregnancy or a decision to become pregnant.
9. Malignancy.
10. Absolute neutrophil count < 800 cells/µL confirmed by repeat testing.
11. Withdrawal of consent for further study participation or for further receipt of IP.
12. Receipt of prohibited medication(s) (see Section 7.5.1).
13. Determination that the subject was ineligible for study participation and continuation of IP could pose a safety risk to the subject in the judgment of the Investigator or Sponsor.
14. Significant noncompliance with the study protocol, as judged by the Investigator or Sponsor.

Severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Section 8.1)

Subjects with Grade 3 SAEs should have their AE data reviewed by the Investigator to specifically address whether or not IP should be discontinued or delayed to ensure patient safety, particularly for Grade 3 SAEs of infection (Section 7.1.1.4). The medical monitor(s) and the SDMC are available for discussions regarding suitability of repeat dosing in a subject who has had a Grade 3 SAE.

The reason(s) for discontinuing IP must be recorded on the appropriate page of the eCRF. If subjects choose to discontinue IP, the reason, such as an AE, lack of efficacy, or other reason, must be recorded in the eCRF.

Subjects who discontinue IP during the RCP should remain in the study and complete all RCP study visits, assessments, and procedures (with the exception of IP administration and associated [redacted] unless they have withdrawn consent for study participation or withdrawn consent for specific assessments (if subjects will not agree to return for visits, safety data can be collected by telephone call if subjects agree).

Subjects who discontinue IP during the RCP may be eligible to enroll in the OLP, if they meet criteria outlined in Section 6.2.3.1. Site Investigators will be trained about the importance of retention of subjects through the completion of the RCP, and patients will be informed about the continued scientific importance of their data even if they discontinue study treatment early.

Subjects who do not participate in the OLP, and subjects who discontinue IP during the OLP, will be asked to return to the clinic for a series of visits occurring every six months for a total of two years after their last dose of IP. These post-discontinuation follow-up visits will include a limited set of assessments including CD20+ B cell counts, immunoglobulins levels, concomitant medications, and adverse events. These visits are described in detail in Section 6.2.4, Safety Follow-Up Period.

6.4.2 Withdrawal from Study

Subjects who wish to withdraw from the study will be invited to return, if willing, for a single additional EDV, unless all study procedures to be completed at the EDV had been completed within the past 30 days.

6.4.3 Subjects Lost to Follow-up

For subjects who are lost to follow-up (ie, those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show due diligence by documenting in the source documents the steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc.

Efforts to ensure complete subject follow-up include proactive site contact of subjects who have missed visits (at least 3 documented attempts to reach by telephone and at least 3 documented attempts to reach by letter) or through emergency/other contact if subjects have provided such contacts. Email can be used for contact and scheduling of visits as long as subjects have given permission for email contact.

6.5 Study Suspension or Termination

The Sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporary suspension or termination of the study may include, but are not limited to, the following:

- The incidence or severity of AEs indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.

- Noncompliance that might significantly jeopardize the validity or integrity of the study.
- Sponsor decision to terminate development.

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

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

6.6 End of Study

The primary analysis of the study data will be conducted when the last subject completes the Day 365 visit of the RCP or discontinues the RCP. The study will be complete when the last active subject completes all protocol-specified visits.

7 STUDY INTERVENTIONS

7.1 Description of Investigational Products

Table 7 provides a description of the IPs to be used in the study.

Table 7 Description of Investigational Products and RCP Dosing

Investigational Product	Concentration and Formulation as Supplied	Route Dose	RCP Dosing Regimen	Manufacturer
Inebilizumab (100 mg per vial, nominal)	Inebilizumab for IV administration is supplied as a sterile liquid filled at a nominal volume of 10 mL in 10R vials. Each vial contains inebilizumab formulated at 10 mg/mL, in 20 mM histidine/histidine hydrochloride, 70 mM NaCl, 106 mM (4% [w/v]) trehalose dihydrate, and 0.01% (w/v) polysorbate 80, pH 6.0	IV 300 mg	Day 1, Day 15, and Week 26	AstraZeneca Nijmegen, B.V. (formerly MedImmune Pharma, BV)
Placebo	Placebo for IV administration is supplied in 10R vials filled with 10 mL (nominal) solution containing 10 mM histidine/histidine hydrochloride, 75 mM NaCl, 106 mM (4% [w/v]) trehalose dihydrate, and 0.02% (w/v) polysorbate 80, pH 6.0	IV	Day 1, Day 15, and Week 26	AstraZeneca Nijmegen, B.V. (formerly MedImmune Pharma, BV)

Table 7 Description of Investigational Products and RCP Dosing

Investigational Product	Concentration and Formulation as Supplied	Route Dose	RCP Dosing Regimen	Manufacturer
				Berkshire Sterile Manufacturing, Inc.

IV = intravenous; NaCl = sodium chloride; RCP = randomized-controlled period; w/v = weight/volume.

7.1.1 Inebilizumab or Matched Placebo

7.1.1.1 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. Both inebilizumab and placebo are supplied as a clear to slightly opalescent, colorless to slightly yellow solution, free from or practically free from visible particles. Inebilizumab is a sterile liquid drug product (100 mg inebilizumab per vial, nominal) intended for IV infusion following dilution in normal saline. Placebo is a sterile liquid product intended for IV infusion following dilution in normal saline.

Any defects with the IP must be reported immediately to the Sponsor's Quality Assurance Department and the site monitor. The Sponsor's Quality Assurance contact information for reporting product complaints is: ClinicalProductComplaints@horizontherapeutics.com . During the investigation of the product complaint, all IP must be stored at labeled conditions unless otherwise instructed.

7.1.1.2 Investigational Product Storage

Investigational product to be diluted for IV use will be appropriately labeled in accordance with national laws and regulations, including required translations. Investigational product is provided as 3 vials per blinded kit.

This IP should not be shaken and requires no special biohazard handling. It must be stored at 2ºC to 8ºC (36ºF to 46ºF) in a refrigerator with adequate temperature monitoring. The IP must not be frozen. It should be stored in the original outer package in a location with limited access.

7.1.1.3 Investigational Product Dose Preparation

Inebilizumab for IV administration and placebo for IV administration are supplied as a sterile liquid in a 10R glass vial at a nominal fill volume of 10 mL with 20-mm stopper and flip-off cap overseal.

No incompatibility has been observed between inebilizumab or placebo and IV infusion bags made of polyolefin or polyvinyl chloride. Inebilizumab and placebo do not contain preservatives and any unused portions must be discarded. Preparation of IP and IV bags is to be performed aseptically.

To prepare each inebilizumab or placebo dose, 3 vials of IP, one 250 mL IV bag containing 0.9% (weight/volume) saline, and one IV infusion pump are required. Each vial should be used only one time to prepare a single dose. With approval of the Sponsor (and using additional

administration instructions), 100 mL or 500 mL saline bags may be used if 250 mL bags are not available or not appropriate.

The dose preparation steps are as follows:

- The tab portion of the vial cap should be removed and the rubber stopper cleaned with 70% ethyl alcohol or equivalent.
- For each dose, 30 mL of blinded IP will be obtained from 3 vials by withdrawing 10 mL from each vial. Use a new needle for each withdrawal.
- Add 30 mL of blinded IP to the saline bag using aseptic technique.
- Gently mix the contents of the IV bag by inversion. Do not shake the solution. The saline bag should then be inspected to ensure the solution is clear.

Total in-use storage time from needle puncture of the IP vials to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Although prepared IP is stable for 24 hours at 2°C to 8°C (36°F to 46°F), the dose of IP must be mixed on the day of administration.

The prepared infusion solution should be at room temperature prior to the start of the IV infusion.

7.1.1.4 Investigational Product Dosing and Administration

Prior to each infusion in the RCP and OLP, the Investigator or other qualified medical personnel must confirm that none of the conditions requiring delay or discontinuation of IP administration are met (Section 6.4.1).

Premedication (from commercial supplies) with a corticosteroid (eg, methylprednisolone 100 mg IV or equivalent), an antihistamine (eg, diphenhydramine 25-50 mg orally or equivalent), and an anti-pyretic (eg, acetaminophen 500-650 mg orally or equivalent) will be administered approximately 30-60 minutes prior to each IP infusion.

Vital signs will be obtained prior to the start of each IP infusion. An experienced and qualified staff member will place the IV access.

The prepared solution will be administered IV via an infusion pump at an incrementally increasing rate through an IV line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter according to the schedule in Table 8.

Table 8 Infusion Rate for Investigational Product after Dilution in a 250 mL IV Bag

Elapsed Time (minutes)	Infusion Rate (mL/hour)
0-30	42
31-60	125
61 to end of infusion	333

IV = intravenous.

Unless an infusion reaction occurs resulting in discontinuation of infusion, the entire infusion bag contents must be administered and the tubing must be flushed with a volume of saline at least as large as that of the tubing to ensure complete delivery of the IP infused at a rate not to exceed 333 mL/hour.

After completion of the infusion, subjects will be observed for at least one hour.

Medically qualified personnel must be immediately available to respond to emergencies during administration of IP. Appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat these reactions. Additionally, appropriate drugs and medical equipment to treat IRRs must be immediately available, and study personnel must be trained to recognize and treat IRRs.

If an infusion reaction occurs, the site may stop or slow the infusion. Resumption of the infusion is at the discretion of the site. Management of infusion reactions will depend on the type and severity of the reaction and is at the discretion of the Investigator. For life-threatening infusion reactions, IP should be immediately and permanently stopped and appropriate supportive treatment administered. For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

7.1.1.5 Monitoring of Dose Administration

Vital signs (body temperature, blood pressure, pulse rate, and respiratory rate) must be obtained:

- Within 60 minutes prior to IP administration
- 15 (± 5) minutes after the start of the infusion and then every 30 (± 10) minutes until completion of infusion
- At the completion of infusion (+ 10 minutes)
- 60 (± 10) minutes after dosing (repeated as needed until stable)

7.1.2 Investigational Product Accountability

Study site staff will maintain a record of the IP doses received, dispensed, administered, and destroyed. All records will be maintained with controlled access. The Investigator will administer the IP only to subjects included in this study and according to the procedures established in this study protocol. Each administration of IP will be documented and transferred to the eCRF.

7.1.3 Investigational Product Handling and Disposal

The Investigator or designee must either destroy unused IP on site or return any unused IP to the Sponsor or designee, regardless of whether the study was completed or terminated prematurely. Destruction or return of IP must be appropriately documented.

7.2 Additional Study Medication

7.2.1 Oral Glucocorticoid Taper

All subjects will receive daily oral prednisone (or equivalent) from Day 1 through Week 8, according to a tapering dose schedule (Table 9). The open-label GCs will be local, commercial products supplied to subjects by the investigational sites.

Table 9 Glucocorticoid Taper Schedule (Randomized-controlled Period)

RCP Week	Oral Prednisone Dose (or Equivalent)
Weeks 1-2	20 mg/day
Weeks 3-4	15 mg/day
Weeks 5-6	10 mg/day
Weeks 7-8	5 mg/day

RCP = randomized-controlled period.

7.3 Assessment and Verification of Compliance

Site staff will administer the infusion IPs at the study center. The dose and date of administration of IP must be recorded in the subject eCRF. Treatment compliance for IV inebilizumab and IV placebo will be assessed based on this information.

Patients are to bring their prednisone (or equivalent) tablets with them each visit until the end of the 8-week GC taper so that a compliance check (pill count) can be performed. An assessment of compliance will be recorded by the study staff in source documentation.

7.4 Treatment Assignment and Bias Minimization

7.4.1 Treatment Allocation for RCP

Subjects will be randomized 1:1 within each stratum (by first or subsequent IgG4-RD manifestation, ie, newly-diagnosed vs recurrent) by the IXRS to either the inebilizumab group or the placebo group.

- Inebilizumab group: Inebilizumab 300 mg IV on Day 1, Day 15, and at Week 26
- Placebo group: Matching IV placebo on Day 1, Day 15, and at Week 26

7.4.2 Treatment Allocation for OLP

All subjects in the OLP will receive open-label inebilizumab 300 mg IV on Day 1 and at Week 26. On Day 15, subjects who were randomized to receive inebilizumab in the RCP will receive a blinded dose of IV placebo, while subjects who were randomized to receive placebo in the RCP will receive a blinded 300 mg dose of inebilizumab. This allocation will be managed by the IXRS to maintain the blinding of sites and subjects to treatment assignment during the preceding RCP. Subsequent administrations of 300 mg IV inebilizumab will occur every six months for the remainder of the OLP.

7.4.3 Randomization Strategy and Procedure

An IXRS will be used for randomization to a treatment group and assignment of IP kit numbers. A subject is considered randomized into the study when the Investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of treatment group.

Additional details are provided in the IXRS manual.

7.4.4 Extent and Maintenance of Blinding

This is a double-blind study in which inebilizumab and placebo are matched in appearance.

The Sponsor will remain blinded until after the database lock for primary efficacy analysis, which will occur after all subjects have completed the Day 365 visit (Visit 15) or discontinued early from the RCP. Subjects, site staff, and contract research organization (CRO) personnel will remain blinded to individual subject treatment assignment until final database lock at the conclusion of the study. Potentially unblinding laboratory data will not be available to investigative site personnel until after final database lock.

If treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, the Sponsor must be notified immediately.

7.4.5 Unblinding Procedures

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

7.5 Concomitant Medications and Treatments

Subjects should receive all medications, including treatments for IgG4-RD, that are considered by their physician to be necessary for their health and well-being.

The Sponsor recommends that Investigators ensure that all patients are up to date with required vaccinations prior to entry into the study.

7.5.1 Prohibited Medications

Patients must receive all treatments that are considered necessary for their health in the judgment of their physician(s). The following prohibited medications will require the discontinuation of IP, but subjects who receive prohibited medications must remain in the study through the final Week 52 RCP visit.

Generally, GC treatment for reasons other than new or worsening IgG4-RD activity is prohibited, but exceptions are described in Section 7.5.2 (GCs for uses other than IgG4-RD). The per-protocol limitations on dose and duration of GC treatment for IgG4-RD flare are described in Section 7.6. The Investigator must provide the indication for each use of GC or other immunosuppressive therapy.

Additional prohibited medications in the RCP and OLP include:

- Biologic or non-biologic immunosuppressive agents other than GCs, including but not limited to, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, leflunomide, cyclophosphamide, rituximab, etanercept, adalimumab, infliximab, certolizumab pegol, golimumab, abatacept, and tocilizumab.
- Live viral vaccines or live therapeutic infectious agents.

Receipt of prohibited medication requires discontinuation of IP as described in Section 6.4.1.

7.5.2 Permitted Glucocorticoid Uses

Aside from the required 8-week GC taper (Section 7.2.1), GCs are generally only permitted in this study to treat IgG4-RD flares (see Section 7.6). However, the following are permitted GC use for indications other than IgG4-RD flare:

- Oral GC treatment for ≤ 2 weeks (for any purpose).
- GCs at a dose of ≤ 2.5 mg of prednisone or equivalent for treatment of adrenal insufficiency (mineralocorticoids are permitted) or intolerance of steroid taper (in this case, continued tapering of steroids should be performed as tolerated). GCs at any dose should not be continued for the purpose of prevention of IgG4-RD related flare.
- Inhaled, intranasal or topical corticosteroids.
- Up to 2 intra-articular steroid injections that do not exceed 40 mg methylprednisolone or equivalent per injection.

7.6 Management of Flare of IgG4-RD During the Study

Treatment of flares is at the discretion of the Investigator. Subjects should be managed in accordance with best medical practice for their condition regardless of whether protocol-defined flare criteria are met. Stenting or other procedures are permitted as medically warranted per the judgment of the Investigator. Unless treatment is urgent, in which case medically appropriate therapy should be instituted without delay, Investigators should conduct flare assessments according to the organ(s) affected prior to initiation of treatment, if possible.

Choice of flare treatment is at the discretion of the Investigator. The use of GCs at a dose exceeding 40 mg/day of prednisone or equivalent, or for a duration exceeding 8 weeks including taper to discontinuation, requires discontinuation of IP. Use of any prohibited immunosuppressive treatment for flares requires discontinuation of IP (Section 7.5.1).

8 SAFETY DATA COLLECTION AND REPORTING

An external, independent SDMC will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the Sponsor regarding further conduct of the study. See Section 11.1 for details on SDMC activities.

8.1 Definitions

- **Adverse event** – An AE is any untoward medical occurrence associated with the use of an intervention in humans, whether or not it is considered intervention-related.
- **Serious adverse event** – A SAE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
  - Death
  - A life-threatening AE. (An event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction [SAR] that, had it occurred in a more severe form, might have caused death.)
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect
  - 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 patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

  For the purposes of this protocol, IgG4-RD disease activity or flare that meets any of the above SAE criteria, including hospitalization for a procedure required to manage an IgG4-RD flare, will not be reported as an SAE unless it results in death or occurs during the screening period. Clinically significant events of IgG4-RD disease activity, as determined by the Investigator, should be reported as AEs.

  A hospitalization for elective or pre-planned treatment of a pre-existing condition that did not worsen from baseline will not be considered an SAE.
- **Causality or relatedness**: The Investigator is required to provide an assessment of the relationship of AEs and SAEs to the IP. An event will be considered "not related" to use of IP if any of the following tests are met:
  - An unreasonable temporal relationship between administration of the IP and the onset of the event (eg, the event occurred either before, or too long after, administration of the IP for it to be considered IP-related)
  - A causal relationship between the IP and the event is biologically implausible (eg, death as a passenger in an automobile accident)
  - A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the IP if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the IP (ie, there are facts, evidence, or arguments to suggest possible causation).

- **Adverse reaction** – An adverse reaction is any AE caused by a drug.
- **Suspected adverse reaction** – A SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting to regulatory agencies, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than an adverse reaction.
- **Unexpected** – An event is considered unexpected if it is not listed in the IB, is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere. Unexpected also refers to events that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular IP.
- **Severity or intensity** – Severity will be graded according to the CTCAE, version 5.0. The determination of severity for events not listed in the CTCAE should be made by the Investigator based upon medical judgment and the severity categories of Grade 1 to Grade 5 as defined here, with the maximum severity recorded:
  - Grade 1 (mild): An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Grade 2 (moderate): An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
  - Grade 3 (severe): A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
  - Grade 4 (life-threatening): An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
  - Grade 5 (fatal): Death (loss of life) as a result of an event.

8.2 Documenting Adverse Events

AEs reported by the subject, spontaneously or in response to an open question from the study personnel, and AEs revealed by observation will be recorded during the study at the investigational site. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken, serious outcome (if

applicable), and whether or not it caused the subject to discontinue the study. The AE term should be reported in standard medical terminology when possible.

8.3 Reporting Adverse Events

All AEs (related and unrelated) will be recorded from written ICF signature up to exit from the study, whether or not related to the study.

In addition to eCRF entry, all SAEs must be reported to the Sponsor within 24 hours of site staff awareness by submitting a SAE Report Form by email to:

Email: Clinicalsafety@horizontherapeutics.com

Alternatively, the SAE Report Form can be submitted by fax to:

US-Only Fax Number: 1-800-860-7836

EX-US Fax Number: 1-224-855-5055

Additional follow-up information, if required or available, should all be reported within one business day of receipt, should be completed on a follow-up SAE form, placed with the original SAE information, and kept with the appropriate section of the eCRF and/or study file.

The Sponsor will work with the Investigator to ensure that all the necessary information is provided within one calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs.

Sponsor or designee is responsible for notifying the relevant regulatory authorities of certain events. Notification of the IRB or IEC of all SAEs that occur at the Investigator's site are the responsibility of the Investigator. Investigators will be notified of all unexpected, serious, drug -related events (7 and 15 Day Safety Reports) that occur at other investigative sites during the clinical trial. Each Investigator is responsible for notifying its IRB or IEC of these additional SAEs.

8.4 Adverse Events of Special Interest

An AESI is an AE of scientific and medical interest specific to understanding of the IP and may require close monitoring and collection of additional information by the Investigator. An AESI may be serious or nonserious.

The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP. All AESIs, regardless of seriousness or investigator-determined relationship to IP, must be reported to the Sponsor within 24 hours of site staff awareness by submitting an AESI Report Form by email to:

Email: Clinicalsafety@horizontherapeutics.com

Alternatively, the AESI Report Form can be submitted by fax to:

US-Only Fax Number: 1-800-860-7836

EX-US Fax Number: 1-224-855-5055

The following AESIs will be particularly monitored in this study:

- Anaphylaxis and serious hypersensitivity reactions
- Infusion-related reactions
- Immune complex disease
- Cytopenia
- Serious and/or opportunistic infections, including PML (see Appendix A for list of opportunistic infections).

8.5 Other Events Requiring Immediate Reporting

8.5.1 Pregnancy

Pregnancy in a female subject who has received IP must be reported to the Sponsor (Section 8.3) within 24 hours of Investigator awareness of the event, by email or fax using the Pregnancy Report Form.

Subjects who become pregnant during the study period must not receive additional doses of IP but will not be withdrawn from the study. If the subject requests to know which treatment she received, this information will be provided to her. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to the Sponsor's Patient Safety group after outcome.

Should the Investigator become aware of a pregnancy in the partner of a male study subject who has received IP, this should be reported to the Sponsor within 24 hours of knowledge of the event, by fax or email using the Pregnancy Report Form (see Section 8.3 for contact information). The Sponsor will endeavor to collect follow-up information on such pregnancies, provided the partner of the study subject provides consent.

8.5.2 Overdose or Misuse

Any instance of overdose of IP (suspected or confirmed) must be communicated to the Sponsor (Section 8.3) within 24 hours of Investigator awareness. Any associated AEs or SAEs must also be reported and their management should be recorded.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations

The analyses with a treatment policy strategy will include all data captured during the 52-week RCP, defined as the period from Day 1 (Dosing) at Visit 2 to the conclusion of the scheduled last RCP visit at Visit 15 (Week 52), inclusive.

The analyses applying the while-on-treatment strategy will include all data captured while subjects are on treatment, defined as the period from Day 1 (Dosing) at Visit 2 and 6 months after the last treatment during the RCP, inclusive.

Summary data will be presented in tabular format by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including N, mean, standard deviation, median, and range. Data listings will be sorted by treatment group and patient number. Additional details of statistical analyses will be described in the statistical analysis plan (SAP).

9.2 Statistical Hypotheses

The following is the null and alternative hypotheses associated with the primary endpoint:

$$H_0: HR = 1 \text{ vs } H_1: HR \neq 1,$$

where *HR* indicates the hazard ratio of treated and AC-determined IgG4-RD flares relative to placebo. The hypothesized treatment effect of a relative reduction of 65% in risk implies a HR of 0.35.

9.3 Determination of Sample Size

A total of 39 flares are required to detect a relative reduction of 65% in risk for time from Day 1 (dosing) to onset of flare during the RCP with at least 90% power, two-sided $\alpha = 0.05$, and a 1:1 randomization ratio based on log-rank test for comparison. Assuming the probability of having a treated and AC-determined IgG4-RD flare during the RCP in the placebo group is 0.35 (Yunyun et al, 2017; Yunyun et al, 2019; Wang et al, 2018), a total of 160 subjects (80 subjects per treatment group) are expected to be randomized and dosed using the following formula:

$$N = \frac{E}{\Pr(Fail)}$$

where

$$\Pr(\text{Fail}) = 0.5P_0 + 0.5P_1$$

is the weighted average of the failure probabilities P_0 and P_1 and in the placebo and inebilizumab groups, respectively. Assuming the probability of having a treated and AC-determined IgG4-RD flare during the RCP in the placebo group is 0.35 and an exponential survival distribution, the hazard rate for the placebo group is -log(1-0.35) = 0.4308. With the hypothesized treatment effect of a relative reduction of 65% in risk, the hazard rate for the inebilizumab group during the RCP is -0.35 log(1-0.35) = 0.1508. Pr(Fail) = (0.35 + [1 - exp(-0.1508)])/2 = 0.245.

The hypothesized 65% reduction in risk is an estimate based on the observed treatment effect for attack reduction with inebilizumab in the phase 3 NMOSD trial (77% reduction in risk), and limited published clinical data on the efficacy of the B cell-depleting agent rituximab in IgG4-RD.

To mitigate uncertainties in the flare event rate in the study population, a blinded event rate assessment may take place after the 50th dosed subject competes the RCP or has a positively treated adjudicated flare or early discontinued from the study during the RCP. This assessment will be performed on all available data and will not take into account treatment information. These first 50 dosed subjects who complete the RCP or have a positively treated adjudicated flare or early discontinued from the study will be randomly sampled and used to simulate

different sample sizes between 160 and 200 in increments of 10. For each of the sample sizes, this simulation process will be repeated 10,000 times to give a distribution of the number of flares. The target sample size is the one that achieves 39 flares 90% of the time.

If the blinded assessment from these first 50 dosed subjects indicates that the number of flares expected with 160 subjects is less than 39, then the sample size may be adjusted based on the above exercise to the number of subjects anticipated to achieve 39 flares with a maximum of 200 subjects (100 subjects per treatment group).

9.4 Analysis Sets

Full Analysis Set: The Full Analysis Set will include all subjects randomized and who receive any dose of IP in the study. Subjects will be analyzed according to the treatment randomized. The efficacy analysis will be based on the Full Analysis Set.

Safety Analysis Set: The Safety Analysis Set will include all subjects who received any dose of IP during the RCP. Subjects will be analyzed according to the treatment that they actually received. Specifically, subjects randomized to inebilizumab who received all placebo doses will be included in the placebo group; conversely, subjects randomized to the placebo group who received at least one dose of inebilizumab will be included in the inebilizumab group. Safety, [redacted] and ADA analyses will be based on Safety Analysis Set.

The Open-label Analysis Set: The Open-Label Analysis Set will include all subjects who receive any dose of inebilizumab during the OLP.

The Any Inebilizumab Analysis Set: The Any Inebilizumab Analysis Set will include all subjects who receive any dose of inebilizumab.

[redacted]

9.5 Methods for Statistical Analyses

9.5.1 Analysis of the Primary Efficacy Endpoint

The primary efficacy analysis will use the treatment policy strategy, which includes all data captured during the 52-week RCP.

The primary efficacy variable is the time in days from Day 1 (dosing) to the date of the first treated and AC-determined IgG4-RD flare within the 52-week RCP. The date of disease flare is defined as the date of initiation of any flare treatment (new or increased GC treatment, other immunotherapy, or interventional procedure) deemed necessary by the Investigator for the flare. The hazard rate in the inebilizumab group will be compared to that in the placebo group using the Cox proportional hazards model with the treatment indicator (inebilizumab or placebo) and the stratification factor as the explanatory variables. The HR of inebilizumab versus placebo will be estimated together with its associated 95% CI. SAS PROC PHREG will be used for fitting this model. The data cutoff for the primary analysis will be when all subjects have completed or discontinued from the RCP.

Subjects who discontinue prematurely from the RCP without a treated and AC-determined flare will be censored in this model at the time of discontinuation.

Additional analysis with the same model will be performed with data from subjects who meet the following criteria, censored at the time the relevant treatment was first received:

- Received any treatment for IgG4-RD, including GC or immunosuppressive treatment, prior to experiencing a treated and AC-determined flare; or
- Received any prohibited GC or immunosuppressive treatment prior to experiencing a treated and AC-determined flare.

9.5.2 Analysis of Secondary Efficacy Endpoints

9.5.2.1 Annualized Flare Rate for Treated and AC-determined Flares During the RCP

The annualized flare rate for treated and AC-determined flares during the RCP will be analyzed with a treatment policy strategy, which includes all data captured during the 52-week RCP. The efficacy variable is annualized flare rate, which will be compared between the inebilizumab group and the placebo group using a negative binomial model. The response variable in the model will be the number of treated AC-determined flares experienced by a subject over the 52-week RCP. The model will include covariates of treatment group (inebilizumab or placebo) and stratification factor. The logarithm of the subject's corresponding follow-up time will be used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

The estimated treatment effect (ie, the rate ratio of inebilizumab versus placebo), corresponding 95% CI, and two-sided p-value for the rate ratio will be presented. In addition, the annual flare rate and the corresponding 95% CI within each treatment group, and the absolute difference between treatment groups with the corresponding 95% CI, will be presented.

9.5.2.2 Annualized Flare Rate for AC-determined Flares During the RCP, Whether or Not Treated

The annualized flare rate for AC-determined flares, whether or not treated, during the RCP will be analyzed with a treatment policy strategy, which includes all data captured during the 52-week RCP. The efficacy variable is the annualized flare rate, which will be compared between the inebilizumab group and the placebo group using a negative binomial model. The response variable in the model will be the number of AC-determined flares, regardless of treatment experienced by a subject, over the 52-week RCP. The model will include covariates of treatment group (inebilizumab or placebo) and stratification factor. The logarithm of the subject's corresponding follow-up time will be used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

The estimated treatment effect (ie, the rate ratio of inebilizumab versus placebo), corresponding 95% CI, and two-sided p-value for the rate ratio will be presented. In addition, the annual flare rate and the corresponding 95% CI within each treatment group, and the absolute difference between treatment groups with the corresponding 95% CI, will be presented.

9.5.2.3 Flare-free Treatment-free Complete Remission

Two types of flare-free complete remission will be analyzed: flare-free treatment-free complete remission and flare-free corticosteroid-free complete remission.

Flare-free treatment-free complete remission is defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no treatment for flare or disease control during the RCP except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence.

Flare-free corticosteroid-free complete remission is defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control during the RCP except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence.

The analysis of the proportion of subjects achieving each flare-free complete remission defined above for the composite estimand will include all data captured during the 52-week RCP. For both of these endpoints, the efficacy variable for each flare-free complete remission is the proportion of subjects achieving the corresponding flare-free complete remission at Week 52, which will be assessed using a logistic regression model respectively. The response variable in the model will be whether or not a subject achieves the corresponding flare-free complete remission at Week 52. The model will have treatment indicator (inebilizumab or placebo) and stratification factor as the explanatory variables.

Subjects who discontinue prematurely from the RCP will be treated as not achieving complete remission at Week 52. The results of the analyses will be presented using odds ratios, together with associated 95% CI and two-sided p-value for inebilizumab versus placebo.

An additional analysis under a treatment policy strategy with the same model will be conducted, with complete remission defined as the lack of evident disease activity at Week 52 and no AC-determined flare during the RCP.

9.5.2.4 Time to Initiation of Treatment for IgG4-RD, Regardless of AC Determination of Flare

The analysis of time to initiation of treatment for IgG4-RD activity by the Investigator within the RCP, regardless of AC determination of flare, will use a treatment policy strategy, which includes all data captured during the 52-week RCP. The date of disease flare is defined as the date of initiation of any flare treatment (new or increased GC treatment, other immunotherapy, or interventional procedure) deemed necessary by the Investigator for the flare.

The efficacy variable is the time in days from Day 1 (dosing) to the date of the first treatment for disease activity by the Investigator within the RCP, regardless of AC determination of flare within the 52-week RCP.

The hazard rate in the inebilizumab group will be compared to that in the placebo group using the Cox proportional hazards model with the treatment indicator (inebilizumab or placebo) and the stratification factor as the explanatory variables. The HR of inebilizumab versus placebo will be estimated together with its associated 95% CI. SAS PROC PHREG will be used for fitting this model.

Subjects who discontinue prematurely from the RCP without receiving treatment for management of flare, as defined above, will be censored in this model at the time of discontinuation.

9.5.2.5 Glucocorticoid Use

The analysis of GC use will include all data captured during the 52-week RCP. For each subject, GC use will be calculated as the cumulative GC dose taken for the purpose of disease control during the RCP.

An analysis of covariance model with treatment indicator (inebilizumab or placebo) and stratification factor as the explanatory variables will be used.

GC use for a purpose other than controlling IgG4-RD will not be included in the analysis. For subjects who discontinue prematurely from the RCP, further GC use will be imputed as 0.

Results will be presented in terms of least square means (LSMEANS), treatment differences in LSMEANS, 95% CIs, and p-values.

9.5.3 Control of Type I Error

The primary null hypothesis will be tested at two-sided $\alpha = 0.05$. If, and only if, the treatment group comparison is statistically significant, the secondary hypotheses will be tested.

The 3 key secondary endpoints to be considered for study-wise type I error control are:

- Annualized flare rate for treated, AC-determined flares during the RCP.
- The proportion of subjects achieving flare-free, treatment-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no treatment for flare or IgG4-RD disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence.
- The proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC taper.

Null hypotheses for the three key secondary endpoints will be tested using Hochberg procedure (Hochberg, 1988). If the largest p-value is < 0.05, the null hypotheses for all three secondary endpoints will be rejected. If the largest p-value is ≥ 0.05 and the second largest one is < 0.025, the null hypotheses corresponding to the two endpoints with smaller p-values will be rejected. If the largest p-value is ≥ 0.05, the second largest one is ≥ 0.025, and the smallest p-value is

< 0.0167, only the null hypothesis corresponding to the endpoint with the smallest p-value will be rejected. Otherwise, no null hypothesis will be rejected.

9.5.4 Subgroup Analyses

Consistency of treatment effect measured by primary and 3 key secondary endpoints in the following subgroups will be investigated for the Full Analysis Set:

- Age (< 65 vs ≥ 65)
- Sex (male vs female)
- Region (US vs non-US; EU vs non-EU; and Asia vs non-Asia)
- Serum IgG4 concentrations at baseline
- Racial/ethnic subgroups as needed for national/regional regulatory filings
- First or subsequent treatment course for IgG4-RD

The nominal p-value and 95% CIs of treatment effect will be provided for each subgroup analysis. Forest plots will be generated to visually present the consistency of treatment effect in different subgroups with overall treatment effect.

9.5.5 Safety Analysis

Safety endpoints will be summarized separately for the RCP, OLP and SFUP. Safety data from the RCP and OLP will be presented based on the Safety Analysis Set and on the Open-label Analysis Set, respectively. Data after subjects receive inebilizumab will be analyzed based on the Any Inebilizumab Analysis Set.

AE and SAE collection begins after the subject signs the informed consent document and lasts until the end of study visit. AESI identification will be based on MedDRA coding. The search criteria for the AESIs will be established prior to database lock for the primary analysis.

The number and percentage of subjects reporting TEAEs and TESAEs will be summarized for each treatment group by system organ class and preferred terms, by severity, and by relationship to the IP. The rate of AEs per 100 person-years at risk, calculated as (total number of AEs)/(total person years) × 100, will also be reported.

AEs and SAEs collected during the RCP will be analyzed using a treatment policy strategy, (which includes all data captured during the RCP) and a while-on-treatment strategy (which includes all data captured while subjects are on treatment). The risk difference and corresponding 95% CI will be presented. In addition, the time to first instance of an AESI and duration of the AESI will summarized by treatment group when appropriate.

Clinically important abnormalities in vital signs, laboratory parameters, ECGs, and physical examinations will be recorded as AEs or SAEs. Laboratory measurements, as well as their changes from baseline at each collection time point and shift from baseline, if applicable, will be summarized descriptively.

Safety subgroup analyses will be investigated when appropriate and may include analyses by age (< 65 vs ≥ 65), sex (male vs female), region (US vs non-US; EU vs non-EU; and Asia vs

non-Asia), serum IgG4 concentrations at baseline, stratification factor, and subgroups as needed for national/regional regulatory submissions.

[redacted]

9.5.7 Immunogenicity Analysis

ADA will be summarized using descriptive statistics for each population. Number and percentage of subjects who developed positive ADA will be summarized by treatment group. The potential impact of ADA on the safety and efficacy of inebilizumab may be explored if data allow.

[redacted]

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), the European Union (EU) Clinical Trials Regulation No 536/2014 and applicable local and regional regulatory requirements.

10.2 Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to Sponsor or representative before he or she can enroll any patient into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising

used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require. The PI is also responsible to adhere to requirements stipulated by the respective IRB/IEC and for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines. Copies of all correspondence between the Investigator and the IRB/IEC is provided to Sponsor's representative.

In Japan the head of the study site should submit a notification of direction/determination, as well as IRB written approval, to the Sponsor and the Principal Investigator before enrollment of any subject into the study.

10.3 Informed Consent

The Investigator or other study site designee with IRB/IEC-approved qualifications will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patients will be informed that their study record and medical records/documents that pertain directly to the study will be reviewed and possibly copied by Sponsor or its designee, or a governmental agency (such as the Food and Drug Administration [FDA]), and that every effort will be made to maintain patient confidentiality. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The ICF must be witnessed and dated by the PI or his/her designee, and the original retained by the Investigator/study site as part of that subject's record.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

Patients may be rescreened within 30 days under the current and signed ICF.

The ICF must be fully approved by an IRB or an IEC prior to its use with study participants.

10.4 Deviation from the Clinical Study Protocol

The Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the Principal Investigator and the Sponsor or IRB/IEC approval, based on deliberations. This shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the subjects, for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (eg, changes to the organization/structure of Sponsor, the name/department of the study site, the address or phone number of the study site or Sponsor, or the job title of the Investigator or Medical Monitor). In such cases, the Principal Investigator must notify Sponsor, the head of the study site, and the IRB as soon as possible about the details of the deviation or change, the reason for the deviation, and a proposed revision in the protocol, if required, to obtain their approval.

For study sites in Japan, a certificate of approval by the head of the study site should be obtained via the head of the study site.

The Investigator(s) should document all deviations from the protocol regardless of the reason(s) or justification.

10.5 Data Privacy

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is obtained from Sponsor. However, authorized regulatory officials, IRB/IEC personnel, Sponsor and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by subject ID numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

The conduct of this study and the processing of any personal data collected from each subject (or from a subject's healthcare professional or other relevant third-party sources) by the Sponsor or its designee, the site, or the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the General Data Protection Regulation (GDPR) EU 2016/679 and EU Directive 95/46/EEC. The Sponsor or its designee shall ensure that, at all times, it has an appropriate legal basis for processing personal data under applicable data protection laws. Site-based organizational and technical arrangements to avoid unauthorized access vary by site but all include access-controlled/access-limited document control and technical solutions, including passwords and security control measures to protect study-specific data, both in paper and electronic format.

The Investigators shall provide coded data to the Sponsor or its designee, which do not reveal the patient's name, full date of birth, or any other information that can identify the patient. All personal information shall be replaced with a SID number before any information leaves the investigative sites.

The Investigator shall report any data breaches that occur to the Sponsor or its designee, without undue delay and in line with GDPR requirements. The Sponsor shall address data breaches in compliance with the requirements of applicable laws and regulations, including the GDPR. Any data breach procedures implemented by Sponsor shall provide specific responses to actual or potential threats and involve investigation, containment, and mitigation. If applicable, the authorities and the data subjects shall be notified of a data breach within the required timeframes of the applicable laws and regulations, including those of the GDPR.

10.6 Disclosure

Sponsor is responsible for preparing and providing the appropriate regulatory authorities with Clinical Study Reports, according to the applicable regulatory requirements.

10.7 Biological Specimens and Data

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

Leftover samples stored for future research (not obtained in China) with patient consent will be labeled with a sample identification number. If the subject withdraws consent for participating in future research, the Sponsor will locate the subject's sample and destroy it. If the subject consents to have his/her samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be stored by the Sponsor with similar samples in a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for future research, the samples will be destroyed by the Sponsor once they are no longer required for the main study. Samples collected in China will be destroyed upon publication of the Clinical Study Report.

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

11 OVERSIGHT

11.1 Safety Data Monitoring Committee

The external, independent SDMC is responsible for safeguarding the interests of study participants via review of accumulating safety data and for supporting study integrity and interpretability based on their review of ongoing study conduct. The SDMC will provide Sponsor with recommendations for actions with respect to study conduct and the management of subjects treated under the study protocol. The SDMC members are independent of Sponsor and any CRO/organization collaborating with Sponsor on the study.

The SDMC will not be charged with any formal interim analysis, will not conduct a futility analysis, and will not be asked to consider early study completion for efficacy.

For additional details, refer to the SDMC Charter.

11.2 Quality Control and Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Sponsor may conduct a quality assurance audit. See Section 11.4 for details regarding the audit process.

11.3 Monitoring

Before an investigational site can enter a subject into the study, a representative of Sponsor or of the CRO will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sponsor or its representatives. This will be documented in a Clinical Study Agreement between Sponsor and the Investigator.

During the study, a representative from Sponsor or the CRO will have regular contact with the investigational site for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm compliance with the principles of GCP and regulatory requirements.
- Review of written ICFs for subjects screened/enrolled.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject medical records at the hospital or practice, and other records relevant to the study for accuracy and completeness. This will require direct access to all original medical and other study-related records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs, confirm that any SAEs have been forwarded to Sponsor or representative, and confirm those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.
- During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the study, make necessary corrections to eCRF entries, respond to data clarification requests, and respond to any other study-related inquiries from the monitor.

11.4 Audits

To ensure compliance with GCP and all applicable regulatory requirements, Sponsor or its authorized representatives may conduct a quality assurance audit.

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

Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study, including the ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

In addition to the above, representatives of Sponsor auditing staff or government inspectors may review the conduct/results of the study at the investigational site. The Investigator should contact Sponsor immediately if contacted by a regulatory agency about an inspection. The Investigator cooperates with the auditor(s), makes available to the auditor all requested documentation, and ensures that issues detected during the course of these audits are satisfactorily resolved. The Investigator supplies Sponsor with copies of all documentation and correspondence related to regulatory agency audits as outlined in the Clinical Trial Agreement. If the results of the audit result in a Form FDA 483 (or similar document from another regulatory agency), the Investigator promptly provides a copy to a Sponsor representative and a draft response to Sponsor prior to submission to the regulatory agency.

11.5 Records

11.5.1 Data Capture and Management

Clinical Data Management (CDM) will be performed according to the Data Management Plan (DMP). The DMP will document procedures and roles and responsibilities related to CDM activities, including data validation, data transfer and reconciliation, CDM communications, medical coding and dictionaries, CDM reports, and data formats.

An electronic data capture system compliant with 21 CFR Part 11 will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the eCRF Completion Guidelines provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs electronically. Upon completion of the study, a copy of the completed eCRFs will be provided to the study site for archival purposes.

11.5.2 Source Documentation

Sponsor or its authorized representative will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, IP stocks, drug accountability records, subject charts, study source documents, and other records relative to study conduct.

11.5.3 Records Retention

Investigators must maintain all documentation related to the study for a period of 25 years. Retention may be shorter in accordance with local regulations, as long as records are maintained for a minimum of 2 years following the last marketing application approval, if marketing applications are filed. Sites must obtain sponsor approval prior to destroying any records.

If it becomes necessary for the Sponsor or a regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

12 PUBLICATION POLICY

The publication policy of Sponsor is discussed in the Investigator's Clinical Research Agreement.

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14 APPENDICES

APPENDIX A STUDY-SPECIFIED OPPORTUNISTIC INFECTIONS THAT MEET EXCLUSION CRITERIA AND REQUIRE DISCONTINUATION OF IP

Definite [a,b] Opportunistic Infection	**Probable [c] Opportunistic Infection**
Pneumocystis jirovecii	Paracoccidioides infections
BK virus disease including polyomavirus-associated nephropathy	*Penicillium marneffei* (Talaromyces)
Cytomegalovirus disease	Sporothrix schenckii
Post-transplant lymphoproliferative disorder (EBV)	Cryptosporidium species (chronic disease only)
Progressive multifocal leukoencephalopathy	Microsporidiosis
Bartonellosis (disseminated disease only)	Leishmaniasis (visceral only)
Blastomycosis	Trypanosoma cruzi infection (Chagas's disease) (disseminated disease only)
Toxoplasmosis	Campylobacteriosis (invasive disease only)
Coccidioidomycosis	Shigellosis (invasive disease only)
Histoplasmosis	Vibriosis (invasive disease due to *Vibrio vulnificus*)
Aspergillosis (invasive disease only)	HCV progression
Candidiasis (invasive disease or pharyngeal)	
Cryptococcosis	
Other invasive fungi: Mucormycosis (zygomycosis) (Rhizopus, Mucor and Lichtheimia), *Scedosporium/Pseudallescheria boydii*, *Fusarium*)	
Legionellosis	
Listeria monocytogenes (invasive disease only)	
Tuberculosis	
Nocardiosis	
Non-tuberculous mycobacterium disease	
Salmonellosis (invasive disease only)	
HBV reactivation	
Herpes simplex (invasive disease only)	
Herpes zoster (any form)	
Strongyloides (hyperinfection syndrome and disseminated forms only)	

EBV = Epstein-Barr visu; HBV = hepatitis B virus; HCV = hepatitis C virus.

a Generally does not occur in the absence of immunosuppression and whose presence suggests a severe alteration in host immunity.

b Can occur in patients without recognized forms of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity.

c Published data are currently lacking, but expert opinion believes that risk is likely elevated in the setting of biologic therapy.

Source: Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis. 2015;74(12):2107-16.

Additional infections may be considered to be exclusionary and to require discontinuation of IP according to the judgment of the Investigator. Investigators can also exercise discretion in recording opportunistic infections as AESIs that are not specified in Appendix A.

APPENDIX B GUIDANCE FOR ANAPHYLAXIS DIAGNOSIS

The National Institute of Allergy and Infectious Disease (NIAID) and Food and Allergy Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories). Their clinical criteria for diagnosing anaphylaxis are:

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 lipstongueuvula)

   AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person’s baseline.

Reference

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

APPENDIX C INVESTIGATOR'S AGREEMENT

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study VIB0551.P3.S2 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by International Council for Harmonisation E6(R2)
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each subject's participation and all data required by the protocol

Name	**Title**	**Institution**
Signature		**Date**

APPENDIX D IGG4-RD FLARE EVALUATION AND CRITERIA

IGG4-RD FLARE EVALUATION AND CRITERIA

Investigational Product	Inebilizumab
Protocol Number	VIB0551.P3.S2
Version	1.0
Version Date	2-Oct-2020

TABLE OF CONTENTS

1 PURPOSE

This document serves two purposes:

- Provide guidance to the investigator regarding information to be entered into the electronic case report form(s) (eCRFs) related to flare assessments. This guidance is also anticipated to be useful to members of the study Adjudication Committee, who will review the information provided by the investigator when evaluating potential flares.

- Establish clear and objective criteria, for each organ or site affected by IgG4-RD, for diagnosis of an IgG4-RD flare for the purpose of this clinical study. The same criteria are used by investigators and AC members for diagnosis of flares.

This document is *not* intended to specify or limit which assessments should be conducted by the investigator and which results should be considered when evaluating a potential flare. Rather, this document specifies the flare-related data that will be entered into the eCRFs and how that data contributes to the diagnosis of flare.

2 FLARE DEFINITION

An IgG4-RD flare is defined as new or worsening signs and symptoms of IgG4-RD disease activity that meet one or more organ-specific flare criteria, and for which there is no clear alternative diagnosis or conflicting biopsy findings.

3 COLLECTION OF DATA RELATED TO FLARE EVALUATION

For each potential flare event, the investigator will provide the following information.

1. **Observation that led to initiation of evaluation for flare**
   - Patient-reported new/worsening symptoms
   - New/worsening physical exam (PE) finding
   - New/worsening laboratory finding
   - Incidental finding on imaging (not imaging triggered by symptom, PE or laboratory finding)
   - Other (describe)
2. **Organ-specific findings**

   Findings are to be recorded separately for every affected organ, even if flare criteria for that organ are not met. Data to be provided include symptoms, physical exam findings, laboratory findings, imaging findings, and biopsy results. In addition, the investigator's opinion whether the organ-specific criteria have been met will be documented, and a narrative providing the rationale for this organ-specific decision will be recorded. See Section 4 for complete organ-specific details.
3. **Investigator Narrative for the Entire Event**

   This free-text 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 results (including fine needle biopsy) collected for the evaluation of this event and should refer to historical data to establish the new/worsening nature of the disease manifestations. The descriptions must be detailed enough to understand the findings and the investigator's interpretation of them. The narrative must describe findings in every involved organ (for which data are also recorded on the organ-specific criteria pages, above).

   The narrative must NOT include any information regarding treatment of the event, response to treatment, or the investigator's decision whether the event met protocol-defined flare criteria.
4. **Treatment**

   If the event was treated, the details of the medical treatment(s) or procedure(s) will be recorded. Categories of treatment to be recorded include:
   - Glucocorticoids
   - Supportive therapy eg, pancreatic enzyme replacement, bile acid sequestrant, artificial saliva/lubricant
   - Immunosuppression other than glucocorticoids
   - Surgical intervention or other procedural intervention (eg, stenting)

5. **Outcome of treatment**

   Outcome of treatment for the event will be recorded as follows:

   - Returned to pre-flare baseline
   - Improved but not completely returned to pre-flare baseline
   - Neither worsened nor improved over pre-flare baseline
   - Flare activity worsened compared to pre-flare baseline
   - Flare activity resolved with sequela (resultant organ damage compared to pre-flare baseline)

4 ORGAN-SPECIFIC FLARE CRITERIA

The following sections describe information to be collected from the investigator regarding organ-specific symptoms and findings, flare criteria, and opinion and decisions regarding the event. This information is presented in the form of a questionnaire which will be recapitulated in a similar manner for entry of data in the eCRFs. The investigator will be required to complete assessments and data entry for those organs(s)/site(s) that are suspected of being involved in the event (ie, those with symptoms or other findings that lead to suspicion of flare), regardless whether flare criteria are deemed to have been met. The investigator is not required to perform assessments or enter data for organs/sites for which no suspicion of involvement exists.

4.1 Pachymeninges

Symptoms and Findings

Symptom(s)	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with pachymeningeal flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Headache			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with pachymeningeal flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
CN palsy, neurologic abnormalities consistent with radiculomyelopathy			
Other (describe)			
None			
Laboratory findings consistent with pachymeningeal flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
CSF pleocytosis			
CSF increased protein			
Other (describe)			
None			
Imaging of pachymeninges			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Meningeal enhancement or thickening			
Other (describe)			
None			
Biopsy results consistent with pachymeningeal flare			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			

Symptom(s)	Observed (✓)	New onset or worsening (N/W)	Description
Biopsy consistent with pachymeningeal flare			
Biopsy not consistent with pachymeningeal flare			

Criteria for Pachymeningitis Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present: 1 and either 2a OR 2b		
1. New or worsening symptom or PE finding consistent with IgG4-RD pachymeningitis		
2. EITHER:		
a. CSF 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 or is not having a pachymeningitis disease flare?

4.2 Pituitary Gland

Symptoms and Findings

Symptom(s)	Observed (✓)	New onset or worsening (N/W)	Descriptions
Symptoms consistent with pituitary flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Visual field abnormalities, headache, symptoms consistent with anterior or posterior pituitary endocrine failure			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with pituitary flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
CN palsy, visual field abnormalities			
Other (describe)			
None			
Laboratory findings consistent with pituitary flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Pituitary endocrine dysfunction			
Other (describe)			
None			
Imaging of pituitary gland			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Pituitary mass or enhancement			
Other (describe)			
None			
Biopsy results consistent with pituitary flare			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			

Symptom(s)	Observed (✓)	New onset or worsening (N/W)	Descriptions
Biopsy consistent with pituitary gland flare			
Biopsy not consistent with pituitary gland flare			

Criterion for Pituitary Gland Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present: at least one of the following		
EITHER New or worsening anterior/posterior pituitary endocrine dysfunction in patient with known pituitary disease 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 or is not having a pituitary gland disease flare?

4.3 Orbits

Symptoms and Findings

Symptom(s) or Finding(s)	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with flare in orbits:			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Diplopia, proptosis, foreign body sensation, 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			
PE findings consistent with orbital flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
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 of orbits			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Compatible with orbital disease (enlargement of extra-ocular muscles, enlargement of optic nerve including abnormalities of retrobulbar space or within cavernous sinus)			
Other (describe)			
None			

Symptom(s) or Finding(s)	Observed (✓)	New onset or worsening (N/W)	Description
Biopsy results consistent with orbital flare			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			
Biopsy consistent with orbital flare			
Biopsy not consistent with orbital flare			

Criterion for Orbital Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present: at least one of the following		
EITHER New or worsening symptom or PE 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 or is not having an orbital disease flare?

4.4 Lacrimal Glands

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with flare in lacrimal glands			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Lacrimal gland discomfort, pain or swelling; redness of the eye, excessive tearing; eyelid crusting; blurred vision			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with lacrimal gland flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Lacrimal gland swelling/mass			
Other (describe)			
None			
Imaging of lacrimal gland			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Consistent with lacrimal gland swelling			
Other (describe)			
None			
Biopsy results consistent with lacrimal gland flare			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			
Biopsy consistent with lacrimal gland flare			
Biopsy not consistent with lacrimal gland flare			

Criterion for Lacrimal Glands Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
New or worsening lacrimal gland enlargement/mass on PE 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 or is not having a lacrimal gland disease flare?

4.5 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 (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Pain orswelling of gland(s)			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with salivary gland flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Salivary gland swelling or tenderness			
Other (describe)			
None			
Imaging of salivary gland			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Compatible with salivary gland swelling			
Other (describe)			
None			
Biopsy results consistent with salivary gland flare			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			
Biopsy consistent with salivary gland flare			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Biopsy not consistent with salivary gland flare			

Criterion for Salivary Gland Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
New or worsening salivary gland enlargement or tenderness on PE or new or worsening 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 or is not having a salivary gland disease flare?

4.6 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 (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Subject reported swelling			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with flare in lymph node(s)			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Lymphadenopathy (specify localized or diffuse			
Other (describe)			
None			
Imaging of lymphadenopathy (localized or diffuse)			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Consistent with lymphadenopathy			
Other (describe)			
None			
Biopsy results consistent with lymph node flare			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			
Biopsy consistent with lymph node flare			
Biopsy not consistent with lymph node flare			

Criterion for Lymph Node Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present: at least one of the following		
In a patient with concurrent IgG4 disease in another organ: Multiple enlarged nodes (primarily nontender) by PE 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 (primarily nontender) by PE 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 or is not having a lymph node disease flare?

4.7 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 (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Dyspnea at rest or with exertion, cough			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with lung flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
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 (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
New or worsening pulmonary function test abnormalities consistent with lung flare			
Other (describe)			
None			
Imaging of lungs			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Pulmonary nodules or mass and/or pulmonary infiltrate/ground glass opacities consistent with interstitial pneumonia and/or pulmonary fibrosis and/or pleural effusion or pleural thickening and/or peribronchovascular and septal thickening and/or paravertebral mass, paravertebral band-like soft tissue in thorax			
Other (describe)			
None			
Biopsy results consistent with lung flare			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			
Biopsy consistent with lung flare			
Biopsy not consistent with lung flare			

Criterion 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 or is not having a lung disease flare?

4.8 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 (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Pain, palpable mass			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with aorta & large blood vessels flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Palpable arterial mass, especially if pulsatile, or bruit			
Other (describe)			
None			
Imaging of aorta & large blood vessels			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Consistent with aneurysm, dissection, thickening/enhancement of vessel wall or other vessel abnormality			
Other (describe)			
None			
Biopsy results consistent with aorta/large blood vessel flare			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			
Biopsy consistent with aorta/large blood vessel flare			
Biopsy not consistent with aorta/large blood vessel flare			

Criterion for Aorta & Large Blood Vessel Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present: At least one of the following		
Either New or worsening aortic or other vessel wall thickening or other evidence of aortitis (dissection, aneurysm) by imaging OR		
Demonstration of new or worsening 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 or is not having an aorta/large blood vessel disease flare?

4.9 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 (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Pain (eg, flank, back, thighs, abdominal, other including chronic pain), leg edema, dyspnea, cough			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with retroperitoneum, mediastinum & mesentery flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
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 estimated glomerular filtration rate (eGFR)			
Other (describe)			
None			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Imaging of retroperitoneum, mediastinum & mesentery			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Finding of mass lesion, ureteral stenosis or hydronephrosis, findings consistent with superior vena cava syndrome, other evidence of inflammation in retroperitoneum typically with 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 not done, unreadable, or report unavailable			
Biopsy consistent with retroperitoneum, mediastinum & mesentery flare			
Biopsy not consistent with retroperitoneum, mediastinum & mesentery flare			

Criterion for Flare in Retroperitoneum, Mediastinum & Mesentery Vessels

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present: At least one of the following		
EITHER New or worsening imaging evidence of involvement of retroperitoneum, mediastinum and/or mesentery OR		
Tissue confirmation at time of surgery or intervention (stenting) that confirms new or worsening 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 & Mesentery Vessels

☐ Yes

☐ No

Why do you believe this patient is or is not having a retroperitoneum/mediastinum/mesentery vessel disease flare?

4.10 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 pancreas/common bile duct			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Pain (eg, flank, back, abdominal), weight loss			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with flare of pancreas/common bile duct			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Abdominal tenderness, jaundice, palpable mass, weight loss			
Other (describe)			
None			
Laboratory findings consistent with flare of pancreas/common bile duct			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Elevated bilirubin, alk phos, GGT, amylase and/or lipase			
Other, including low fecal elastase, high glucose/HbA1C (describe)			
None			
Imaging of pancreas/common bile duct			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Consistent with pancreatic mass or diffuse pancreatic enlargement with loss of lobulations, diffuse pancreatic enlargement, pseudocapsule, pancreatic duct stricture, common bile duct abnormality			
Other (describe)			
None			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Biopsy results consistent flare of pancreas/common bile duct			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			
Biopsy consistent with pancreatic/common bile duct flare			
Biopsy not consistent with pancreatic/common bile duct flare			

Criterion 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 PE finding AND new or worsening laboratory finding consistent with flare in disease of pancreas/common bile duct OR		
Imaging or endoscopic finding that confirms new or worsening involvement of pancreas/common bile duct		
In a patient with no prior history of IgG4-related autoimmune pancreatitis:		
New symptom, PE finding and/or laboratory finding consistent with involvement of the pancreas/common bile duct, AND EITHER		
New imaging or endoscopic finding that confirms involvement of the pancreas/common bile duct, 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 or is not having a pancreas/common bile duct disease flare?

4.11 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 ducts/biliary tree			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Itching, abdominal pain, right upper quadrant pain			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with flare of bile ducts/biliary tree			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Abdominal tenderness, jaundice, right upper quadrant fullness			
Other (describe)			
None			
Laboratory findings consistent with flare of bile ducts/biliary tree			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Elevated bilirubin, ALT/AST, alkaline phosphatase, GGT			
Other (describe)			
None			
Imaging of bile ducts/biliary tree			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Thickening, mass, strictures, dilatation of extra-hepatic and/or intrahepatic bile ducts			
Other (describe)			
None			
Biopsy results consistent with bile ducts/biliary tree flare			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Biopsy of liver or biliary tree consistent with bile duct/biliary tree flare			
Biopsy not consistent with bile duct/biliary tree flare			

Criterion for Flare in Bile Ducts/Biliary Tree

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
In a patient with a prior history of IgG4-related sclerosing cholangitis, EITHER:		
New or worsening laboratory finding consistent with biliary tree flare OR		
New or worsening imaging or endoscopic finding that confirms worsening involvement of bile ducts/biliary tree		
In a patient with no prior history of IgG4-related sclerosing cholangitis:		
New laboratory finding consistent with biliary tree flare, AND		
Imaging or endoscopic finding that confirms involvement of the bile ducts/biliary tree		
Required to be absent:		
Alternative diagnosis or inconsistent biopsy findings		

Investigator Conclusion – Flare in Bile Ducts/Biliary Tree

☐ Yes
☐ No

Why do you believe this patient is or is not having a biliary tree disease flare?

4.12 Kidney

Kidney flare is specifically intrinsic renal disease or ureteropelvic junction (UPJ) 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 (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Fatigue, mental status changes			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with kidney flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Edema			
Other (describe)			
None			
Laboratory findings consistent with kidney flare			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Elevated creatinine, decreased eGFR, hematuria or proteinuria			
Other, including hypocomplementemia (describe)			
None			
Imaging of kidneys			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Diffuse kidney enlargement, renal abnormality including, hypodense lesions in the renal cortex,renal atrophy, and/or 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 not done, unreadable, or report unavailable			
Biopsy consistent with kidney disease flare			
Biopsy not consistent with kidney disease flare			

Criterion for Kidney Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
In a patient with a prior history of IgG4-related renal 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 or is not having a kidney disease flare?

4.13 Skin

Symptoms and Findings

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Symptoms consistent with flare of skin disease			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Rash			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with flare of skin disease			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
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 not done, unreadable, or report unavailable			
Biopsy consistent with skin disease flare			
Biopsy not consistent with skin disease flare			

Criterion for Skin Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present:		
New or worsening IgG4-RD skin lesions from symptoms or PE **AND EITHER**		
Prior biopsy proven IgG4-related 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 or is not having a skin disease flare?

4.14 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: (pulldown menu)

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 (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Site dependent, describe			
Systemic/constitutional			
Other (describe)			
None			
PE findings consistent with flare of sclerotic/mass forming disease			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Site dependent, describe			
Other (describe)			
None			
Laboratory findings consistent with flare of sclerotic/mass forming disease			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Site dependent, describe			
Other (describe)			
None			
Imaging			**Describe (1) Each finding and (2) Why worsened from recent baseline (or new onset)**
Consistent with sclerotic/mass-forming disease			
Other (describe)			
None			
Biopsy results consistent with sclerotic/mass forming disease			**Describe tissue and reading**
Biopsy not done, unreadable, or report unavailable			
Biopsy consistent with sclerotic/mass forming disease flare			

Symptom(s) or Findings	Observed (✓)	New onset or worsening (N/W)	Description
Biopsy not consistent with sclerotic/mass forming disease flare			

Criterion for Sclerotic/Mass Forming Flare

Criteria for Flare	Present (✓)	Absent (✓)
Required to be present: At least one of the following		
EITHER New or worsening imaging result that confirms involvement (specify) OR		
Any new biopsy evidence of new or worsening 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 or is not having an "other" organ-specific disease flare?

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