1. Protocol

A Phase II, Single-Site, Open-Label Study of Zanubrutinib in Patients with IgG4-Related Disease

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2. Synopsis

Name of Investigational Product:	Zanubrutinib
Title of Study:	A Phase II, Single-Site, Open-Label Study of Zanubrutinib in Patients with IgG4-Related Disease
Number of Planned Subjects:	10
Phase of Development:	II
Length of Study:	All consented subjects will enter a screening period of up to 35 days. Eligible subjects with symptomatic IgG4-related disease affecting the submandibular and/or lacrimal glands with prior inadequate response to, or intolerance of, glucocorticoids, or who experience recurrent symptoms after previous treatment with glucocorticoids, will receive study drug (zanubrutinib) over a period of 24 weeks. Patients will return 8 weeks later for a final safety visit.
Primary Objective:	To demonstrate that zanubrutinib treatment reduces the volume of the submandibular and/or lacrimal glands on PET/MRI at week 24 compared to baseline.
Secondary Objectives:	To determine the effect of zanubrutinib on change in FDG avidity of the submandibular, parotid, and/or lacrimal glands on PET, changes in submandibular, parotid, and/or lacrimal gland architecture on MRI, changes in serum IgG4 level, plasmablast count, and regulatory B cell count, change in IgG4-RD responder index, changes in physician and patient global, FACIT-F fatigue score, visual analog scales for ocular and salivary symptoms, changes in laboratory values, and safety parameters including adverse events.
Study Design:	This will be a single-site, open-label study in patients with symptomatic IgG4-related disease affecting the submandibular and/or lacrimal glands with prior inadequate response to, or intolerance of, glucocorticoids, or who experience recurrent symptoms after previous treatment with glucocorticoids. All patients will receive zanubrutinib orally at a dose of 80mg BID for 24 weeks.

Main Criteria for Inclusion:	• Are men or women aged 18 to 85, inclusive, at the time of initial screening • Meet the 2019 ACR/EULAR Classification Criteria for IgG4-Related Disease • Have involvement of either the lacrimal gland(s) and/or the submandibular gland(s) • Have active symptoms from their enlarged submandibular or lacrimal gland • Have a prior inadequate response to, or intolerance of, glucocorticoids, or who experience recurrent symptoms after previous treatment with glucocorticoids • All women must test negative for pregnancy and agree to use a reliable method of birth control • No current treatment with immunosuppressive medications other than prednisone ≤40mg daily (or other glucocorticoid equivalent) with stable dosing for ≥28 days (glucocorticoids are permitted as above, but glucocorticoid use is not required to be eligible for the study)
Main Criteria for Exclusion:	• Unstable prescribed dose of glucocorticoids within 28 days prior to baseline • Any treatment with a synthetic DMARD including but not limited to hydroxychloroquine, methotrexate, leflunomide, or sulfasalazine within 28 days prior to baseline • Any treatment with a cytotoxic or immunosuppressive drug including but not limited to cyclophosphamide, mycophenolic acid, azathioprine, cyclosporine, sirolimus, or tacrolimus within 28 days prior to baseline • Any treatment with a BTK inhibitor within 6 months before baseline

	• Any treatment with a JAK inhibitor within 28 days prior to baseline • Use of biologic agents including infliximab, abatacept, or tocilizumab within 56 days prior to baseline • Use of a B cell depleting therapy (such as rituximab) within 12 months prior to baseline • A history of, or current, inflammatory or autoimmune disease (that could affect the interpretation of safety or efficacy outcomes) other than IgG4-related disease • Evidence of active tuberculosis, HIV, or hepatitis B or C infection • History of cancer other than non-melanoma skin cancer, cervical dysplasia or carcinoma in situ (cured >1 year), prostate cancer (cured >5 years), or colon cancer (cured >5 years)
Investigational Product, Dosage, and Mode of Administration:	Zanubrutinib will be given orally at a dose of 80mg twice daily.
Comparator, Dose, and Mode of Administration:	No comparator will be used.
Planned Duration of Treatment:	Zanubrutinib will be given over a 24-week period, starting at Baseline (Day 1).
Criteria for Evaluation:	Efficacy will be assessed through the change in submandibular and/or lacrimal gland volume and FDG avidity by PET/MRI
Evaluation Methods:	Imaging of the head and neck will be performed using positron emission magnetic resonance imaging at the PET/MRI suite at the Lucas Imaging Center at Stanford University. For positron emission tomography (PET) imaging, participants will be injected intravenously (IV) with 5 mCi (+/- 20%) or 185 MBq (+/- 20%) of 18F Fluorodeoxyglucose (18F FDG). Submandibular gland, lacrimal gland, parotid gland, and lymph node SUVmax will be assessed [2].

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A Phase II, Single-Site, Open-Label Study of Zanubrutinib in Patients with IgG4-Related Disease

4. Abbreviations and Definitions

Ab	Antibody
ACR	American College of Rheumatology
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activities of daily living
AE	Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AIP	Autoimmune pancreatitis
AL	Aggressive lymphoma
ALT	Alanine aminotransferase
ANA	Anti-nuclear autoantibody
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
AUC	Area under the concentration versus time curve
BGB-3111	Zanubrutinib
BID	Twice daily
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
BSA	Body surface area
CBC	Complete blood count
CIB	Clinical investigation brochure
CK	Creatinine kinase
CLL	Chronic lymphocytic leukemia
Clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician or other medical officer.

CNS	Central nervous system
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DMARDs	Disease modifying anti-rheumatic drugs
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
End of trial	End of trial is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last subject.
Enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
Enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethics Review Board
EULAR	European League Against Rheumatism
FACIT	Functional assessment of chronic illness therapy
FL	Follicular lymphoma
GCP	Good clinical practice: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
GI	Gastrointestinal
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBV	Hepatitis B virus
HCV Ab	Hepatitis C antibody
HCV	Hepatitis C virus
Hgb	Hemoglobin

HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.
ICF	Informed consent form
Ig	Immunoglobulin
IgG	Immunoglobulin G
IgG4	Immunoglobulin G subclass 4
IgG4-RD	IgG4-related disease
IL	Interleukin
Informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IP	Investigational product
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
LASIK	Laser-assisted in situ keratomileusis
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MCL	Mantle cell lymphoma
MTD	Maximal tolerated dose
MZL	Marginal zone lymphoma
NOAEL	No-observed-adverse-effect level
NSAIDs	Non-steroidal anti-inflammatory drugs
OS	Overall survival

PK	Pharmacokinetic
PLT	Platelet
PR	Partial response
PRO	Patient-reported outcome
QD	Once daily
Q2W	Every 2 weeks
RBC	Red blood cells
Re-screen	To screen a subject who was previously declared a screen failure for the same study
RF	Rheumatoid factor
R/R	Relapsed or refractory
RR	Response rate
SAE	Serious adverse event: any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
SC	Subcutaneous
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures. For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SD	Standard deviation
SEM	Standard error of the mean
SJC	Swollen joints count
SS	Sjogren's syndrome
SS-A	Sjogren's syndrome antigen A. Also known as anti-Ro; autoantibody associated with Sjogren's syndrome
SS-B	Sjogren's syndrome antigen B. Also known as anti-La; autoantibody associated with Sjogren's syndrome
TB	Tuberculosis
TEAEs	Treatment emergent adverse events
TJC	Tender joints count
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
U/S	Ultrasound
v	Version

VAS	Visual analog scale
WBC	White blood cell

5. Introduction

5.1. Zanubrutinib Background

Zanubrutinib (also known as BGB-3111) is a novel, irreversible, second-generation Bruton's tyrosine kinase (BTK) inhibitor with great potency and selectivity. Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies and autoimmune disease. Ibrutinib (PCI-32765) is a first-in-class, orally active inhibitor of BTK that covalently binds to the cysteine Cys-481 of BTK, inhibiting its autophosphorylation at Tyr-223, resulting in irreversible inactivation of the kinase. Only 9 other kinases in the human genome, including ITK, EGFR, and JAK3, among others, contain this similar cysteine residue. In both biochemical and cellular assays, zanubrutinib has demonstrated potent BTK inhibition activity. Zanubrutinib is more selective than ibrutinib against off-target kinases, including EGFR, JAK3, HER2, TEC, ITK, and others. Furthermore, zanubrutinib has favorable PK properties with excellent oral bioavailability and rapid clearance in rodents and dogs. Zanubrutinib has also demonstrated better antitumor activity than ibrutinib in human MCL and DLBCL xenograft models. Unlike ibrutinib, zanubrutinib has not been shown to interfere with the anti-CD20 antibody-induced ADCC effect.

5.2. IgG4-Related Disease Background

IgG4-related disease (IgG4-RD) is a systemic, immune-mediated disease that manifests as inflammatory, fibrotic, tumor-like lesions that can form throughout the body [1]. It was first described in Japan in 2001, when patients with sclerosing pancreatitis were found to have elevated serum levels of IgG4 [2]. It was subsequently discovered that many patients presenting with enlarged, fibrotic tissues elsewhere in the body, including most commonly the submandibular glands, lacrimal glands, and lymph nodes, all shared a common tissue histopathology. It is now understood that the characteristic pathologic findings of IgG4-RD include a lymphoplasmacytic infiltrate comprised of IgG4+ plasma cells, storiform fibrosis, and obliterative phlebitis [3]. In addition, the majority (~80%) of IgG4-RD patients have elevated serum IgG4 [4, 5] and elevated peripheral blood plasmablasts [6]. Clinically, IgG4-RD has a large spectrum of severity depending on the organs or tissues involved, ranging from sicca symptoms and discomfort from enlarged glands to potentially life-threatening aortitis, pancreatitis, pachymeningitis, or retroperitoneal fibrosis. Patients typically respond well to glucocorticoid treatment, but the majority will flare within one year if additional immunosuppressive medications are not initiated [7]. This, in addition to the significant side effects from glucocorticoids [8] and the contraindication to their use in some patients, highlights the importance of developing alternative approaches. There is a significant unmet need for safe, effective therapies to treat and maintain remission in patients with IgG4-RD.

5.3. Known and Potential Risks and Benefits of Zanubrutinib

Through the date of 16 September 2018, approximately 1200 patients have received zanubrutinib in B-cell malignancies either as monotherapy or in combination with another agent. Safety and efficacy data are derived from this experience.

5.3.1. Known and Potential Risks of Zanubrutinib

5.3.1.1 Known Risks of Zanubrutinib

Hemorrhage

Serious and fatal hemorrhagic events have occurred in patients with hematological malignancies treated with zanubrutinib monotherapy. All hemorrhagic events were reported in 46.3% of patients with hematological malignancies in the combined database of 671 patients who were treated with zanubrutinib monotherapy, with the majority (44.1%) consisting of Grade 1 and 2 events. Petechiae, purpura, and contusion were reported in 28.2% of the patients, and all of the petechiae, purpura, and contusion events were Grades 1 and 2, except for one. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 2.2% of these patients.

The mechanism for the bleeding events is not well understood.

Zanubrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding zanubrutinib for 3-7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

5.3.1.2 Potential Risks of Zanubrutinib

Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred in patients with hematological malignancies treated with zanubrutinib monotherapy. Infections have occurred in 66.6% of patients with hematological malignancies in the combined database of 671 patients who were treated with zanubrutinib monotherapy. Grade 3 or higher infections occurred in 21.3% of these patients. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred. Patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, are pre-disposed to opportunistic infections as a result of disease and treatment-related factors. In patients with a high risk for opportunistic infections, including Pneumocystis jirovecii pneumonia (PJP), prophylaxis should be considered as per institutional standards.

Consider prophylaxis according to standard of care in patients who are at increased risk for infections. Monitor patients for signs and symptoms of infection and treat appropriately.

Cytopenias

Cytopenias including neutropenia, thrombocytopenia, and anemia based on laboratory measurements were reported in 41.1%, 39.3%, and 23.4%, respectively, in patients with hematologic malignancies in the combined database of 671 patients who were treated with zanubrutinib monotherapy. Grade 3 or 4 events occurred in 19.8%, 8.5%, and 6.5% of these patients with neutropenia, thrombocytopenia, and anemia, respectively.

Monitor complete blood counts during treatment.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma have occurred in 7.9% of patients with hematological malignancies in the combined database of 671 patients who were treated with zanubrutinib monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma, 3.6%, and squamous cell carcinoma of skin, 1.9%).

Advise patients to use sun protection.

Atrial Fibrillation and Flutter

Atrial fibrillation and atrial flutter have occurred in 1.8% of patients with hematological malignancies in the combined database of 671 patients who were treated with zanubrutinib monotherapy, particularly in patients with cardiac risk factors, hypertension, and acute infections.

Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Toxic Epidermal Necrolysis

One case (0.1%) of toxic epidermal necrolysis was reported in a patient receiving zanubrutinib treatment along with febuxostat which is known to be associated with toxic epidermal necrolysis and severe hypersensitivity reaction in the combined database of 671 patients.

Severe skin reactions will be closely monitored.

Death

Of the 44 fatal events (in 40 patients) reported as of 16 September 2018 in the zanubrutinib monotherapy studies, 9 fatal events were assessed by the investigator as related to study drug (pneumonia [in 3 patients], arthritis bacterial, toxic epidermal necrolysis, death, cerebral haemorrhage, platelet count decreased, and 1 event with an unreported term from a blinded study).

In the zanubrutinib combination studies (BGB-3111-GA101, BGB-3111-213, and BGB-3111-A317-Study_001), 9 fatal events (renal impairment, skin squamous cell carcinoma metastatic, dyspnoea, pleural effusion, abdominal pain and completed suicide [same patient], abdominal pain, multiple organ dysfunction syndrome, and sepsis), in 8 patients, had been reported as of 16 September 2018; none of these fatal events were assessed by the investigator as related to zanubrutinib or either study treatment (zanubrutinib or tislelizumab in Study BGB-3111-A317-Study_001).

5.3.2. Reproductive and Developmental Toxicity

The risk of fertility impairment was considered to be low as zanubrutinib had no impact on fertility or early embryonic development to implantation in male or female rats at doses up to 300 mg/kg or

histopathological changes in reproductive organs in rats or dogs in up to 91-day repeat-dose studies.

No apparent treatment-related maternal or embryo-fetal toxicities were noted at doses up to 150 mg/kg/day in both rats and rabbits; no apparent teratogenicity was noted in the rabbit fetus at any dose levels; and the only teratogenicity included one 3-chambered heart (0.3%), one 2-chambered heart (0.3%), and five 3-chambered hearts (1.5%) noted in rat fetuses at doses of 30, 75, and 150 mg/kg/day, respectively.

No pre- and post-natal developmental toxicity was noted in the maternal or offspring rats, with the exception that an increased incidence (26% to 42%) and severity of multiple ophthalmic lesions were noted in the treated animals as compared to the concurrent control group (26%).

5.3.3. Known and Potential Benefits of Zanubrutinib

Nothing is known about the potential benefits of zanubrutinib therapy for IgG4-RD, although a scientific rationale does exist for hypothesizing that this drug may improve the signs and symptoms of this disease.

5.4. Rationale and Justification for the Study

The pathogenesis of IgG4-RD is incompletely understood, but based on elevations in serum IgG4 and plasmablast levels, as well as the significant improvement seen with B cell depleting and inhibiting therapies [9, 10], B cells are believed to play an important role [11]. Follicular helper T cells [12, 13] and CD4+ cytotoxic T cells [14] are also expanded in patients with IgG4-RD, and their numbers correlate with plasmablast levels, suggesting they may be involved in disease pathogenesis. It remains unknown whether these T cells promote B cell activation, or conversely, whether B cells may act as antigen presenting cells to the T cells. In addition, several groups have identified potential autoantibodies in IgG4-RD [15, 16], which may provide further support for therapies directed at the B cell compartment. Ultimately, given the success of drugs like rituximab, targeting B cells with novel agents that are safer and more easily titrated holds great promise.

Bruton's tyrosine kinase (BTK) activity, downstream of B cell receptor (BCR) signaling, contributes to B cell survival through activation of NF-kB [17-19]. In humans, BTK deficiency results in the B cell immunodeficiency syndrome X-linked agammaglobulinemia (XLA) [20]. In mice, overexpression of BTK in B cells results in spontaneous germinal center formation, plasma cell differentiation, and the production of autoantibodies, similar to human autoimmune diseases such as systemic lupus erythematosus and Sjogren's syndrome [21]. Furthermore, BTK overexpressing B cells are resistant to apoptosis and to elimination when self-reactive. In IgG4-RD patients, BTK gene expression is elevated in lacrimal glands compared to healthy controls [22].

The evidence suggests BTK plays a critical role in the development and propagation of a number of autoimmune diseases, and this likely includes IgG4-RD. Currently, there is a paucity of disease modifying treatments for IgG4-RD. The patient population that will be treated in this study has symptomatic enlargement of the submandibular and/or lacrimal glands and has failed a course of glucocorticoids (or was intolerant to glucocorticoid use). These patients require treatment for their symptoms (pain/pressue, dryness, headaches, disfigurement) and to potentially help prevent the disease from spreading to additional sites in the body. The standard of care treatments, including moderate to high doses of glucocorticoids, DMARDs such as azathioprine, and rituximab all have

potential toxicities and side effects. Given the critical role of BTK in B cell activation and survival of autoreactive B cells, BTK inhibition is a compelling and rational strategy for the treatment of IgG4-RD, and may provide a much needed alternative therapy for these patients.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to demonstrate that zanubrutinib treatment reduces the volume of the submandibular and/or lacrimal glands on PET/MRI at Week 24 compared to Baseline.

6.2. Secondary Objective

The secondary objectives of this study are to determine the effect of zanubrutinib on:

- Change in FDG avidity (SUVmax) [23] of submandibular and/or lacrimal glands on PET from Baseline to Week 24
- Change in metabolic lesion volume (MLV) of submandibular and/or lacrimal glands on PET from Baseline to Week 24
- Change in total lesion glycolysis (TLG) of submandibular and/or lacrimal glands on PET from Baseline to Week 24
- Change in submandibular glands on MRI (parenchymal architecture scored 0 to 4 and sialography scored 0 to 4) from Baseline to Week 24
- Change in parotid glands on MRI (parenchymal architecture scored 0 to 4 and sialography scored 0 to 4) from Baseline to Week 24
- Change in lacrimal glands on MRI (parenchymal architecture scored 0 to 4 and sialography scored 0 to 4) from Baseline to Week 24
- Change in the volume of the parotid glands on PET/MRI from Baseline to Week 24
- Change in the volume of the submandibular glands on PET/MRI from Baseline to Week 12
- Change in the volume of the lacrimal glands on PET/MRI from Baseline to Week 12
- Change in the volume of the parotid glands on PET/MRI from Baseline to Week 12
- Change in FDG avidity (SUVmax) of submandibular and/or lacrimal glands on PET from Baseline to Week 12
- Change in metabolic lesion volume (MLV) of submandibular and/or lacrimal glands on PET from Baseline to Week 12
- Change in total lesion glycolysis (TLG) of submandibular and/or lacrimal glands on PET from Baseline to Week 12
- Change in submandibular glands on MRI (parenchymal architecture scored 0 to 4 and sialography scored 0 to 4) from Baseline to Week 12
- Change in parotid glands on MRI (parenchymal architecture scored 0 to 4 and sialography scored 0 to 4) from Baseline to Week 12
- Change in lacrimal glands on MRI (parenchymal architecture scored 0 to 4 and sialography scored 0 to 4) from Baseline to Week 12
- Change in serum IgG4 level from Baseline to Week 24
- Change in serum IgG4 level from Baseline to Week 12
- Change in plasmablast count from Baseline to Week 24
- Change in plasmablast count from Baseline to Week 12
- Change in absolute regulatory B cell count from Baseline to Week 24
- Change in absolute regulatory B cell count from Baseline to Week 12

- Change in the IgG4-RD Responder Index [24-26] from Baseline to Week 24
- Change in the IgG4-RD Responder Index from Baseline to Week 12
- Proportion of patients with no disease flares between Week 12 and Week 24
- Change in total salivary grey scale ultrasound score (TUS) from Baseline to Week 24
- Change in total salivary grey scale ultrasound score (TUS) from Baseline to Week 12
- Change in highest score among the salivary glands for the grey scale ultrasound score (HSUS) from Baseline to Week 24
- Change in highest score among the salivary glands for the grey scale ultrasound score (HSUS) from Baseline to Week 12
- Change in glandular inflammation total ultrasound score (iTUS) from Baseline to Week 24
- Change in glandular inflammation total ultrasound score (iTUS) from Baseline to Week 12
- Change in highest score among the salivary glands for the glandular inflammation ultrasound score (iHSUS) from Baseline to Week 24
- Change in highest score among the salivary glands for the glandular inflammation ultrasound score (iHSUS) from Baseline to Week 12
- Change in physician global assessment of disease from Baseline to Week 24
- Change in physician global assessment of disease from Baseline to Week 12
- Change in patient global assessment of disease from Baseline to Week 24
- Change in patient global assessment of disease from Baseline to Week 12
- Change in VAS for ocular symptoms from Baseline to Week 24
- Change in VAS for ocular symptoms from Baseline to Week 12
- Change in VAS for salivary symptoms from Baseline to Week 24
- Change in VAS for salivary symptoms from Baseline to Week 12
- Change in FACIT-F fatigue score from Baseline to Week 24
- Change in FACIT-F fatigue score from Baseline to Week 12
- Change in RAND Short Form-36 from Baseline to Week 24
- Change in RAND Short Form-36 from Baseline to Week 12
- Change in labs: C3, C4, total IgG, IgE, IgG1, ESR, and CRP from Baseline to Week 24
- Change in labs: C3, C4, total IgG, IgE, IgG1, ESR, and CRP from Baseline to Week 12
- Safety parameters including adverse events and abnormal laboratory results

7. Investigational Plan

7.1. Summary of Study Design

This study is a single-site, open-label study in subjects with histopathologically confirmed, symptomatic IgG4-related disease affecting the submandibular and/or lacrimal glands with prior inadequate response to, or intolerance of, glucocorticoids, or who experience recurrent symptoms after previous treatment with glucocorticoids, being conducted at the Stanford University rheumatology clinic. Ten subjects will be included in the study. All eligible subjects will receive zanubrutinib 80mg BID over a period of 24 weeks and will be followed up for an additional 8 weeks after the last dose. Patients are not required to be taking glucocorticoids, but those patients on prednisone ≤40mg daily (or other glucocorticoid equivalent) will undergo a scheduled taper over the first 8 weeks (see Table 2 for prednisone taper schedule).

After the Screening visits, consenting patients will be seen in clinic on day 1 (Baseline) and return to clinic on Weeks 2, 4, 8, 12, 16, 20, 24, and 32. For the complete schedule of events, see Section 15: Study Schedule.

At Screening (up to 35 days before baseline), a complete medical history, physical exam, vital signs, clinical laboratory tests [comprehensive metabolic panel, complete blood count, IgG subclasses (including IgG4), ANA, RF, anti-Ro, anti-La, serum pregnancy test for females, HIV serologies, hepatitis B serologies, hepatitis C serologies, quantiFERON test for tuberculosis], chest x-ray, and electrocardiogram will be conducted.

At all subsequent visits, at a minimum, a complete physical exam, vital signs, focused history, and clinical laboratory tests (comprehensive metabolic panel, complete blood count, and urine pregnancy test for females) will be conducted.

At Baseline, Week 4, Week 12, and Week 24 additional labs including total IgG, IgG subclasses (including IgG4), B cell phenotyping (including plasmablast number), complement levels (C3, C4), ESR, and CRP will be collected.

At, or just prior to, Baseline, Week 12, and Week 24, PET/MRI and salivary gland ultrasound will be performed.

At Week 12 and Week 24 an electrocardiogram will be obtained.

At each visit, patients will record their global assessment of disease as well as visual analog scales for ocular and salivary symptoms and the FACIT-F for fatigue and RAND SF-36, and the physician will calculate the IgG4-RD Responder Index score as well as physician global assessment of disease.

In addition, safety will be assessed for all patients.

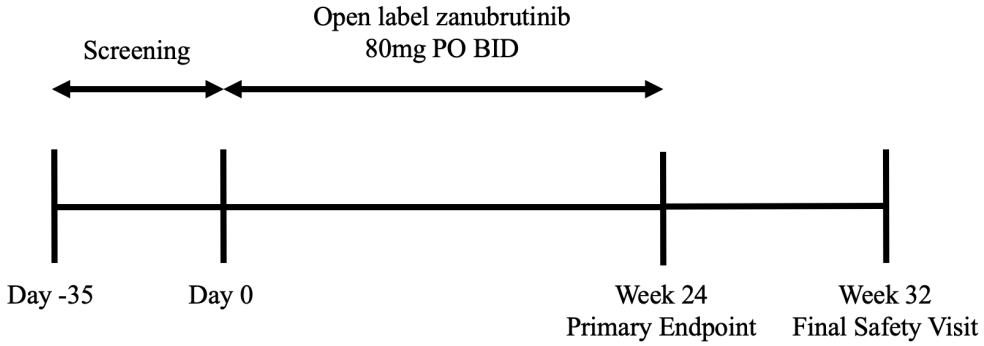

Figure 1 Study design

7.2. Discussion of Design and Control

IgG4-RD was selected as a relevant patient population based on the mechanism of action of zanubrutinib and the current understanding of the pathogenesis of the disease. An open-label design was chosen based on practical considerations regarding the number of patients that could be recruited. Although open-label studies are subject to bias, objective primary endpoints were intentionally chosen to minimize this concern.

8. Study Population

8.1. Criteria for Enrollment

Eligibility of subjects for study enrollment will be based on the results of a screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiogram (ECG).

Posteroanterior (PA) and lateral chest x-rays will be completed at screening, unless obtained within 90 days prior to initial screening and the x-rays and/or report are available for investigator review. Variations on the chest x-ray view requirements will only be permitted if the parameters are within local guidelines of care for standard tuberculosis (TB) screening.

The nature of any conditions present at the time of the physical examination and any preexisting conditions/medical/surgical history will be documented at screening.

Screening may occur up to 35 days before baseline.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once in certain situations. For example, the following subjects may be eligible for re-screening:

1. Subjects who had a transient condition(s) which no longer applies or for which the condition has been medically managed so that there is no longer a safety concern for trial participation.
2. Subjects whose previous prohibited treatments have since been discontinued and subsequently meet the specified time frame described in the inclusion/exclusion criteria.
3. Subjects who have become eligible to enroll in the study as the result of a protocol Amendment.

If re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new subject identification number. Chest x-rays and/or TB testing (including an interferon-gamma release assay) do not need to be repeated if completed within 90 days of the re-consent date, at the discretion of the investigator. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

8.1.1. Inclusion Criteria

Subjects are eligible for enrollment in the study only if they meet all of the following criteria:

- Have given written informed consent
- Are men or women aged 18 to 85, inclusive, at the time of initial screening
- All women (regardless of childbearing potential) must test negative for pregnancy at the time of screening (see Section 8.1.4. for more information about women of childbearing potential). Women must also agree to use a reliable method of birth control from screening until 12 weeks following last dose of study drug (adequate contraceptive measures include: intrauterine devices, hormonal contraceptives, complete sexual abstinence, or vasectomized partner), unless they are not of child-bearing potential as defined by meeting either of the following:

    - Are at least 6 weeks after bilateral oophorectomy, tubal ligation, or hysterectomy
    - Are postmenopausal, as defined by having had spontaneous amenorrhea for at least 12 months and a follicle-stimulating hormone level >40 mIU/mL at screening
- Meet the 2019 ACR/EULAR Classification Criteria for IgG4-Related Disease
- Have involvement of either the lacrimal gland(s) and/or the submandibular gland(s)
- Have symptoms from their enlarged submandibular and/or lacrimal glands including pain, dryness, headache, or vision changes
- Have had a prior inadequate response to, or intolerance of, glucocorticoids, or who experience recurrent symptoms after previous treatment with glucocorticoids
    - Inadequate response is defined as treatment with glucocorticoids with minimal or no improvement in symptoms, or an initial response with relapse upon stopping glucocorticoids
    - Intolerance of glucocorticoids is based on the investigator's discretion but includes events such as mood disturbances (severe lability and/or psychosis), poorly controlled diabetes, osteoporosis, and avascular necrosis.
- Are not receiving current treatment with immunosuppressive medications other than prednisone ≤40mg daily (or other glucocorticoid equivalent) with stable dosing for ≥28 days (glucocorticoids are permitted as above, but glucocorticoid use is not required to be eligible for the study)
- Are willing to undergo a scheduled glucocorticoid taper (including reducing to prednisone ≤40mg daily before Day -28) if they are on glucocorticoids per Table 2 in Section 9.7.1
- Have venous access sufficient to allow for blood sampling, as per the protocol
- Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

8.1.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria:

- Have previously been treated with a BTK inhibitor within 6 months before Baseline
- Have synthetic disease-modifying antirheumatic drug (DMARD) or immunosuppressive use as follows:
    - Treatment with synthetic DMARDs including but not limited to hydroxychloroquine, methotrexate, leflunomide, or sulfasalazine within 28 days prior to baseline or planned treatment during the study
    - Treatment with cytotoxic or immunosuppressive drugs including but not limited to cyclophosphamide, mycophenolic acid, azathioprine, cyclosporine, sirolimus, or tacrolimus within 28 days prior to screening or planned treatment during the study
    - Treatment with a janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, upadacitinib, or filgotinib) within 28 days prior to baseline or planned treatment with a JAK inhibitor during the study
- Have had treatment with biologic DMARDs as follows:
    - Treatment with etanercept, adalimumab, or anakinra within 28 days before baseline or planned treatment during the study
    - Treatment with infliximab, certolizumab pegol, golimumab, abatacept, or tocilizumab within 56 days before baseline or planned treatment during the study
    - Treatment with a B cell depleting agents including but not limited to rituximab, ocrelizumab, obinutuzumab, and obexelimab (XmAb5871) within 12 months before

baseline or planned treatment during the study
    - Treatment with a BAFF antagonist (such as belimumab or tabalumab) within 6 months before baseline or planned treatment during the study
    - Treatment with an IL-17 antagonist (such as secukinumab, ixekizumab, brodalumab) within 6 months before baseline or planned treatment during the study
    - Treatment with other biologic agents may be allowed at the discretion of the protocol director
- Are currently enrolled in a clinical trial involving an investigational product or off-label use of a drug, are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, or have received:
    - Any nonbiologic investigational product within 30 days or 5 half-lives (whichever is longer) of their baseline (Day 1) visit
    - Any biologic investigational product within 3 months or 5 half-lives (whichever is longer) of their baseline visit, or any leukocyte depleting agent within 12 months of baseline
- Have a prescribed dose >40 mg/day of oral prednisone (or equivalent) within 28 days before baseline, or plan to increase >40 mg/day during the study. (Stable prescriptions ≤40 mg/day are allowed.) Parenteral corticosteroids are not permitted within 28 days prior to baseline.
- Have received a live (attenuated) vaccine within 28 days prior to baseline or intend to receive one during the study
- Have clinically significant hematological abnormalities at screening, including: hemoglobin <9.0 g/dL, total platelet count <100,000 cells/uL, total white blood cell count <3000 cells/uL, neutrophil count <1200 cells/uL, or lymphocyte count <800 cells/uL. A repeat analysis is allowed per judgment of investigator before making a final determination of eligibility. The repeat laboratory test does not require a reconsent, as the result does not constitute a screen-fail until the clinically significant, out-of-range value is confirmed.
- Have abnormal liver function tests at screening, including: aspartate transaminase >2 times the upper limit of normal, alanine transaminase >2 times the upper limit of normal, total bilirubin >2 times the upper limit of normal, unless patient has a known history of Gilbert syndrome. A repeat analysis is allowed per judgment of the investigator before making a final determination of eligibility. The repeat laboratory test does not require a reconsent, as the result does not constitute a screen-fail until the clinically significant, out-of-range value is confirmed.
- Have an estimated glomerular filtration rate at screening <30 mL/min/1.73 m^2 by Modification of Diet in Renal Disease Study (MDRD) equation. A repeat analysis is allowed per judgment of the investigator before making a final determination of eligibility. The repeat laboratory test does not require a reconsent, as the result does not constitute a screen-fail until the clinically significant, out-of-range value is confirmed.
- Have an abnormality in the chest x-ray or 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study
- Have human immunodeficiency virus infection/acquired immunodeficiency syndrome (AIDS) or positive human immunodeficiency virus antibodies at screening
- Have evidence of active hepatitis C virus (HCV) infection. The HCV panel includes HCV antibody as well as quantitative HCV RNA by PCR if the patient is HCV antibody positive. Patients positive for HCV antibody, but negative for HCV RNA, must undergo monthly HCV RNA screening. Patients with HCV RNA ≥ 15 IU/mL should stop study drug and

antiviral therapy should be initiated. Resumption of study drug in patients whose HCV reactivation resolves should be discussed with, and approved by, the medical monitor and physicians with expertise in managing HCV infection. All patients with a history of hepatitis B and C viral infection and baseline negative PCR that develop elevations in liver function tests should be evaluated for viral hepatitis reactivation. The medical monitor should be informed of any suspected HBV or HCV reactivation. See Table 1 for a description of how the results for HCV testing at Screening relate to study eligibility.

- Have evidence of active hepatitis B virus (HBV) infection. The HBV panel includes HBsAg, HBcAb, and hepatitis B surface antibody (HBsAb). Patients positive for HBsAg and/or with detectable levels of HBV DNA are not eligible for the study. Patients who are HBcAb positive are also not eligible for the study. Subjects who are only HBsAb positive at screening (with a history of immunization) are permitted to enroll. All patients with a history of hepatitis B and C viral infection and baseline negative PCR that develop elevations in liver function tests should be evaluated for viral hepatitis reactivation.
- Have evidence of TB as documented by chest-x ray, medical history, physical examination or a positive interferon-gamma release assay (ie QuantiFERON®-TB Gold). If the interferon-gamma release assay is indeterminate, a retest is allowed, per investigator judgment. If the retest is also indeterminate, the subject will be excluded from the study. Subjects with chest x-rays obtained within 90 days prior to initial screening may be exempt from a screening chest x-ray if deemed medically appropriate in the judgment of the investigator. The images and/or written report must be available for investigator review and filed with the subject's records at the site. Image views must be as per above, unless in accordance with local standard of care for TB screening. Subjects with a history of latent TB must have documented evidence of having completed a full course of prophylactic treatment, have no known history of reexposure, and no evidence of active TB on chest x-ray, medical history or physical examination. These subjects are exempt from interferon-gamma release testing. Subjects with any history of active TB, whether treated or untreated, are excluded.
- Have any history of cancer except for skin basal or squamous cell carcinoma, cervical dysplasia or carcinoma in situ that has been treated and is considered cured >1 year prior to baseline, prostate cancer considered cured for >5 years with a normal prostate specific antigen, or colon cancer considered cured >5 years.
- Have a history of arrhythmia or underlying cardiac disease that could predispose to development of arrhythmia (including cardiomyopathy and/or coronary artery disease)
- Have a blood dyscrasia or are at increased risk of bleeding
- Have planned surgical procedures during the study
- Use of known strong or moderate CYP3A inducers or inhibitors within 3 days of Baseline
- Have known hypersensitivity or allergy to the study drug
- Have a history of, or current, inflammatory or autoimmune disease (that could affect the interpretation of safety or efficacy outcomes) other than IgG4-RD
- Are women who intend to become pregnant or breastfeed during any portion of the study
- Have a psychiatric disorder rendering the subject incapable of providing informed consent
- Have any condition that, in the opinion of the investigator, may compromise the safety of the subject in the study; confound the analysis of the data, render the subject unable to understand the nature, scope, and possible consequences of the study; or preclude the subject from following and completing the protocol

Table 1 Active Hepatitis B or Hepatitis C Infection (Detected Positive by Polymerase Chain Reaction)

Screening assessment	Meets inclusion criteria	To be excluded
HBV	HBsAg (-) and HBcAb (-)	HBsAg (+)
	HBsAg (-) and HBcAb (+) and HBV DNA "Not detected" *Perform monthly monitoring of HBV DNA*	HBsAg (-) and HBcAb (+) and HBV DNA detected
HCV	Antibody (-)	Antibody (+) and HCV RNA detected
	Antibody (+) and HCV RNA "Not detected" *Perform monthly monitoring of HCV RNA*	

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, viral hepatitis B; HCV, viral hepatitis C.

8.1.3. Rationale for Exclusion of Certain Study Candidates

Exclusion criteria were chosen to prevent conflict of interest in study participants and to exclude medical conditions, medication intolerance, and concomitant medication use that may constitute a risk for the subject and/or may confound the assessment of study endpoints.

8.1.4. Females of Childbearing Potential and Contraception

A woman is considered of childbearing potential (ie, fertile) after menarche and until becoming postmenopausal unless surgically sterilized. Surgical sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

- Contraception methods include the following:
- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation − Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation − Oral, injectable, implantable
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day before first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of study drug).

Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal,

postovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and, if used, this method must be used in combination with another acceptable method listed above.

If a woman of childbearing potential is using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must also be used.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

8.2. Discontinuation

The reason for, and date of, discontinuation will be collected for all subjects. All enrolled subjects who discontinue, regardless of whether or not they received investigational product, will have procedures performed as shown in the Study Schedule.

8.2.1. Discontinuation of Subjects

8.2.1.1. Subjects Inadvertently Enrolled

The criteria for enrollment must be followed explicitly. If the investigator identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the investigator will discuss with the DSMC and a decision will be made regarding continuation or removal.

8.2.1.2. Discontinuations from Investigational Product or from the Study

Subjects will be discontinued from study drug and/or from the study in the following circumstances:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Investigator decision:
    - The investigator decides that the subject should be discontinued from the study
    - If the subject, for any reason, requires protocol excluded treatment, discontinuation from the study drug should occur prior to introduction of the other agent (in some cases, the subject may continue in the study for the purpose of assessments without receiving further study drug)
- Subject decision:
    - The subject requests to be discontinued from the study

Following the investigator's determination that clinically significant event criteria have been met and the investigator's judgment of relatedness to the investigational product is documented, a decision will be made between the investigator and DSMC regarding subject discontinuation.

The nature of any conditions, clinical signs or symptoms, or abnormal laboratory values present at the time of discontinuation and any applicable follow-up procedures will be documented.

8.2.1.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit and these should be documented.

8.2.2. Discontinuation of the Study

The study will be discontinued if the protocol director or sponsor judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

9. Treatment

9.1. Treatment Materials and Supplies

9.1.1. Packaging and Labeling

Zanubrutinib will be supplied to the investigator. Clinical trial materials are manufactured in accordance with current Good Manufacturing Practices and labeled according to regulatory requirements. All study medication will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

Zanubrutinib 80mg capsules will be provided in a child-resistant, high-density polyethylene bottle with induction seal and bottle label. The contents of the label will be in accordance with all applicable local regulatory requirements. Zanubrutinib 80mg capsules are formulated as hard gelatin capsules with the same appearance.

Zanubrutinib drug product contains BGB-3111 active pharmaceutical ingredient, microcrystalline cellulose (VIVAPUR 102) as a filler, croscarmellose sodium (VIVASOL) as a disintegrant, sodium lauryl sulfate (Killiphor®SLS Fine) as a wetting agent, colloidal silica (AEROSIL200) as a glidant, and magnesium stearate (Ligamed MF-2-V) as a lubricant, all of which are standard compendial excipients (USP/Ph. Eur) and provided by qualified suppliers.

9.1.2. Handling and Storage

The study drug will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledging receipt of all study drug shipments. All study drug must be stored in a secure area, with access limited to the investigator and authorized study center personnel and kept under physical conditions that are consistent with study drug-specific requirements. The study drug must be kept at the temperature condition as specified on the labels.

Study drug bottles must be stored at room temperature 15ºC to 30ºC (59ºF to 86ºF). Study drug must be dispensed or administered according to procedures described herein. Only patients enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only sponsor authorized study center personnel may supply or administer study drug.

9.1.3. Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or guardian.

The investigator and/or study personnel will keep accurate records of the quantities of study drug dispensed and used by each patient. This information must be captured in the source document at each patient visit. The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the sponsor, the amount supplied, and/or the amount administered to and returned by patients, if applicable.

9.1.4. Disposal and Destruction

After completion of the study and after final drug inventory reconciliation by the monitor, the study site, upon sponsor's election, will destroy or return all unused study drug supplies to sponsor. The inventoried supplies can be destroyed on site or at the depot according to institutional policies after receiving prior written sponsor approval.

9.2. Treatment Administration

All subjects will be administered zanubrutinib 80mg orally twice daily (BID) over a period of 24 weeks starting on Baseline Day 1.

Zanubrutinib tablets are to be taken with or without food approximately 12 hours apart. Gastrointestinal tolerability may be better if given with food.

Patients may also be on glucocorticoids, which are not to exceed 40mg/day of prednisone (or its equivalent), and which will be tapered over a maximum of 10 weeks as per Table 2 in Section 9.7.1.

The investigator or designee is responsible for:

- Explaining the correct use of the investigational agent to the subject
- Verifying that instructions are followed properly
- Maintaining accurate records of investigational product dispensing and collection

Subjects will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

All clinical trial material provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the investigational products will be fully documented. Detailed records of the amounts of the investigational product received, dispensed and remaining at the end of the study will be maintained.

9.3. Rationale for Selection of Dose

The dose level and regimen planned for this study was selected based on analyses of BTK occupancy, PK/PD, safety, and efficacy from the Phase 1 BGB-3111-AU-003 study [27]. The dose of 80mg BID was considered optimal based on high BTK inhibition, low rates of adverse events, and potential for efficacy in this patient population.

9.4. Specific Restrictions/Requirements

Before beginning the study, all subjects will complete written, informed consent and baseline tests.

As the risk of zanubrutinib to the human fetus is unknown, all female subjects of child-bearing potential must agree to use a reliable method of birth control (ie, surgical sterilization, intrauterine devices, hormonal contraceptives, complete abstinence from sexual intercourse with men, or vasectomized partner) from screening to 12 weeks after last dose of study drug. Male subjects should use a reliable method of birth control (vasectomy, barrier contraception during intercourse

with female partners, or abstinence from sexual intercourse with women) from screening to 12 weeks after last dose of study drug.

9.5. Dose Modification for Toxicity

A dose reduction of zanubrutinib from 80mg BID to 80mg QD will be permitted for management of toxicity at the discretion of the investigator. Rationale for dose reduction may include, but is not limited to, laboratory abnormalities and mild side effects such as increased bruising/bleeding, rash, or diarrhea.

The study treatment will be suspended if the subject develops a significant infection or AE. If the infection or AE resolves, then the study treatment may be restarted at the next scheduled dose. It is up to the discretion of the investigator whether zanubrutinib is restarted at 80mg BID or 80mg QD.

9.6. Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours via the SAE reporting process. There is no specific antidote for an overdose of zanubrutinib. In the event of an overdose, patients should be closely monitored and given appropriate supportive treatment.

9.6.1. Minor Surgical Procedures

For minor procedures (eg, central venous catheter, arterial line placement) that are urgently needed and could result in bleeding, immediately stop study drug and consider transfusion with platelets just prior to procedure. Study drug should be held for 24 hours after procedure. If there is ongoing bleeding after the procedure, additional platelet transfusions can be administered and study drug held to 24 hours after bleeding stops. No drug hold or platelet transfusions are needed for routine venipunctures or peripheral IV placement.

9.6.2. Elective Major Surgical Procedures

For any elective surgery or invasive procedure requiring sutures or staples for closure, study drug should be discontinued and the subject should exit the study.

9.6.3. Emergency Major Surgery Procedures

For emergency procedures that could result in bleeding and require sutures or staples for closure, transfusion with platelets prior to the procedure should be given and study drug should be discontinued and the subject should exit the study.

9.7. Continued Access to Investigational Product

The investigational product should only be administered to study subjects as per protocol and will not be made available at the conclusion of this study.

9.8. Blinding

This is an open-label study and neither the subject nor the investigator will be blinded.

9.9. Concomitant Therapy

The introduction of new prescriptions or over-the-counter drugs is to be avoided during the study, unless required to treat an AE. Any additional medication used during the course of the study must be documented.

If the need for concomitant medication arises, inclusion or continuation of the subject will be at the discretion of the protocol director and investigator.

Reductions in background synthetic DMARDs will be permitted for toxicity and safety issues and should be documented.

9.9.1. Glucocorticoid Taper

Glucocorticoids may be prescribed during the screening period with a dose of ≤40mg daily of prednisone (or other glucocorticoid equivalent). Patients are not required to be taking glucocorticoids, but those who are should be on an approved starting dose listed in Table 2 (40mg, 30mg, 20mg, 15mg, 10mg, or 5mg daily) and remain on that dose stably for ≥28 days before Baseline.

The glucocorticoid dose will be tapered over a maximum of 8 weeks per the schedule in Table 2.

Table 2 Prednisone Taper Schedule

Prednisone 8-Week Taper						
Week	**Starting Dose, mg/day**					
0	40	30	20	15	10	5
2	20	15	10	7.5	5	2.5
3	15	10	7.5	5	2.5	0
4	10	7.5	5	2.5	0	
5	7.5	5	2.5	0		
6	5	2.5	0			
7	2.5	0				
8	0					

9.9.2. Effects of Zanubrutinib on Exposure of Other Concomitant Medications

A clinical drug-drug interaction study (Study BGB-3111-108) indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19. Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs.

Because ethinylestradiol (a key ingredient in a variety of combined oral contraceptives) is partly metabolized by CYP3A4, patients using hormonal contraceptives (eg, birth control pills or devices)

must use a barrier method of contraception (eg, condoms) as well (Section 5.2.2).

Repeated dosing of zanubrutinib increased exposure of digoxin (P-gp substrate) with a mean increase of 11% for AUC0-t and 34% for Cmax. The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution as zanubrutinib may increase their concentrations.

9.9.3. Permitted Medications for Treatment of IgG4-Related Disease

Glucocorticoids are permitted (but not required) for IgG4-RD during the study, and should be maintained at a stable dose before Baseline and tapered during the first 8 weeks of the study per Table 2. No other treatments specific for IgG4-RD are permitted during the study.

9.9.4. Rescue Medications

No rescue medications will be allowed during this study. If a patient needs to adjust or add to their immunosuppressive regimen, they will stop the study drug and exit the study.

9.9.5. Prohibited Medications

- Any BTK inhibitor (other than zanubrutinib)
- Synthetic DMARDs such as hydroxychloroquine, methotrexate, leflunomide, or sulfasalazine
- Cytotoxic or immunosuppressive drugs including but not limited to cyclophosphamide, mycophenolic acid, azathioprine, cyclosporine, sirolimus, and tacrolimus
- Any investigational or marketed biologic DMARDs, including but not limited to etanercept, infliximab, adalimumab, golimumab, certolizumab pegol, rituximab, ocrelizumab, obinutuzumab, obexelimab (XmAb5871), tocilizumab, anakinra, abatacept, secukinumab, ixekizumab, brodalumab, belimumab, or tabalumab. Other biologic treatments may be allowed with sponsor approval.
- Any janus kinase (JAK) inhibitor including but not limited to tofacitinib, baricitinib, upadacitinib, or filgotinib
- Parenteral glucocorticoids
- Strong and moderate inducers of CYP3A including but not limited to avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, modafinil, and nafcillin.
- Strong and moderate inhibitors of CYP3A including but not limited to clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole, telaprevir, telithromycin, and voriconazole. For a more complete list, please refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2.

10. Investigational Agent

10.1. Zanubrutinib

Zanubrutinib is a potent, specific, and irreversible BTK inhibitor that was designed to be more specific than ibrutinib; similar to ibrutinib, zanubrutinib potently inhibited BTK kinase in biochemical assays, with a 50% inhibitory concentration (IC50) of 0.3 nM, and in vitro cellular assays also show that zanubrutinib inhibited BTK signaling in mantle cell lymphoma (MCL) cell lines and cellular growth of several MCL cell lines.

Zanubrutinib is more selective than ibrutinib for the inhibition of kinase activity of BTK versus EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, and TEC. Cellular assays also confirmed that zanubrutinib is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold). Zanubrutinib was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced antibody-dependent cell-mediated cytotoxicity (ADCC). In a randomized clinical trial comparing zanubrutinib versus ibrutinib in patients with Waldenström macroglobulinemia, fewer adverse events were noted in the zanubrutinib arm. Adverse events > Grade 3 occurred in 58.4% of patients in the zanubrutinib arm and 63.3% of patients in the ibrutinib arm of the study. Four percent of zanubrutinib-treated patients discontinued therapy because of adverse events, and 1% had a Grade 5 event; 9.2% of ibrutinib-treated patients discontinued because of an adverse event, and 4.1% had Grade 5 events. For zanubrutinib and ibrutinib, respectively, the rates of all-grade atrial fibrillation/flutter were 2% and 15.3%, of minor bleeding were 48.5% and 59.2%, of major hemorrhage were 5.9% and 9.2%, and of diarrhea were 20.8% and 31.6%. Neutropenia was more common with zanubrutinib (29.7%) than with ibrutinib (13.3%).

10.1.1. Summary of Nonclinical Studies

10.1.1.1. Pharmacokinetics

Pharmacokinetic parameters of zanubrutinib were determined for rats and dogs after intravenous (IV) and oral dosing.

The kinetics were linear after oral administration over the dose range of 10, 30, and 100 mg/kg in female rats, and 2.5, 7.5, and 25 mg/kg in dogs. The linearity in male rats from 10 to 100 mg/kg was not as good, with the dose-normalized AUC at 30 mg/kg slightly higher (1.5 to 2.1-fold) than those at 10 mg/kg and 100 mg/kg. There was no significant difference in AUC0-inf of the 7th dose over the 1st dose for rats or dogs, suggesting no accumulation of zanubrutinib following multiple oral dosing in both rats and dogs. Although exposures in female rats were significantly higher than that in male rats (1.7 to 4.9-fold), this difference is not expected to be of clinical relevance as gender difference in elimination pathways in rats are much more pronounced compared with those in dogs or humans.

Following single dose oral administration at 3 different dose levels in both rats and dogs, the bioavailability of zanubrutinib ranged from 9.3% to 41% in rats, and from 45% to 50% in dogs. Permeability studies in Caco-2 monolayers suggested a high permeability of zanubrutinib in human intestine. Zanubrutinib exhibited high plasma clearance (CL) in rats and medium plasma CL in dogs. Steady-state volume of distribution (Vdss) in both rats and dogs were low which is

typical for neutral/weakly basic compound such as zanubrutinib. Elimination half-life (T1/2) ranged from 1.2 to 2.6 hours in rats and 1.4 to 3.9 hours in dogs after single-dose oral administration.

10.1.1.2. Absorption, Distribution, Metabolism, and Excretion

The oral bioavailability of zanubrutinib was found to range from 9.3% to 41% in rats and from 45% to 50% in dogs. Elimination half-lives ranged from 1.2 to 2.6 hours in rats and 1.4 to 3.9 hours in dogs after oral administration. Clearance was high in rats (52.3 mL/min/kg) and moderate in dogs (23.6 mL/min/kg). The steady-state volume of distribution (Vdss) in rats and dogs was 1.4 L/kg and 1.7 L/kg, respectively. The kinetics was mostly linear over the dose range of 10 to 100 mg/kg in rats, and 2.5 to 25 mg/kg in dogs. There was no accumulation of zanubrutinib following multiple oral dosing in both species. Plasma protein binding (PPB) for zanubrutinib ranged from 93% to 97% in human, monkey, dog, rat, and mouse plasma. The red blood cell (RBC)/plasma ratio result showed that zanubrutinib had a partitioning preference in plasma in humans.

Zanubrutinib was considered to be a moderate- to high-turnover compound in human, monkey, dog, rat, and mouse liver microsomes, with the lowest clearance rate observed in dog liver microsomes. Zanubrutinib was extensively metabolized in rats and humans and drug-related materials were excreted primarily in feces. A total of 20 metabolites were identified in humans after oral administration of 14C-BGB-3111. The major metabolic pathways in humans involved mono-oxidation, di-oxidation, acrylamide hydrolysis, hydrogenation, dehydrogenation, oxidative ring opening, N-glucuronidation, cysteine conjugation, O-sulfation, O-glucuronidation (following oxidation), and combinations thereof. A cytochrome P450 (CYP) phenotyping study using human liver microsomes with selective CYP inhibitors and recombinant CYP enzymes suggested that CYP3A was the major CYP isoform responsible for zanubrutinib metabolism.

In the reversible CYP inhibition study, zanubrutinib exhibited IC50 values of 4.03, 5.69, and 7.80 μM for CYP2C8, CYP2C9 and CYP2C19, respectively, IC50 > 10 μM for CYP2D6 and CYP3A, and IC50 > 100 μM for CYP1A2 and 2B6. Based on estimates of R1 values for reversible CYP inhibition following FDA guidance, zanubrutinib is predicted to cause clinically relevant inhibition of intestinal CYP3A and hepatic CYP2C8. Zanubrutinib is not a timedependent CYP inhibitor for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. The human hepatocytes data suggest that zanubrutinib is not an inducer of CYP1A2, but zanubrutinib is predicted to cause clinically relevant induction of CYP3A4 and CYP2B6 based on assessment of R3 values using the FDA's basic static model of induction.

In vitro drug transporter studies suggest that zanubrutinib is not the substrate of BCRP, OATP1B1, OATP1B3, OCT2, OAT1, or OAT3, except for showing marginal substrate potential on P-gp. Based on various estimates of the FDA's ratios for inhibition of drug transporters, zanubrutinib is predicted to cause clinically relevant inhibition on the intestinal efflux transporters P-gp and BCRP, but not on the hepatic uptake transporters, OATP1B1 and OATP1B3, or the renal uptake transporters, OAT1, OAT3, and OCT2.

Following a single oral dose of 30 mg/100 μCi/kg [Carbonyl-14C]zanubrutinib to rats, a total of 98.08% (up to 168 hours) of the total radioactivity dosed was recovered in the urine and feces,

with the majority of radioactivity excreted via feces. Less than 0.1% of zanubrutinib parent drug was excreted in urine and bile, and less than 2% was excreted in feces in rats.

10.1.1.3. Single-Dose Toxicology

The single-dose toxicology studies were conducted in both rats and dogs. No mortality or severe toxicity was noted up to 1000 mg/kg i.e. the maximum tolerated dose (MTD) was > 1000 mg/kg in both species.

10.1.1.4. Repeat-Dose Toxicology

Repeat-dose studies have been performed in rats of durations of 28 days, 13 weeks, and 26 weeks. Further details of these studies can be found in the IB. Based on the result of the 28-day study, the MTD was 500 mg/kg/day. Based on the result of the 13-week study, the MTD was 300 mg/kg/day. Based on the results of the 26-week study, the No-Observed Adverse Effect Level (NOAEL) was 300 mg/kg/day.

Repeat-dose studies have also been performed in dogs of durations of 28 days, 13 weeks, and 39 weeks. Further details of these studies can be found in the IB. Based on the result of the 28-day study, the MTD was greater than 100 mg/kg/day. Based on the result of the 13-week study, the MTD was greater than 100 mg/kg/day. Based on the results of the 39-week study, the No-Observed Adverse Effect Level (NOAEL) was 100 mg/kg/day.

10.1.1.5. Summary of Nonclinical Safety

The toxicity of zanubrutinib was well-characterized in rats and dogs in up to 6- and 9- month repeat-dose studies, respectively. Test article-related clinical pathology changes were slight in magnitude, including increased WBCs and decreased RBCs; reversible histopathology changes were mainly noted in rats, including pancreas, spleen, prostate gland, cecum, colon, rectum, skin (lip and/or nose), and uterus. None of these findings were adverse.

Systemic exposure increased dose-proportionally without accumulation for as long as 6- or 9-months in duration in both species. The sex difference in systemic exposure was only noted in rats, which is not expected to be of clinical relevance, as it reflects differences in elimination pathways in rats for which gender differences are much more pronounced than in dogs and humans.

No genotoxic potential was observed in a core battery of genotoxicity studies for zanubrutinib. No mutagenic potential was observed for a total of 29 impurities identified to date, following an assessment based on ICH M7 guidance.

No treatment related gross lesions or histopathological changes were noted in male or female reproductive organs in rats and dogs in up to 6- or 9-month repeat-dose studies; no apparent general toxicity was noted in maternal or fetal rats and rabbits, and no teratogenicity was noted, with the exception that one 3-chambered heart (0.3%), one 2-chambered heart (0.3%), and five 3-chambered hearts (1.5%) were noted in rat fetuses at doses of 30, 75, and 150 mg/kg/day, respectively. No pre- and post-natal developmental toxicity was noted in the maternal or offspring rats, with the exception that an increased incidence (26% to 42%) and severity of multiple ophthalmic lesions were noted in the treated animals as compared to the concurrent

control group (26%).

No abnormal findings or changes in respiratory function or central nervous system function were observed in the rat single-dose study, nor were any abnormal findings or changes in cardiovascular function observed in the dog single-dose study or in the rat or dog repeat-dose studies of up to 6- or 9-months in duration. No QT interval prolongation was noted in the cardiovascular function study in conscious dogs nor in the 9-month repeat-dose toxicity studies in dogs.

10.1.1.6. Efficacy

Zanubrutinib is a potent, specific, and irreversible BTK inhibitor that was designed to be more specific than ibrutinib; similar to ibrutinib, zanubrutinib potently inhibited BTK kinase in biochemical assays, with a 50% inhibitory concentration (IC50) of 0.3 nM, and in vitro cellular assays also show that zanubrutinib inhibited BTK signaling in MCL cell lines and cellular growth of several MCL cell lines.

In vivo studies showed that zanubrutinib induced dose-dependent antitumor effects against REC-1 MCL xenografts engrafted either subcutaneously or systemically in mice. Zanubrutinib was found to be more effective than ibrutinib in both models. In addition, zanubrutinib demonstrated better antitumor activity than ibrutinib in a TMD-8 DLBCL subcutaneous xenograft model.

Zanubrutinib was more selective than ibrutinib for the inhibition of kinase activity of BTK vs. EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, and TEC. Cellular assays also confirmed that zanubrutinib is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold). Zanubrutinib was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced antibody-dependent cell-mediated cytotoxicity (ADCC).

A complete battery of Good Laboratory Practice (GLP)-compliant safety pharmacology studies was conducted with zanubrutinib. Zanubrutinib moderately inhibited hERG current in vitro, with an IC50 = 9.11 μM; however, no cardiovascular findings, including effects on QT or QTc, were observed in telemetry-instrumented conscious dogs at single doses of zanubrutinib up to 100 mg/kg. In addition, no abnormal changes in electrocardiogram (ECG) or cardiovascular function were noted in repeat-dose toxicity studies in dogs at doses up to 100 mg/kg. No abnormal findings or changes in respiratory or central nervous system function were observed in single- or repeat-dose studies in rat.

10.1.2. Summary of Clinical Studies

As of 16 September 2018, a total of 5 Phase 1 clinical pharmacology studies have been conducted and completed: a food effect study (Study BGB-3111-103); a drug-drug interaction (DDI) study with a strong CYP3A inducer and inhibitor (Study BGB-3111-104); an absorption, metabolism, and excretion (AME) study (Study BGB-3111-105); a thorough QT (TQT) study (Study BGB-3111-106); and a cocktail DDI study to assess the effect of zanubrutinib on the PK of substrates of CYP3A (midazolam), CYP2C9 (warfarin), CYP2C19 (omeprazole), P-gp (digoxin), BCRP (rosuvastatin) (BGB-3111-108). An additional Phase 1 clinical pharmacology study (BGB-3111-107: a safety, tolerability, and pharmacokinetics study of zanubrutinib in subjects with varying degrees of hepatic impairment) is ongoing.

Additionally, 14 clinical studies investigating zanubrutinib in patients are ongoing.

10.1.2.1. Pharmacokinetics, Pharmacodynamics, and Product Metabolism in Humans

Zanubrutinib is rapidly absorbed and eliminated after oral administration in human subjects. The mean t1/2 was between 2 to 4 hours, and peak concentrations occurred around 2 hours postdose. The Cmax and the drug exposure (the AUC) increased in a nearly dose proportional manner from 40 mg to 320 mg, both after the single-dose and repeat-dose administrations.

Human absorption, metabolism, and excretion (AME) study indicated that zanubrutinib was primarily eliminated by hepatic metabolism and fecal excretion. An approximately 87.1% of the radiolabeled dose was excreted in feces with only 0.4% of the dose excreted in urine as parent drug, zanubrutinib.

Single oral doses of zanubrutinib at a therapeutic dose of 160 mg and a supratherapeutic dose of 480 mg did not have a clinically relevant effect on ECG parameters, including QTc intervals and other ECG intervals. Because of the short half-life and no accumulation seen upon multipledosing, these results are also applicable for steady-state conditions.

Coadministration of zanubrutinib with strong CYP3A inducer rifampin (600 mg once daily for 8 days) decreased exposure of zanubrutinib by 13.5-fold for AUC0-∞, and 12.6-fold for Cmax, in healthy subjects. Coadministration of zanubrutinib with strong CYP3A inhibitor itraconazole (200 mg once daily for 4 days) increased exposure of zanubrutinib by 3.8-fold for AUC0-∞, and 2.6-fold for Cmax. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib. Coadministration with food or PPI/other ARA did not appear to significantly impact the PK of zanubrutinib.

Zanubrutinib has no effect on CYP2C9 enzyme and BCRP activity. Zanubrutinib is a mild CYP3A4 and CYP2C19 inducer per FDA guidelines). AUC0-t and Cmax values were approximately 47% and 30% lower, respectively, when midazolam was coadministered with zanubrutinib. AUC0-t and Cmax values were approximately 36% and 20% lower, respectively, when omeprazole was coadministered with zanubrutinib.

10.1.2.2. Safety

Zanabrutinib has been evaluated in 18 clinical pharmacology studies. These studies included healthy subjects and subjects with B cell malignancies.

10.1.2.3.1. Study BGB-3111-103

Overall, 40 treatment-emergent adverse events (TEAEs) were reported for 14 (77.8%) of the 18 subjects. In the HF-fed state, 15 TEAEs were reported for 8/15 (53.3%) subjects, 12 TEAEs (6/16 [37.5%] subjects) in the LF-fed state, and 13 TEAEs (8/15 [53.3%] subjects) in the fasted state.

No deaths or SAEs were reported. Three (16.7%) subjects had TEAEs that led to discontinuation of study. The TEAE of ECG QT prolonged led to discontinuation in 2 patients (both assessed by the investigator as not related to study drug), and the TEAE of pyelonephritis led to

discontinuation in 1 patient (assessed by the investigator as severe in intensity and related to study drug).

There were 14 drug-related TEAEs reported for 10 (55.6%) subjects.

In the fasted state, a severe TEAE (pyelonephritis) was reported for 1 (6.7%) subject.

The most frequently reported TEAEs by Preferred Term (PT) (≥ 10% of subjects overall) were headache (4 [22.2%] subjects), lymphadenopathy (3 [16.7%] subjects), pharyngitis, catheter site pain, ECG QT prolonged, contusion, skin abrasion, and rhinorrhoea (2 [11.1%] subjects each).

No unexpected safety issues were identified during the study. Oral doses of 320 mg zanubrutinib were safe and well-tolerated in subjects either with HF-fed, or LF-fed, or fasted state.

10.1.2.3.2. Study BGB-3111-104

Single doses of 320 mg and 20 mg zanubrutinib administered alone and coadministered with 600 mg rifampin and 200 mg itraconazole, respectively, were safe and well tolerated in healthy subjects in this study.

In both parts, no subject reported a TEAE higher than Grade 2 or an SAE, and no subject discontinued due to a TEAE. The majority of TEAEs were considered not related to the study drugs, were Grade 1 in severity, and resolved without treatment.

No clinically significant changes or findings were noted in clinical laboratory evaluations, vital signs, physical examinations, or body weight in this study. No subject had a QTcF value > 450 msec or an increase from baseline in QTcF of > 60 msec during the study.

10.1.2.3.3. Study BGB-3111-105

A single oral dose of 320 mg of zanubrutinib containing ~200 μCi of [14C]-zanubrutinib was well tolerated during the study.

Four (66.7%) subjects reported a total of 13 TEAEs during the study. All of the TEAEs were assessed as being mild in severity. Two (33.3%) subjects reported a total of 2 TEAEs that were considered to be possibly related to study drug. All of the remaining 11 TEAEs were considered to be unlikely related or not related to study drug.

The most frequently reported TEAEs by System Organ Class (SOC) were Gastrointestinal (GI) disorders; 4 (66.7%) subjects reported a total of 9 TEAEs in this SOC. These TEAEs were assessed as being unlikely related or not related to study drug. The next most frequently reported TEAEs by SOC were Nervous system disorders; 2 (33.3%) subjects reported TEAEs of dizziness that were assessed by the investigator as being possibly related to study drug. These TEAEs resolved on the same day without concomitant medication. All other TEAEs in the study were assessed by the investigator as being either unlikely related to study drug or not related to study drug.

All TEAEs resolved by the end of the study without intervention. There were no deaths, other

SAEs, or severe TEAEs reported and no subjects withdrew from the study because of a TEAE.

10.1.2.3.4. Study BGB-3111-106

Overall, zanubrutinib 160 mg and 480 mg oral doses were safely administered and well tolerated by the subjects in this study.

In Part A of the study, 2 (25.0%) subjects reported a total of 5 TEAEs. In 1 subject receiving zanubrutinib 480 mg, individual TEAEs of diarrhoea, proteinuria, thrombocytopenia, and viral infection, each of mild or moderate severity, were reported. In 1 subject receiving placebo, a TEAE of mild blood creatinine increased was reported. All TEAEs were assessed as related to study drug by the investigator.

In Part B of the study, 12 (37.5%) subjects reported a total of 24 TEAEs, distributed across all 4 treatments (zanubrutinib 160 mg, zanubrutinib 480 mg, placebo, and moxifloxacin 400 mg). All TEAEs occurred in single instances. The TEAEs reported by SOC were Gastrointestinal disorders (4 subjects, 12.5%) (TEAEs of abdominal pain, diarrhoea, dry mouth, and dyspepsia), Metabolism and nutrition disorders (3 subjects, 9.4%) (hyperglycaemia, hypophosphataemia, and polydipsia), Musculoskeletal and connective tissue disorders (2 subjects, 6.3%) (back pain, musculoskeletal pain, and myalgia), Nervous system disorders (2 subjects, 6.3%) (headache and presyncope), Renal and urinary disorders (2 subjects, 6.3%) (dysuria, haematuria, and proteinuria), Blood and lymphatic disorders (1 subject, 3.1%, neutropenia), General disorders and administration site conditions (1 subject, 3.1%, fatigue), Infections and infestations (1 subject, 3.1%, urinary tract infection), Investigations (1 subject, 3.1%, alanine aminotransferase increased and aspartate aminotransferase increased), and Skin and subcutaneous tissue disorders (1 subject, 3.1%, dermatitis). All TEAEs were mild in intensity except for one TEAE of urinary tract infection assessed as moderate in intensity. All TEAEs were assessed as related to study drug by the investigator, except for TEAEs of dermatitis and presyncope which were assessed as not related to study drug by the investigator.

There were no deaths, other SAEs, or severe TEAEs reported and no subjects withdrew from the study because of a TEAE. There were no dose-related AEs observed with the zanubrutinib 480 mg dose relative to the 160 mg dose and no individual AE was reported in more than 1 subject.

10.1.2.3.5. Study BGB-3111-107

Overall, the single 80 mg zanubrutinib dose was safely administered and well tolerated by the subjects in this study and all 20 subjects (6 with mild hepatic impairment, 6 with moderate hepatic impairment, and 8 healthy control subjects) completed the study.

A total of 2 (10.0%) subjects reported a total of 2 TEAEs. Both events were reported in the Nervous system disorders SOC. One (5.0%) subject in the mild hepatic impairment group experienced dizziness that was assessed as not related to study drug by the investigator and 1 (5.0%) subject in the moderate hepatic impairment group experienced somnolence that was assesses as related to study drug by the investigator. There were no deaths or other SAEs reported and no subjects withdrew from the study because of a TEAE.

10.1.2.3.6. Study BGB-3111-108

Seventeen of the 18 (94.4%) subjects were administered zanubrutinib and completed the study; 1 (5.6%) subject withdrew from the study before receiving zanubrutinib. In general, the 160 mg twice daily doses of zanubrutinib were well tolerated during the study.

TEAEs were grouped in 3 ways based on the design of the study. Any TEAEs occurring following the administration of any probe drug on Day 1 until the administration of zanubrutinib on Day 7 were reported as a group. Any TEAEs occurring following the administration of zanubrutinib on Day 7 until the administration of warfarin or vitamin K or midazolam on Day 14 were assigned to a group ("zanubrutinib only"). Any TEAEs occurring at the administration of warfarin, vitamin K or midazolam on Day 14 through the Follow-up visit were assigned to a third group.

A total of 6 (33.3%) subjects reported a total of 9 TEAEs during the study; all of mild (Grade 1) severity. Three (16.7%) subjects experienced TEAEs in the probe drugs only group and were therefore not related to zanubrutinib. In the zanubrutinib-only group, 2 (11.8%) subjects experienced a total of 3 TEAEs; all assessed by the investigator as related to zanubrutinib. In the final group (Day 14 through the Follow-up visit), 2 (11.8%) subjects experienced a total of 2 TEAEs assessed by the investigator as related to zanubrutinib and 1 (5.9%) subject experienced a TEAE assessed by the investigator as not related to zanubrutinib. The event counts in this group include patients who may also have experienced separate TEAEs in the previous 2 groups.

In the overall study population, the most frequently reported TEAEs by SOC were Nervous system disorders and Skin and subcutaneous tissue disorders (2 [11.1%] subjects each). The only TEAE reported in more than 1 subject was petechiae (2 subjects [11.1%] in the Day 14 through the Follow-up group; both assessed as related to zanubrutinib). Other individual TEAEs included abdominal discomfort, diarrhea, and dizziness assessed as related to zanubrutinib; and headache, vessel puncture site pain, periorbital hematoma, and pollakiuria assessed as not related to zanubrutinib.

There were no deaths or other SAEs, or severe TEAEs reported and no subjects withdrew from the study because of a TEAE.

10.1.2.3.7. Study BGB-3111-AU-003

As of the data cutoff, 358/365 patients (98.1%) had experienced at least 1 TEAE while on study, including 122/123 patients (99.2%) with CLL/SLL, 78/78 (100%) with WM, 48/50 (96.0%) with MCL, 39/40 (97.5%) with DLBCL, 32/33 (97.0%) with FL, 18/18 (100%) with MZL, 10/12 (83.3%) with hairy cell leukemia (HCL), and 9/9 (100%) with RT.

As of the data cutoff, 248/365 patients (67.9%) had experienced at least 1 TEAE assessed by the investigator as related (related or with missing assessment of the causal relationship) to study treatment, including 94/123 patients (76.4%) with CLL/SLL, 56/78 (71.8%) with WM, 33/50 (66.0%) with MCL, 18/40 (45.0%) with DLBCL, 24/33 (72.7%) with FL, 12/18 (66.7%) with MZL, 6/12 (50.0%) with HCL, and 4/9 (44.4%) with RT.

As of the data cutoff, 152/365 patients (41.6%) had experienced an SAE, including 49/123 patients (39.8%) with CLL/SLL, 37/78 (47.4%) with WM, 19/50 (38.0%) with MCL, 21/40 (52.5%) with

DLBCL, 12/33 (36.4%) with FL, 7/18 (38.9%) with MZL, 2/12 (16.7%) with HCL, and 4/9 (44.4%) with RT. The most common SAEs overall were pneumonia (6.3%), cellulitis (2.5%), and pyrexia (2.2%).

Due to the issue with GCP deviations described above, analyses of safety in which the data from patients enrolled at Site 003 from Study BGB-3111-AU-003 were excluded. A total of 12 patients were enrolled at this site. BeiGene performed analyses of safety and efficacy for the IB Edition 5.0 showing that a total of 21 SAEs were reported in 9 patients, of which 2 SAEs, febrile neutropenia and pleural effusion, were assessed as related to the study drug during the reporting period. All other SAEs were assessed as not related. There were no death or fatal reports identified.

As of the data cutoff, 38 patients (10.4%) had discontinued due to an TEAE including 4/123 patients (3.3%) with CLL/SLL, 8/78 (10.3%) with WM, 11/50 (22.0%) with MCL, 7/40 (17.5%) with DLBCL, 3/33 (9.1%) with FL, 1/18 (5.6%) with MZL, 1/12 (8.3%) with HCL, and 3/9 (33.3%) with RT. The most frequently reported TEAEs leading to discontinuation were pneumonia (n = 4; 1.1%) and nausea, acute kidney injury, and pleural effusion (n = 2 each; 0.5%). All other TEAEs occurred in single instances.

Nine (2.5%) patients experienced TEAEs leading to treatment discontinuation that were assessed by the investigator as related to study treatment. This includes 1 patient in the WM group with a TEAE of arthritis bacterial that had no attribution and was therefore conservatively counted as related.

As of the data cutoff, there were 18 patients (4.9% overall) that experienced fatal TEAEs including 5/78 (6.4%) with WM, 5/50 (10.0%) with MCL, 5/40 (12.5%) with DLBCL, 2/33 (6.1%) with FL, and 1/9 (11.1%) with RT. The most frequently reported TEAEs leading to death were pneumonia (n = 4; 1.1%) and septic shock (n = 2; 0.5%). All other TEAEs occurred in single instances.

Two (0.5%) patients experienced fatal TEAEs that were assessed by the investigator as related to study treatment (1 patient in the FL group with a TEAE of pneumonia and 1 patient in the WM group with TEAE of arthritis bacterial that had no attribution and was therefore conservatively counted as related).

10.1.2.3.8. Study BGB-3111-1002

As of the data cutoff, 43/44 patients (97.7%) had experienced at least 1 TEAE on study.

As of the data cutoff, 41/44 (93.2%) of all patients had experienced a TEAE assessed by the investigator as related to treatment: 9/9 (100%) with CLL/SLL, 2/2 (100%) with MCL, 2/2 (100%) with WM, 23/26 (88.5%) with FL, and 5/5 (100%) with MZL.

As of the data cutoff, 8/44 patients (18.2%) had experienced an SAE.

As of the data cutoff, 2 patients (4.5%) had discontinued due to a TEAE.

As of the data cutoff, there had been one fatal TEAE reported in this study. Patient 102005 in the MZL disease group experienced a fatal, related event of toxic epidermal necrolysis.

10.1.2.3.9. Study BGB-3111-GA101-Study_001

As of the data cutoff, 118/119 patients (99.2%) had experienced at least 1 TEAE on study.

As of the data cutoff, 98/119 patients (82.4%) had experienced at least 1 TEAE assessed by the investigator as related to zanubrutinib, including 41/45 patients (91.1%) with CLL/SLL, 15/23 (65.2%) with DLBCL, 27/36 (75.0%) patients with FL, 5/5 (100%) patients with MCL, 3/3 (100%) patients with MZL, and 7/7 (100%) with WM.

As of the data cutoff, 54/119 patients (45.4%) had experienced an SAE.

As of the data cutoff, 9 patients (7.6%) had discontinued either study drug due to an TEAE: 3 (6.7%) patients with CLL/SLL, 2 (8.7%) patients with DLBCL, 3 (8.3%) patients with FL, and 1 (14.3%) patient with WM.

As of the data cutoff (16 September 2018), there had been 2 fatal TEAEs reported in the study: 1 TEAE in an MCL patient (renal impairment) and 1 AE in a CLL/SLL patient (skin squamous cell carcinoma metastatic). Neither fatal event was assessed by the investigator as related to zanubrutinib.

10.1.2.3.10. Study BGB-3111-205

As of the data cutoff, all 91 patients (100%) had experienced at least 1 TEAE while on study.

As of the data cutoff, 89/91 (97.8%) patients had experienced at least 1 TEAE assessed by the investigator as related (probably and possibly related, or with missing assessment of the causal relationship) to study treatment.

As of the data cutoff, 28/91 patients (30.8%) had experienced an SAE.

As of the data cutoff, 8 patients (8.8%) had discontinued due to TEAEs.

As of the data cutoff, 3 patients (3.3%) experienced TEAEs that led to death. In 1 patient, 3 fatal events had been reported (cardiac failure, lung infection, and respiratory failure). The other 2 patients experienced events of multiple organ dysfunction syndrome and cardiopulmonary failure, respectively. None of these fatal TEAEs were assessed by the investigator as related to study drug.

10.1.2.3.11. Study BGB-3111-206

As of the data cutoff, 83/86 patients (96.5%) had experienced at least 1 TEAE while on study.

As of the data cutoff, 75/86 patients (87.2%) had experienced at least 1 TEAE assessed by the investigator as related (related, probably related, possibly related or with missing assessment of the causal relationship) to study treatment.

As of the data cutoff, 18/86 patients (20.9%) had experienced an SAE.

As of the data cutoff, 9/86 patients (10.5%) had discontinued due to a TEAE; of which 6 events were considered related to study treatment.

As of the data cutoff, 7 total fatal AEs (8.1%) had been reported in 7 patients. Four events (death [no other PT noted], pneumonia, cerebral hemorrhage, and platelet count decreased) were reported as related to study drug as assessed by the investigator. This count includes all fatal AEs even those considered non-treatment emergent because they occurred after the start of post-treatment anticancer therapy.

10.1.2.3.12. Study BGB-3111-207

As of the data cutoff, 36/41 patients (87.8%) had experienced at least 1 TEAE while on study.

As of the data cutoff, 30/41 patients (73.2%) had experienced at least 1 TEAE assessed by the investigator as related (definitely, probably, or possibly) to study treatment.

As of the data cutoff, 11/41 patients (26.8%) had experienced an SAE.

As of the data cutoff, 5/41 patients (12.2%) had discontinued due to a TEAE; of which 1 event was considered related to study treatment.

As of the data cutoff, 4 fatal events (9.8%) had been reported in 4 patients. One event (pneumonia) was reported as related to study drug as assessed by the investigator.

10.1.2.3.13. Study BGB-3111-210

As of the data cutoff, 42/44 patients (95.5%) had experienced at least 1 TEAE while on study.

As of the data cutoff, 38/44 patients (86.4%) had experienced at least 1 TEAE assessed by the investigator as related (definitely, probably, or possibly) to study treatment.

As of the data cutoff, 15/44 patients (34.1%) had experienced an SAE.

As of the data cutoff, 5/44 patients (11.4%) had discontinued due to a TEAE; of which 2 events were considered related to study treatment.

As of the data cutoff, a total of 2 fatal events (4.5%) had been reported in this study. Neither event (death [no other PT noted] and Waldenstrom's macroglobulinaemia) were reported as related to study drug as assessed by the investigator. This count includes all fatal AEs even those considered non-treatment emergent because they occurred > 30 days after the last dose of study drug.

10.1.2.3.14. Study BGB-3111-212

As of the data cutoff, 7/11 patients (63.6%) had experienced at least 1 TEAE while on study.

As of the data cutoff, 6/11 patients (54.5%) had experienced at least 1 TEAE assessed by the investigator as related to study treatment.

As of the data cutoff, 2/11 patients (18.2%) had experienced an SAE. These serious TEAEs consisted of 1 event of pneumonia (assessed as not related to study treatment by the investigator) and 1 event of infusion related reaction (assessed as related to study treatment by the investigator).

As of the data cutoff, no patients had experienced TEAEs that led to treatment discontinuation or death.

10.1.2.3.15. Study BGB-3111-213

As of the data cutoff, 27/32 patients (84.4%) had experienced at least 1 TEAE while on study.

As of the data cutoff, 19/32 patients (59.4%) had experienced at least 1 TEAE assessed by the investigator as related to study treatment (10/20 [50.0%] patients in the non-GCB DLBCL cohort, 5/8 [62.5%] patients in the FL cohort, and 4/4 [100%] in the MZL cohort.

As of the data cutoff, 7/32 patients (21.9%) had experienced an SAE.

As of the data cutoff, 4/32 patients (12.5%) had discontinued due to a TEAE; none of the TEAEs were considered related to study treatment.

As of the data cutoff, 3 patients (9.4%) had reported in a total of 4 fatal events. None of the TEAEs were reported as related to study drug as assessed by the investigator.

10.1.2.3.16. Study BGB-3111-302

As of the data cutoff, 207/228 patients (90.8%) had experienced at least 1 TEAE while on study.

As of the data cutoff, 163/228 patients (71.5%) taking either zanubrutinib or ibrutinib had experienced at least 1 TEAE assessed by the investigator as related to study treatment.

As of the data cutoff, 57/228 patients (25.0%) taking either zanubrutinib or ibrutinib had experienced an SAE.

As of the data cutoff, 13 patients (5.7%) taking either zanubrutinib or ibrutinib had discontinued due to a TEAE. Nine of these patients (3.9%) had TEAEs leading to treatment discontinuation assessed by the investigator as being treatment-related.

As of the data cutoff, 5 (2.2%) fatal TEAEs had been reported in Study BGB-3111-302. One patient (0.4%) had a fatal TEAE assessed by the investigator as being treatment-related.

10.1.2.3.17. Study BGB-3111-304

As of the data cutoff, 91/113 patients (80.5%) had experienced at least 1 TEAE while on study.

As of the data cutoff, 68/113 patients (60.2%) had experienced at least 1 TEAE assessed by the investigator as related to study treatment.

As of the data cutoff, 22/113 patients (19.5%) had experienced an SAE.

As of the data cutoff, 5/113 patients (4.4%) had discontinued due to a TEAE. One patient (0.9%) had a TEAE leading to treatment discontinuation assessed by the investigator as being treatment-related.

As of the data cutoff, no fatal events had been reported in Study BGB-3111-304.

10.1.2.3.18. Study BGB-3111-A317-Study_001

As of the data cutoff, 40/43 of patients (93.0%) had experienced at least 1 TEAE on study.

As of the data cutoff, 24/43 (55.8%) of all patients had experienced a TEAE assessed by the investigator as related to either study treatment: 4/5 (80.0%) with CLL, 2/2 (100%) with WM, and 18/36 (50.0%) with NHL.

As of the data cutoff, 30/43 patients (69.8%) had experienced an SAE, including 3/5 patients (60.0%) with CLL, 25/36 (69.4%) with NHL, and 2/2 (100%) with WM.

Two subjects with WM who received zanubrutinib in combination with tislelizumab experienced serious hemolytic transfusion reaction. These events resulted in hospitalizations and required treatment with RBC transfusion and medical therapy, including steroids.

As of the data cutoff, 13 patients (30.2%) had discontinued either study drug due to an TEAE, including 3 patients (60.0%) with CLL, 2 patients (100%) with WM, and 8 patients (22.2%) with NHL. Four (4) patients (9.3%) had TEAEs leading to treatment discontinuation assessed by the investigator as being treatment-related.

As of the data cutoff, 3 patients (7.0%) had reported in a total of 3 fatal events. None of the TEAEs were reported as related to study drug as assessed by the investigator.

10.1.2.3. Serious Adverse Events and Serious Adverse Events with a Fatal Outcome

Of the 44 fatal events (in 40 patients) reported as of 16 September 2018 in the zanubrutinib monotherapy studies, 9 fatal events were assessed by the investigator as related to study drug (pneumonia [in 3 patients], arthritis bacterial, toxic epidermal necrolysis, death, cerebral haemorrhage, platelet count decreased, and 1 event with an unreported term from a blinded study).

In the zanubrutinib combination studies (BGB-3111-GA101, BGB-3111-213, and BGB-3111-A317-Study_001), 9 fatal events (renal impairment, skin squamous cell carcinoma metastatic, dyspnoea, pleural effusion, abdominal pain and completed suicide [same patient], abdominal pain, multiple organ dysfunction syndrome, and sepsis), in 8 patients, had been reported as of 16 September 2018; none of these fatal events were assessed by the investigator as related to zanubrutinib or either study treatment (zanubrutinib or tislelizumab in Study BGB-3111-A317-Study_001).

10.1.2.4. Expected Adverse Events

A listing of expected adverse drug reactions, defined as adverse events experienced by patients receiving zanubrutinib monotherapy that the sponsor considers expected for the purpose of determining requirements for expedited reporting, is presented in Table 3.

Table 3 Expected Adverse Drug Reactions

System Organ Class Preferred Term	Zanubrutinib Monotherapy Number of subjects exposed (N) = 671 SARs		
	All SARs n* (%)	Occurrence of fatal SARs n (%)	Occurrence of life-threatening SARs n (%)
Blood and lymphatic system disorders			
Anaemia^	4 (0.6)	0 (0.0)	0 (0.0)
Neutropenia	3 (0.4)	0 (0.0)	3 (0.4)
Thrombocytopenia+	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders			
Diarrhoea	1 (0.1)	0 (0.0)	0 (0.0)
Infections and infestations			
Pneumonia	15 (2.2)	3 (0.4)	1 (0.1)
Lung infection	8 (1.2)	0 (0.0)	0 (0.0)
Urinary tract infection	3 (0.4)	0 (0.0)	0 (0.0)
Investigations			
Platelet count decreased+	4 (0.6)	1 (0.1)	3 (0.4)
Neutrophil count decreased	2 (0.3)	0 (0.0)	1 (0.1)
Haemoglobin decreased^	0 (0.0)	0 (0.0)	0 (0.0)

* n = number of subjects who have experienced the SAR.
^ The preferred term haemoglobin decreased represents a similar medical concept to anemia.
+ The preferred term thrombocytopenia represents a similar medical concept to platelet count decreased.
Abbreviation: SAR = serious adverse reaction.
Note: Fatal and life-threatening events are considered unexpected.
Note: The SAR diarrhoea was reported in two patients in IB v5.0; in IB v6.0, one event of diarrhea was re-reported as "intestinal infection (diarrhea)" which was coded to "Enteritis infectious". The incidence of ≥ Grade 3 diarrhea was increased from 0.7% in IB v5.0 to 0.9% in IB v6.0. The sponsor considers medically significant diarrhea to be causally related to the treatment of zanubrutinib.
Note: Grades were evaluated based on NCI-CTCAE version 4.03.

10.1.2.5. Adverse Events Considered Possibly Related to Zanubrutinib

A listing of AEs experienced by patients that the Sponsor considers possibly related to zanubrutinib and will be monitored in ongoing studies, is presented in Table 4.

Table 4 Adverse Events Considered Possibly Related to Zanubrutinib

System Organ Class Preferred Term	Zanubrutinib Monotherapy N = 671 All AEs All Grades n* (%)	 ≥ Grade 3 n (%)
General disorders and administration site conditions		
Fatigue	71 (10.6)	5 (0.7)
Infections and infestations		
Upper respiratory tract infection	211 (31.4)	16 (2.4)
Injury, poisoning and procedural complications		
Contusion	114 (17.0)	0 (0.0)
Metabolism and nutrition disorders		
Hypokalaemia	61 (9.1)	11 (1.6)
Renal and urinary disorders		
Haematuria	74 (11.0)	2 (0.3)
Respiratory, thoracic and mediastinal disorders		
Cough	116 (17.3)	0 (0.0)
Pleural effusion	13 (1.9)	5 (0.7)
Skin and subcutaneous tissue disorders		
Rash	117 (17.4)	0 (0.0)
Toxic epidermal necrolysis	1 (0.1)	1 (0.1)

*n = number of subjects who have experienced the adverse events.
Abbreviation: AE = adverse event.
Note: Grades were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

10.1.2.6. Efficacy

No information is available regarding efficacy in patients with IgG4-RD at this time. As demonstrated by clinical data obtained to date, zanubrutinib is a highly selective and orally bioavailable BTK inhibitor that not only achieves high systemic exposure for complete BTK occupancy in the blood and lymph nodes; it also remains highly tolerable, despite its exposure and occupancy advantages. Below is an overview of key efficacy data from treatment of patients with B cell malignancies.

Study BGB-3111-206 is an ongoing single-arm, open-label, multicenter ongoing Phase 2 study conducted in China in patients with histologically documented mantle cell lymphoma (MCL) who have no response or relapse after ≥ 1 but < 5 prior lines of therapy, in which patients were treated with zanubrutinib at a dose of 160 mg orally twice a day. As of the cutoff date of 27 March 2018, 86 patients with MCL had been enrolled. The objective response rate was 83.5% (71/85), with a complete response rate of 58.8% (50/85) and a partial response rate of 24.7% (21/85). Subgroup analysis revealed that the treatment benefit of zanubrutinib was generally consistent across all

subgroups analyzed. The responses achieved by zanubrutinib treatment appear durable although longer follow-up is needed (median DOR and PFS were not reached).

Study BGB-3111-GA101-Study_001 is an ongoing global Phase 1b, open-label, multicenter study of the combination of zanubrutinib and obinutuzumab in patients with B-cell malignancies—specifically, chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia (WM), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and diffuse large B-cell lymphoma (DLBCL). As of 01 June 2017, 45 patients with CLL/SLL (20 patients treatment naïve (TN); 25 patients relapsed or refractory (R/R)), and 22 patients with R/R FL had been enrolled. Preliminary efficacy results for these patients are described below. Objective response rates (complete response [CR] + partial response) were 89%, 92%, and 69% in TN CLL/SLL, R/R CLL/SLL, and R/R FL, respectively, with 5 CRs in TN CLL/SLL, 4 CRs in R/R CLL/SLL, and 5 CRs in FL. Four patients (1 R/R CLL; 3 FL) experienced disease progression; no instances of disease transformation occurred.

Study BGB-3111-AU-003 is an ongoing global FIH, Phase 1, open-label, multiple-dose, dose-escalation and dose-expansion study of zanubrutinib that was initiated in Australia in August 2014. As of the cutoff date of this IB (16 September 2018), 365 patients had been dosed in this clinical study. In Part 1, the primary objectives are to determine the safety and tolerability of zanubrutinib in patients with B-cell malignancies (CLL/SLL, NHL, and WM) and determine the RP2D and regimen of zanubrutinib when given continuously, orally. The secondary objectives are to characterize the PK of zanubrutinib after drug administration, determine the extent of BTK inhibition in peripheral blood mononuclear cells (PBMCs) after treatment with zanubrutinib, and describe the preliminary antitumor activity of zanubrutinib. In Part 2, the primary objective is to further assess the safety and tolerability of zanubrutinib administered orally either once or twice daily in patients with specified B-cell malignancies, while the secondary objectives are to assess the preliminary antitumor activity of zanubrutinib at RP2D(s) in patients with specific B-cell malignancies, further characterize the PK profile of zanubrutinib, and determine the extent of BTK inhibition in PBMCs after treatment with zanubrutinib. Based on the safety, tolerability, PK, and PD (as measured by BTK occupancy in PBMCs) profiles of zanubrutinib observed in this study, the RP2D has been selected as 160 mg twice daily. As of 24 July 2018, 48 patients with mantle cell lymphoma (MCL) had been enrolled. The objective response rate was 88.9% (40/45), with a complete response rate of 26.7% (12/45) and a partial response rate of 62.2% (28/45). The overall duration of response was 16.2 months (95% CI 12.6, 28.2). As of the data cut off, 53.3% (24/45) of efficacy evaluable MCL patients remained on treatment. The estimated median progression-free survival for relapsed or refractory (R/R) patients was 18 months. As of 24 July 2018, 77 patients with Waldenström macroglobulinemia (WM) had been enrolled. The objective response rate was 91.8% (67/73), with a major response rate of 82.2% (60/73): very good partial response (VGPR) in 41.1% (30/73) and partial response (PR) in 41.1% (30/73). Median time to response was 85 days. Data show an increased depth of response over time. The estimated progression-free survival at 12 months was 89%. In 32 patients with HGB < 10 g/dL at baseline, median HGB increased from a median of 8.85 g/dL (6.3 to 9.8) to 13.4 g/dL (7.7 to 17.0). Median IgM decreased from a median of 32.7 g/L (5.3 to 91.9) at baseline to 8.2 g/L (0.3 to 57.8). As of 15 December 2016, 68 patients with chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL) had been enrolled. Of the 54 patients evaluable for response (> 12 weeks follow-

up or discontinuation before 12 weeks), the objective response rate (ORR) was 96% (52/54), with partial response in 67% (36/54), partial response with lymphocytosis in 30% (16/54), stable disease in 1 R/R patient, and no assessment for 1 R/R patient because of AE. No instances of disease progression or Richter transformation were reported. Zanubrutinib is well tolerated and highly active in R/R and TN CLL/SLL. With only 7.2 months of median follow-up, only 1 toxicity-related discontinuation, and no progressive disease was seen thus far on study. As of 18 May 2017, 75 patients with non-Hodgkin lymphoma (NHL) had been enrolled, including 23 diffuse large B-cell lymphoma (DLBCL), 31 mantle cell lymphoma (MCL), 14 follicular lymphoma (FL), and 7 marginal zone lymphoma (MZL) patients. Of the 62 NHL patients evaluable for response (> 12 weeks follow-up or discontinuation before 12 weeks), the ORR was 58.1% (36/62) overall, 60.9% (28/46) in the aggressive lymphoma (AL) group (DLBCL and MCL), and 50.0% (8/16) in the indolent lymphoma (IL) group (FL and MZL). Most responses were partial responses: 45.2% (28/62) overall, 45.7% (21/46) in AL, and 43.8% (7/16) in IL. Stable disease was seen in 13/62 (21.0%) overall. Nine patients progressed by the first response assessment (all DLBCL patients), and 4 AL patients discontinued before assessment.

11. Sample Collection and Safety Data Collection

11.1. Laboratory Samples

Blood and urine samples will be collected to determine whether subjects meet inclusion/exclusion criteria and to monitor subject health. Routine clinical laboratory tests will be analyzed by the Stanford University Hospital central laboratory.

Investigators must document their review of each laboratory safety report.

Tests will be run and confirmed promptly whenever scientifically appropriate.

11.2. Samples for Research

11.2.1. Exploratory Samples (Peripheral Blood Mononuclear Cells and Plasma)

Blood will be collected at Baseline, Week 12, and Week 24 and processed for peripheral blood mononuclear cells (PBMCs) and plasma. This will be stored for future investigations into how specific biomarkers, cytokine levels, and immune cell phenotypes correlate with treatment response. The exploratory samples will be coded with the subject number and stored for up to a maximum of 25 years after the last subject visit for the study**.**

11.3. Other Exploratory Evaluations

The following have been selected to explore the clinical effects of zanubrutinib in subjects with IgG4-RD.

11.3.1. Patient-Reported Outcomes

All patient-reported outcomes (PROs) should be collected from the subject before other study visit assessments, to the extent possible.

11.3.1.1. Patient's Global Assessment of Disease Activity

This assessment will be taken at selected visits as outlined in the Study Schedule. The subject will be asked to give an overall assessment of their IgG4-RD over the last week. She/he will be asked to place a single vertical mark on a 100-mm horizontal visual analog scale (VAS). The leftmost end of the scale is equivalent to "no IgG4-RD symptoms," whereas the rightmost end of the scale is equivalent to "extremely severe IgG4-RD symptoms." The question will be: "How severe has your IgG4-RD been over the past week? Please place a vertical mark on the line to indicate the severity of the disease." Results are expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line, as placed by the subject. Measurements will be verified by the sponsor or sponsor's designee. This applies for all VAS scales used in the trial.

11.3.1.2. Patient's Global Assessment of Fatigue

The subject will assess his or her fatigue from IgG4-RD at selected visits as outlined in the Study Schedule. The subject will be asked to assess his or her current level of fatigue using a VAS as described in Section 10.3.1.1. The leftmost end of the scale is equivalent to "no fatigue," whereas the rightmost end of the scale is equivalent to "worst imaginable fatigue." The question will be:

"Please indicate how severe your fatigue has been over the past week by placing a vertical mark on the line."

11.3.1.3. Patient's Global Assessment of Ocular Symptoms

The subject will assess his or her ocular symptoms from IgG4-RD at selected visits as outlined in the Study Schedule. The subject will be asked 3 questions to assess his or her current level of ocular symptoms using a VAS as described in Section 11.3.1.1. The 3 questions will include 1.) "Please indicate how severe your current eye dryness from IgG4-RD has been over the past week by placing a vertical mark on the line", 2.) "Please indicate how severe your current eye swelling from IgG4-RD has been over the past week by placing a vertical mark on the line", 3.) "Please indicate how severe your current eye pain or pressure from IgG4-RD has been over the past week by placing a vertical mark on the line." The leftmost end of the scale is equivalent to no eye symptoms, whereas the rightmost end of the scale is equivalent to the worst imaginable eye symptoms.

11.3.1.4. Patient's Global Assessment of Salivary Symptoms

The subject will assess his or her salivary symptoms at selected visits as outlined in the Study Schedule. The subject will be asked 2 questions to assess his or her current level of salivary symptoms using a VAS as described in Section 11.3.1.1. The 2 questions will include 1.) "Please indicate how severe the dryness of your mouth from IgG4-RD has been over the past week by placing a vertical mark on the line", 2.) "Please indicate how severe your current salivary gland swelling from IgG4-RD has been over the past week by placing a vertical mark on the line." The leftmost end of the scale is equivalent to no salivary symptoms, whereas the rightmost end of the scale is equivalent to the worst imaginable salivary symptoms.

11.3.1.5. RAND Short Form-36

This assessment will be taken at selected visits as outlined in the Study Schedule. The RAND Corporation SF-36 is a 36-item, patient-completed measure designed to be a short, multipurpose assessment of health in the areas of physical functioning, role-physical, role-emotional, bodily pain, vitality, social functioning, mental health, and general health. The two overarching domains of mental well-being and physical well-being are captured by the Physical and Mental Component Summary scores, respectively. The summary scores range from 0 to 100, with higher scores indicating better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The recall period is the preceding 4 weeks.

11.3.1.6. FACIT-F

This assessment will be taken at selected visits as outlined in the Study Schedule. The FACIT measurement system was first developed in 1987 to assess fatigue levels and quality of life in patients with chronic illness. The recall period is 7 days. There are 13 questions, each worth 0-4 points. The overall score is obtained by adding up the points from each question. Higher overall score means less fatigue. Respondent burden is 5-10 minutes.

11.3.2. Physician Assessments

11.3.2.1. Physician's Global Assessment of Disease

This assessment will be taken at selected study visits according to the Study Schedule. The

investigator will give an overall assessment of the subject's disease activity using a VAS as described in Section 10.3.1.1. The leftmost end of the scale is equivalent to "no IgG4-RD activity," whereas the rightmost end of the scale is equivalent to "extremely active IgG4-RD." The question will be: "Please indicate the subject's current IgG4-RD activity at this visit (independent of the subject's self-assessment) by placing a vertical mark on the line."

11.3.2.2. IgG4-Related Disease Responder Index

This assessment will be taken at selected study visits according to the Study Schedule. The IgG4-RD RI is designed to detect changes in disease activity in each affected organ system in a composite scoring system. At specified visits, the investigator will assess the status by assigning a 0-3 score after the organ/site listed with: 0 = absence of active disease in that site; 1 = improved but persistent activity in that site; 2 = new or recurrent disease activity in that site while off treatment, or unchanged from previous visit; 3 = worse or new despite treatment. Any urgent disease at a site or IgG4-RD related damage in the organ-site will be recorded in the IgG4-RD RI form. Urgent disease is defined as IgG4-RD activity within an organ system that requires therapy immediately to prevent the development of potentially permanent organ damage. Damage is defined as the occurrence of permanent tissue injury or organ dysfunction that results from active or previously active IgG4-RD. Damage in this context does not refer to treatment-induced injury. PET/MRI will be employed for disease assessment of the salivary and lacrimal glands at Baseline, Week 12, and Week 24.

11.3.3. Other Study Procedures

11.3.3.1. Positron Emission and Magnetic Resonance Imaging of the Head and Neck

Imaging of the head and neck will be performed using positron emission magnetic resonance imaging at the PET/MRI suite at the Lucas Imaging Center at Stanford University. The total volume of the bilateral lacrimal glands and bilateral salivary glands (submandibular and parotid glands) will be calculated.

In addition, MRI of the salivary glands and lacrimal glands in IgG4-RD patients demonstrates inhomogeneity of the parenchyma on both T1- and T2-weighted sequences. The following grading system will be used [28]: grade 0, homogeneous intensity distribution, no abnormal fat signals detected, normal parotid glands; grade 1, sparse distribution of streaks-like fat signals; grade 2, diffusive distributed, honeycomb-like fat signals; grade 3, diffusive patchy fat signal, less than 50% of total area of whole parotid glands, nodular appearance of residual glands; grade 4: massive homogeneously distributed fat signal on T1-weighted images, more than 50% of whole parotid glands, barely see any normal gland structure. A similar grading system will be used to assess the lacrimal glands.

MR sialography [28, 29] will be scored as follows: stage 0 = normal. Stage 1 = punctate, in which diffuse, spherical areas of high-signal intensity, 1 mm or less in diameter and uniform in size, are distributed evenly throughout the gland. Stage 2 = globular: in this stage of disease, the spherical areas of high signal intensity increase to 1 to 2 mm in diameter. Stage 3 = cavity: with further disease progression, the areas of high intensity coalesce and enlarge further, more than 2 mm in diameter. Stage 4 = destructive, in which there is marked dilation of the main duct with an irregular diameter, as well as irregular branching.

For positron emission tomography (PET) imaging, participants will be injected intravenously (IV) with 370 MBq of ^{18}F-Fluorodeoxyglucose (^{18}F-FDG). Parotid gland, submandibular gland, lacrimal gland, and lymph node SUVmax will be assessed using MIM PACS (MIM Software, Cleveland OH) [23]. The maximum standard uptake value (SUVmax), metabolic lesion volume (MLV), and total lesion glycolysis (TLG) will be measured. The SUVmax is calculated as (decay-corrected activity/tissue volume) divided by (injected dose/body weight). For MLV, a threshold of SUVmax 2.5 will be used to define contour margins around FDG target lesions and boundaries will be drawn to include all areas of metabolically disease. TLG is defined as the product of SUVmean and MLV. The metabolic parameters, SUV (max and mean), MLV, and TLG as calculated and displayed by the MIM software package will be recorded [23, 30-33].

11.3.3.2. Salivary Gland Ultrasonography

Salivary gland ultrasound reveals characteristic abnormalities in the echo structure of the salivary glandular parenchyma and vascularity. Salivary gland ultrasound will be conducted by the same ultrasonographer for all patients using a standard GE Logiq E machine. OMERACT grey scale ultrasound salivary scoring and OMERACT glandular inflammation scores will be used to assess structural changes and inflammatory changes respectively [34, 35]. Both scoring systems are semiquantitative, ranging from 0-3 assessed for each gland. Scoring systems will be applied to each parotid and submandibular gland at each time point. The highest score among the salivary glands and the total summed scores across all four glands will assessed for both grey scale and glandular inflammation.

11.4. Safety Evaluations

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Protocol Director or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of subjects during the study. Planned safety assessments and measures are detailed in Section 11.4.3, but additional assessments and safety tests may be performed at the investigator's discretion. Further follow-up beyond 8 weeks after the last dose may be implemented as clinically indicated.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical trial records throughout the study.

11.4.1. Adverse Events

The investigator is responsible for the detection and documentation of events meeting the definition of an AE or SAE as provided in this protocol. In addition, a separate Data Safety Monitoring Committee (DSMC) will be formed to monitor the safety (including lack of efficacy) of the study on a periodic basis.

Study site personnel will record the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

Cases of pregnancy that occur during maternal or paternal exposures to the investigational product should be reported. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

After the informed consent is signed, site personnel will record any change in the subject's condition and the occurrence and nature of any AEs. All AEs related to protocol procedures are to be reported to the DSMC and Stanford IRB.

Any clinically significant findings from ECGs, laboratory test results, vital sign measurements, other procedures, etc, should be reported as AEs to the DMSC and Stanford IRB. In addition, all AEs occurring after the subject receives the first dose of the investigational product must be reported as well.

11.4.1.1 Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of AEs include the following:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In these instances, all patient identifiers will be blinded on the copies of the medical records before submission to the sponsor. When a new infection is reported, the site of infection and the diagnostic test used to make the diagnosis will be recorded.

If a subject's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly document this and report to the DMSC and Stanford IRB the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

11.4.1.2 Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0.

Toxicities that are not specified in the NCI-CTCAE v5.0 will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities.

11.4.1.3 Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgement. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should consult the IB in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator assesses causality for every SAE before transmission of the SAE report to the sponsor because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality in light of follow-up information and amend the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including the following:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An AE should be considered "related" to study drug if any of the following criteria are met, otherwise the event should be assessed as not related:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is

unlikely.
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

11.4.1.4 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor

11.4.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator; in general, these are laboratory test abnormalities that are associated with clinical signs or symptoms, require active medical intervention, or lead to dose interruption or discontinuation, require close observation, more frequent follow-up assessments, or further diagnostic investigation.

Lymphocytosis is considered an expected manifestation of treatment with zanubrutinib and therefore may not be an AE; clinical correlates should be present if reporting lymphocytosis as an AE. Patients who develop marked and persistent lymphocytosis should have an analysis (ie, flow cytometry) to rule out an underlying hematologic malignancy disorder.

For information on procedures for the monitoring and prevention of hepatitis B and hepatitis C see

Section 8.1.2 and Table 1.

11.4.3. Lack of Efficacy

Lack of efficacy will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

11.4.4. Serious Adverse Events

11.4.4.1. Serious Adverse Event Definitions

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

Note: the term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it was more severe.

- Requires hospitalization or prolongation of existing hospitalization

Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

- Results in disability/incapacity

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgment (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study, necessitating a change in the date or extent of the planned surgery.

11.4.4.2. Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the IB. These should be documented and reported to the DSMC and Stanford IRB within 24 hours.

11.4.4.3. Serious Adverse Events Reporting

Study site personnel must alert the DSMC and Stanford IRB of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method (see Table 5). If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Table 5 Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the AE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE form

Abbreviations: AE, adverse event; SAE, serious adverse event.

SAE collection begins after the subject has signed informed consent and has received investigational product. If a subject experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

SAEs occurring up to and including the subject's last study visit will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at the sponsor.

The investigator does not need to actively monitor subjects for AEs once the trial has ended. However, if an investigator becomes aware of an SAE occurring to a subject after the subject's participation in the trial has ended, the investigator should report the SAE to the sponsor, regardless of the investigator's opinion of causation, and the SAEs will be entered in the pharmacovigilance system at the sponsor.

11.4.5. Sponsor Investigator Reporting Responsibilities to BeiGene

Investigator Sponsor will report all Serious Adverse Events (as defined in the Protocol) to the applicable regulatory authorities and the appropriate ethics committee as required by the Protocol and applicable law and/or regulation within the requisite applicable timeframes. Investigator will conduct follow-up activities with respect to Adverse Events as required by the Protocol and

applicable law and/or regulation. Investigator Sponsor will report Serious Adverse Events (as such term is defined in the Protocol) requiring expedited reporting to applicable regulatory authorities via an CIOMS I report form or MedWatch 3500a report form, as applicable, or other locally required form and concurrently provide a copy of such report to BeiGene.

For expedited reports, Investigator Sponsor will send the report to BeiGene no later than seven (7) days for initial or follow-up life-threatening and death reports, and fifteen (15) days for all other initial or follow-up serious and unexpected suspected adverse reactions (SUSARs), from the time of receipt of the SAE by Investigator.

For non-expedited SAE reports (i.e., unrelated to Study Drug or listed/expected event), Investigator Sponsor will send a quarterly line listing to BeiGene within 10 days after the start of each quarter (e.g., April 10th for Quarter 1 data due each year).

11.4.6. Other Safety Measures

11.4.6.1. Physical Examination

Complete physical examinations and symptom-directed physical examinations will be conducted as specified in the Study Schedule and as clinically indicated. A complete physical examination should include evaluation of the following regions/systems:

- General appearance
- Head, ears, eyes, nose, throat
- Lymph nodes
- Cardiovascular
- Respiratory
- Abdominal
- Extremities (tender/swollen joint counts to be documented separately)
- Neurologic

On visit days where a complete physical examination is not required as detailed in the Study Schedule, the investigator may conduct a symptom-directed physical examination as clinically indicated.

11.4.6.2. Vital Signs

Blood pressure and heart rate will be measured as specified in the Study Schedule and as clinically indicated.

Blood pressure and heart rate should be measured after at least 5 minutes of sitting.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If the subject feels unable to stand, sitting or supine vital signs should be recorded.

Additional vital signs may be measured during each study visit if warranted by the investigator. Body temperature will be measured as specified in the Study Schedule and as clinically indicated.

11.4.6.3. Body Weight and Height

Body weight will be recorded as specified in the Study Schedule and as clinically indicated. Height will be measured only at screening, with the subject's shoes removed.

11.4.6.4. Electrocardiograms

For each subject, a 12-lead ECG will be collected at the Screening, Week 12, and Week 24 visits. Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high quality records. All ECGs recorded should be stored at the investigational site.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant finding is identified after enrollment, the investigator should determine if the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of collection. Any clinically significant finding should be reported as an AE.

11.4.7. Safety Monitoring

The investigator will monitor safety data throughout the course of the study.

The investigator will review SAEs within 24 hours and periodically review:

- Trends in safety data
- Laboratory test results
- AEs including injection site reactions, hypersensitivity/allergic reactions, infections, and/or cytopenias

SAEs will be reported to the DSMC and Stanford IRB within 24 hours.

11.4.8. Stopping Criteria for Subjects

Subjects may be removed from the study at any time if it is deemed to be in the patient's best interest by the investigator. If a patient meets any of the stopping criteria listed below, the patient will complete the Early Termination assessments followed by a Safety Follow-up Visit 8 weeks later.

Stopping criteria:

- Development of life-threatening IgG4-related disease manifestations during treatment with zanubrutinib
- Development of a grade 3 TEAE
- Development of hepatic dysfunction defined as:
    - Aspartate transaminase (AST) >8 times the upper limit of normal
    - Alanine transaminase (ALT) >8 times the upper limit of normal

    - AST or ALT >5 times the upper limit of normal for more than 2 weeks
    - AST or ALT >3 times the upper limit of normal and total bilirubin >2 times the upper limit of normal or INR >1.5 times the upper limit of normal
    - AST or ALT >3 times the upper limit of normal with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
    - Total bilirubin >5 times the upper limit of normal
- Development of a serious allergic reaction to zanubrutinib including anaphylaxis
- Development of human immunodeficiency (HIV)/acquire immune deficiency syndrome (AIDS) during the study
- Development of hepatitis B or hepatitis C infection during the study
- Development of a new arrhythmia, including atrial fibrillation, during the study
- Serious bleeding that requires surgical intervention or hospitalization
- Pregnancy
- Any medical condition that, in the opinion of the investigator, puts the subject's life at risk by continuing zanubrutinib
- If the investigator believes discontinuation of zanubrutinib is in the patient's best interest
- Violation of the protocol, if the investigator believes it would significantly compromise data interpretation or patient safety

11.4.9. Stopping Criteria for the Study

An independent Data and Safety Monitoring Committee (DSMC) will be formed, consisting of two experienced rheumatology clinicians at Stanford University. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

The DSMC will convene once 5 subjects have completed Week 12, and all safety data will be reviewed. If the DSMC agrees there are no safety concerns, the study will continue. The DSMC will convene again once all 10 subjects have completed Week 12 to review safety data. The DSMC may recommend the trial be terminated if major safety concerns related to zanubrutinib occur.

11.5. Appropriateness and Consistency of Measurements

The clinical safety parameters and laboratory measurements in this study are routine elements of clinical health assessment and Phase 2 drug development. The efficacy measurements are used both in clinical practice and in clinical trials for IgG4-RD.

11.6. Compliance

Every attempt will be made to select subjects who have the ability to understand and comply with

instructions. Noncompliant subjects may be discontinued from the study. The time and day of drug administration will be recorded. Drug accountability records will be maintained by the study site.

12. Sample Size and Data Analyses

12.1. Determination of Sample Size

A sample size of 10 was calculated based on practical considerations and enrollment feasibility. Based on prior B cell directed therapies, in which 97% of patients responded to rituximab [9] and 93% responded to XmAb5871 (a humanized anti-CD19 antibody with an Fc engineered for increased affinity to FcγRIIb) [10], we anticipate seeing meaningful benefit with only 10 subjects.

12.2. Data Analysis Plans

12.2.1. General Considerations

The primary endpoint comparing Baseline and Week 24 changes in submandibular and/or lacrimal gland size on MRI will be conducted using the Wilcoxon signed-rank test. The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all randomized subjects who received at least one dose of study drug. For the secondary endpoints such as change in imaging at 12 weeks and change in subjective disease activity metrics the Wilcoxon signed-rank test will be used. Laboratory results will be treated as continuous variables and analyzed with the Wilcoxon signed-rank test. Adverse events and abnormal labs will be counted and described. With regard to missing data, all subjects will have baseline data, or they will not be entered into the study. The study duration is intentionally short, without excessive visits or testing, to minimize dropout. In addition, given the small *n*, we will remain in close contact with each subject for the duration of the study to ensure compliance and completion of the study.

12.2.2. Study Participant Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

12.2.3. Study Participant Characteristics

The subject's age, sex, weight, body mass index, height, race/subrace, or other demographic characteristics will be recorded.

12.2.4. Safety Analyses

12.2.4.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed; if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur before study treatment administration will be distinguished from those reported as new or increased in severity after study treatment is initiated. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of investigational product-related SAEs will be reported.

12.2.4.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

12.3. Interim Analyses

There are no planned interim analyses given the small number of subjects (n = 10) and short duration of the study (24 weeks).

13. Data Management Methods

13.1. Data Quality Assurance

To ensure accurate, complete, and reliable data, the investigators will do the following:

- Train all study personnel including study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- Review and evaluate CRF data to detect errors in data collection.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ethics review boards with direct access to the original source documents.

13.2. Data Capture Systems

13.2.1. Source Data and Case Report Form

The Protocol Director and team will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed as paper forms and will be kept in a locked office, only accessible to the research team.

14. Informed Consent, Ethical Review, and Regulatory Considerations

14.1. Informed Consent

The investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each subject before the study is started. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of the investigational product.

As used in this protocol, the term "informed consent" includes consent given by subjects.

14.2. Ethical Review

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation.

14.3. Regulatory Considerations

This study will be conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- ICH GCP Guideline
- Applicable laws and regulations

14.3.1. Investigator Information

Contact information for the investigator and study coordinator will be provided to all subjects.

14.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

14.3.3. Final Report Signature

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study

report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

14.3.4. Data and Safety Monitoring Plan

An independent Data and Safety Monitoring Committee (DSMC) will be formed, consisting of two experienced rheumatology clinicians at Stanford University. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

15. Study Schedule

	Screening Day -35 to 0	Baseline Day 1	Weeks 2, 8, 16, 20	Week 4	Week 12	Week 24	Week 32	ET	Unscheduled visit
Written IC	X								
Medical history	X								
Vital signs	X	X	X	X	X	X	X	X	X
Complete PE	X							X	
Limited PE		X	X	X	X	X	X		X
IgG4-RD Responder Index		X	X	X	X	X	X	X	
Physician/Patient global		X	X	X	X	X	X	X	
Patient VAS symptoms		X	X	X	X	X	X	X	
FACIT-F		X		X	X	X	X	X	
RAND Short-Form 36		X		X	X	X	X	X	
Routine clinical labs:									
Metabolic panel	X	X	X	X	X	X	X	X	X
CBC w/diff	X	X	X	X	X	X	X	X	X
Urine pregnancy		X	X	X	X	X	X	X	X
Urinalysis, urine prot/creat		X		X	X	X			
IgG4-RD labs:									
IgG subclasses	X	X		X	X	X	X	X	
B cell phenotyping		X			X	X			
IgG, IgA, IgM, IgE		X		X	X	X			
C3, C4		X			X	X			
ESR, CRP		X		X	X	X			
Safety labs:									
Serum pregnancy	X								
HIV-1/2 serology	X								
Hepatitis B serologies	X								
Hepatitis C Ab	X								
QuantiFERON TB	X								
Screening tests:									
EKG	X				X	X			
Chest x-ray	X								
ANA, RF	X								
Anti-Ro, Anti-La	X								
IgG4-RD tests:									
PET/MRI neck/face		X			X	X			
Salivary gland ultrasound		X			X	X			
Research labs:									
Serum and PBMCs		X			X	X			
Review AEs and meds	X	X	X	X	X	X	X	X	X
Study drug dispensing		X			X				
Drug accountability			X	X	X	X	X	X	

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