Clinical Study Protocol

ZANUBRUTINIB, A SECOND GENERATION BTK INHIBITOR, IN ANTI-MAG ANTIBODY NEUROPATHY: A PHASE II ITALIAN MULTICENTER CLINICAL TRIAL (MAZINGA)

Eu CT number 2025-523091-23-00

Protocol Number: "MAZ-01"

Protocol abbreviation: MAZINGA

Date and version of the Protocol: v2.1 03DEC2025

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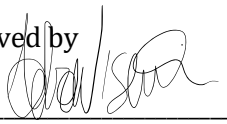
Conduct: Conducted in compliance with this Protocol, International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), with Regulation EU No. 536/2014 on Clinical Trials, and in accordance with local regulatory requirements.

PROTOCOL APPROVAL SIGNATURE PAGE

I have read and understand the contents of V2.1 of this clinical study Protocol for Study No. MAZ-01 dated 03 December 2025 and I agree to meet all the obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Date 04/12/2025

Approved by



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Dr ANDREA VISENTIN

PRINCIPAL INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

I have read and understood the contents of Version 2.1 of this clinical protocol for Study No. MAZ-01 dated 03 Dec 2025 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practices and applicable EMA and local regulatory requirements.

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Principal Investigator's Signature Date

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LIST OF ABBREVIATIONS

ACBP Adult Subjects of Childbearing Potential
AE Adverse Event
AESI Adverse Event of Special Interest
AIFA Agenzia Italiana del Farmaco
ALT Alanine Aminotransferase
ANC Absolute Neutrophil Count
ASaT All-subject-as-treated
ASCO American Society of Clinical Oncology
AST Aspartate Aminotransferase
AUC Area Under the Curve
BM Bone Marrow
BTK Bruton's Tyrosine Kinase
CANOMAD Chronic Ataxic Neuropathy, Ophthalmoplegia, IgM Monoclonal Abnormal protein, Disialosyl antibodies
CBC Complete Blood Count
cfDNA Cell-Free DNA
CIOMS Council for International Organizations of Medical Sciences
CLL Chronic Lymphocytic Leukemia
CMAP Compound Action Muscle Potential
CR Complete Response
CRF Case Report Form
CRi Complete Response with Incomplete Bone Marrow Recovery
CSF cerebrospinal fluid
CTCAE Common Terminology Criteria for Adverse Event
CXCR4 Chemokine Receptor type 4
CYP3A Cytochrome P450, family 3, subfamily A
ddPCR Droplet Digital Polymerase Chain Reaction
DML Distal Motor Latency
EC Ethics Committee
ECG Electrocardiogram
ECOG Electrocorticography
EFNS European Federation of Neurological Societies
EKG electrocardiogram
EMA European Medicines Agency
EMG Electromyography
ENG Electroneurography
EU European Union
GCP Good Clinical Practice
Gdna Genomic DNA
GMP Good Manufacturing Practice
GVP Good Pharmacovigilance Practice
HBcAb Hepatitis B core Antibody
HBsAg Hepatitis B surface Antigen
HBV Hepatitis B Virus
HCV Hepatitis C Virus

ICF Informed Consent Form
ICH International Council for Harmonisation
IgM Immunoglobulin M
INCAT Inflammatory Neuropathy Cause and Treatment
IRB Institutional Review Board
I-RODS Inflammatory Rasch-Built Overall Disability Scale
ISS INCAT Sensory Sum Score
IU International Unit
LDH Lactate Dehydrogenase
MAG Myelin-associated Glycoprotein
MCV Motor Conduction Velocity
MGUS Monoclonal Gammopathy of Undetermined Significance
MRC Medical Research Council
MYD88 Myeloid Differentiation Primary Response
MZL Marginal Zone Lymphoma
NRS Numeric Rating Scale
NRS Numeric Rating Scale
ONLS Overall Neuropathy Limitations Scale
ORR Overall Response Rate
OS Overall Survival
PLCG2 Phospholipase C Gamma 2
PNS Peripheral Nerve Society
POEMS Patient-Oriented Evidence that Matters
PQC Product Quality Complaint
PR Partial Response
QOL Quality of Life
QPPV Qualified Person for Pharmacovigilance
SAE Serious Adverse Event
SCV Sensory Conduction Velocity
SNAP Sensory Nerve Action Potential
SUSAR Suspected Unexpected Serious Adverse Reaction
TLI Terminal Latency Index
TP53 Tumor Protein P53
U.O.C Unità Operative Complessa
ULN Upper Limit of Normal
VGPR Very Good Partial Response
WBC White Blood Cells
WHO World Health Organization
WM Waldenstrom Macroglobulinemia
WMA World Medical Association
WOCBP Women of Childbearing Potential

ZANUBRUTINIB, A SECOND GENERATION BTK INHIBITOR, IN ANTI-MAG ANTIBODY NEUROPATHY: A PHASE II ITALIAN MULTICENTER CLINICAL TRIAL (MAZINGA)

1 Introduction

Monoclonal gammopathy of neurological significance is an emerging often unrecognized condition characterized by several facets, of which polyneuropathy with antibodies to the myelin-associated glycoprotein (MAG) is the most common entity. Anti-MAG antibody polyneuropathy is a rare and disabling neuropathy, orphan of specific and effective therapies. Patients are usually elderly presenting with distal, symmetric, sensory involvement with gait ataxia and postural tremor at upper limbs. Motor impairment occurs late in the course of the disease. Although slowly progressive, the neuropathy may become severely disabling after several years (25% at 10 years, 50% after 15 years)[1,2] sometimes requiring the use of a wheelchair. All patients have an IgM monoclonal paraprotein that only in half of cases is related to a hematological malignancy such as Waldenstrom macroglobulinemia (WM)[3], marginal zone lymphoma (MZL) or chronic lymphocytic leukemia (CLL).

Anti-MAG antibodies have a pathogenic role, since pathological studies on nerve biopsies show segmental demyelination with IgM M-protein and complement deposition on nerve myelin[4]. Moreover, serum from patients with anti-MAG antibody neuropathy induces demyelination[5] and also a demyelinating neuropathy in experimental model[6]. These considerations have prompted the use of immunologic therapies in patients (such as steroids, plasma-exchange, cyclophosphamide, azathioprine, interferon, high dose immunoglobulin) but with disappointing results7. Some open pilot trials have addressed the effect of rituximab on IgM paraproteinemic neuropathies. In particular, the Italian peripheral nerve study group treated 13 patients with anti-MAG antibody polyneuropathy showing a reduction of the anti-MAG antibody titers in more than 50% of subjects with mild improvement in clinical status, especially in the sensory items[8]. IgM MGUS and WM-associated anti-MAG neuropathies display similar response to rituximab therapy, with less than 50% of patients reporting clinical benefit[9].

Rituximab has been assessed in two randomized controlled trials[10,11] with controversial results, both of them, however, accounting only for MGUS patients, WM being an exclusion criteria. The first study enrolled 26 patients undergoing a single course of rituximab or placebo. In the 13 patients treated with rituximab, 4/13 improved by ≥1 point on the Inflammatory Neuropathy Cause and Treatment (INCAT) disability leg score, and the majority of them (69%) showed significant improvement in the 'time to walk 10 m')[10]. The second study that included 54 patients treated with a single course of rituximab or placebo.[11] Changes were observed in the rituximab group only in some secondary outcome measures, including improvement by ≥2 points on the INCAT disability scale, improvement in the self-evaluation scale and in two sub-scores of the Short Form 36 questionnaire[11]. A comparison between the two studies is difficult, because of the different inclusion criteria and the different disease duration before starting treatment (12.9 yrs in the first study vs 3.8 in the second study, respectively). A Cochrane review[12] concluded that there is inadequate reliable evidence from trials of immunotherapies in anti-MAG paraproteinemic neuropathy to recommend any treatment. The meta-analysis of two clinical trials, recruiting a total of 80 patients, provides evidence of improvement in 50-60% patients of disability scale and self-evaluation, reduction of lymphocytes, IgM levels and anti-MAG titer with rituximab single agent[11]. For these reasons, rituximab has become the standard treatment of anti-MAG neuropathy. A recent study assessed rituximab in 23 patients with anti-MAG neuropathy. Authors found that some neurophysiological variables, such as ulnar nerve Terminal Latency Index and distal motor latency and ulnar nerve sensory nerve action potential (SNAP) amplitude might be useful for monitoring the efficacy of Rituximab in these patients[13].

Previous human experience

Ibrutinib, the first in class Bruton's tyrosine kinase (BTK) inhibitor, has significantly improved the prognosis and management of patients with B-cell malignancies with an optimal safety profile when used as single agent[14] or in combination with rituximab[15]. Treon et al[16] reported a reduction of anti-MAG antibody titer and clinical improvement in 3 patients with WM and concomitant anti-MAG antibody neuropathy. While patients with anti-MAG antibody neuropathy and a B-cell lymphoma (20-25% of cases) could benefit from therapy with ibrutinib and/or rituximab, the majority (75-80%) with IgM monoclonal

component of unknown significance (MGUS) could not. Moreover, recent studies on the biology of the disease showed that patients with anti-MAG antibody polyneuropathy are characterized by recurrent $MYD88^{L265P}$ mutations but very low incidence of $CXCR4^{whim}$ and TP53 mutations[17]. This molecular profile is predictive of high and durable response rates to ibrutinib in WM[18]. Furthermore, molecular remission of MYD88 recently emerged as an independent predictor of progression-free survival in patients with WM treated with rituximab-based chemo-immunotherapy[19].

Recently, Castellani et all report the clinical efficacy of ibrutinib in 3 MYD88-mutated patients with WM anti-MAG peripheral neuropathy[20]. Treatment was well tolerated, and all 3 patients reported a subjective early benefit during ibrutinib treatment as well as an improvement of INCAT disability and sensory scores. Zanubrutinib is a second generation BTK inhibitor, characterized by a more selective kinase profile compared to ibrutinib, that proved to be highly active as well as better tolerated in several B-cell hematological malignancies. In particular, the Aspen[21] study compared zanubrutinib and ibrutinib in patient with WM within a phase 3 clinical trials. Twenty-nine (28%) zanubrutinib patients and 19 (19%) ibrutinib patients achieved a VGPR (very good partial response). Duration of response and progression free survival of zanubrutinib was superimposable to ibrutinib. However, atrial fibrillation, bruising, diarrhea, muscle spasms, and pneumonia, as well as adverse events leading to treatment discontinuation, were less common among zanubrutinib recipients. In a subgroup analysis, zanubrutinib proved its activity in MYD88-wild type patients[22]. At a median follow-up of 17.9 months, 7 of 26 MYD88-wild type patients (27%) had achieved a VGPR and 50% at least a partial response. At 18 months, the estimated progression-free survival and overall survival rates were 68% and 88%. Furthermore, zanubrutinib prove to be highly active in CLL and MZL[23,24].

These results demonstrate that zanubrutinib and ibrutinib are highly effective in the treatment of WM, but zanubrutinib treatment was associated with a trend toward better response quality, in particular in MYD88 wild type patients, and less toxicity, particularly the cardiovascular toxicity.

With this background, we would like to perform a multicenter, open label, single arm phase IIA trial to evaluate the activity, safety and tolerability of zanubrutinib in patients with symptomatic IgM related anti-MAG antibody neuropathy.

2 Objective of the trials

Primary objective

To investigate whether 12 months zanubrutinib treatment led to an improvement of at least 1 point in at least 2 neurological scales as a decrease for the Overall Neuropathy Limitations Scale (ONLS), INCAT disability, INCAT sensory sum scores (ISS), but an increase with the MRC sum and I-RODS functional score.

Secondary objectives

- To evaluate ENG/EMG improvement, in particular a reduction of distal motor latency, or an increase of terminal latency index or an increase of sensory nerve action potential amplitude (see criteria of evaluation) after zanubrutinib treatment at 12, 24 and 48 months;
- To evaluate the efficacy by hematological overall response rates, event free survival, time to progression (defined as worse of at least 1 point in two neurological scales), overall survival;
- To study the safety profile of zanubrutinib in patients with anti–MAG antibody polyneuropathy.

Exploratory objectives

- To evaluate the quality of life or patients by FACT-GOG-NTX-13 QOL questionnaire;
- To identify any correlation between neurologic response (assessed by the neurological scaled mentioned in the primary endpoint) and hematologic overall response (CR, VGPR, PR) at 24 and 48 months, event free survival, time to progression and overall survival with demographic, clinical, molecular and pathological (MGUS vs lymphoma) features of the patients at baseline;
- To evaluate the reduction of MYD88 mutational burden by cf-DNA during treatment;

  To evaluate the emergence of BTK and PLCG2 mutational status in relapsing patients.

3 Endpoints of the trial

Primary endpoint
The proportion of patients with neurological improvement defined as improvement of at least 1 point in at least 2 neurological scales (a decrease of the ONLS, INCAT disability, INCAT sensory sum scores (ISS), but an increase of MRC sum and I-RODS functional score) at 12 months of zanubrutinib treatment.
Secondary endpoints

- the proportion of patients with neurological improvement after 24 and 48 months of zanubrutinib;
- the proportion of patients with ENG/EMG improvement since the baseline, assessing decrease of distal motor latency, increase of terminal latency index, increase of sensory nerve action potential amplitude (see criteria of evaluation) at upper limbs after zanubrutinib treatment at 12, 24 and 48 months;
- levels of monoclonal protein, IgM and of anti-MAG antibody titers at 12, 24 and 48 months.
- Type, frequency and severity of adverse events, severe adverse event and adverse event of special interest with zanubrutinib in patients with anti–MAG antibody polyneuropathy;
- Overall response rate, defined as the proportion of patients achieving complete response (CR), complete response rate with incomplete bone marrow recovery (CRi), very good partial response (VGPR), partial response according to guidelines;
- Event free survival, defined as time from the start of therapy to relapse or death or start of a new therapy (event) or last known follow-up (censured);
- Time to progression, defined as time from the start of therapy worse of neurological symptoms defined as worse of least 1 point in at least 2 neurological scales such as Overall Neuropathy Limitations Scale (ONLS), INCAT disability, INCAT sensory sum scores (ISS), MRC sum score, I-RODS functional score after the nadir
- overall survival, defined as time from the start of therapy to death (event) or last known follow-up (censured).

Exploratory endpoints

- Quality of life will be assessed by FACT-GOG-NTX-13 QOL questionnaire every 3 months during the first year and then every 6 months;
- correlation between neurologic responses (assessed by the neurological scaled reported for the primary endpoint) and hematologic overall response (CR, VGPR, PR) at 24 and 48 months, event free survival, time to progression and overall survival with demographic, clinical,molecular and and pathological (MGUS vs lymphoma) features of the patients at baseline;
- reduction of MYD88 mutational burden by cf-DNA during treatment;
- BTK and PLCG2 mutation status in relapsing patients.

4 Selection of patients

Inclusion criteria

- Age ≥18 years;
- diagnosis of anti-MAG antibody polyneuropathy;
- Neurophysiological (ENG/EMG) evidence of a demyelinating polyneuropathy with evidence of disproportionately prolonged distal motor latency in one or more nerves -excluding the median nerve if related to carpal tunnel syndrome- [Joint Task Force of the EFNS and the PNS, 2010].
- IgM monoclonal protein underlying MGUS (based on the WHO definition of clonal lympho- plasmocytes <10%), Waldenstrom macroglobulinemia (based on the WHO definition of clonal lympho-plasmocytes ≥10%), marginal zone lymphoma, chronic lymphocytic leukemia or low- grade lymphoma not otherwise specified;
- Presence of anti MAG antibodies (titer ≥ 7.000 BTU);
- Neurophysiological (ENG/EMG) evidence of demyelinating polyneuropathy;
- ONLS at lower limbs at least ≥1 and/or INCAT ≥2.
- Adequate bone marrow function as defined by:
    - Absolute neutrophil count (ANC) ≥ 1000/mm3, except for patients with bone marrow involvement in which ANC must be ≥ 500/mm3

- Platelet ≥ 75,000/mm3, except for patients with bone marrow involvement in which the platelet count must be ≥ 30,000/mm3

- Women should avoid becoming pregnant while taking Brukinsa and for up to 1 month after ending treatment. Male patients with a female partner of childbearing potential are eligible if vasectomized or if they agree to the use of barrier contraception with other methods described above during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib.
- Women of childbearing potential (WOCBP[1]) should avoid becoming pregnant while taking Brukinsa and for up to 1 month after ending treatment. Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use highly effective methods of contraception:
    - 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
    - Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day before the first dose of study treatment, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib, for ≥ 28 days after the last dose of lenalidomide, or according to the approved obinutuzumab and rituximab product/prescribing information, whichever is later). 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, post-ovulation 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.
For patients using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must be used.

- Male patients with a female partner of childbearing potential are eligible if abstinent, vasectomized or if they agree to the use of barrier contraception with other methods or agree to use a condom during sexual contact with a pregnant women or a women of childbearing potential during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib.

[1] WOCBP is a woman who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Exclusion criteria

- Previous treatment with BTK inhibitors
- Aggressive non-Hodgkin lymphoma or IgM multiple myeloma
- Evidence of moderate or severe motor nerve axonal damage, defined when occurring diffuse polyneuropathic denervation or a recruitment pattern lower than intermediate in ≥50% of muscles examined, and/or INCAT at lower limbs ≥4.
- ECOG >3
- Use of strong CYP3A inducers within 14 days prior to the first dose of zanubrutinib (see Drug-

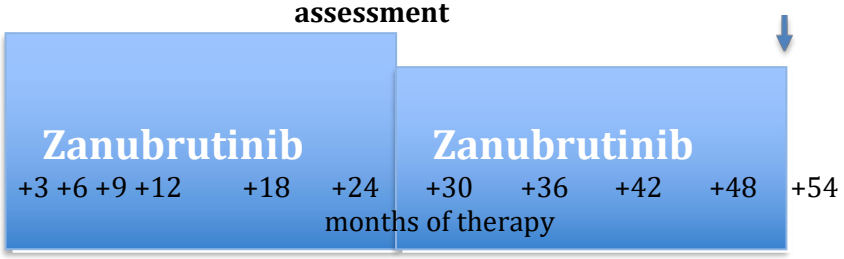
interaction section).
- creatinine clearance <30mL/min
- Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase, and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase> 2.5 × upper limit of normal (ULN); Serum total bilirubin >2 x ULN.
- presence of other possible causes of neuropathy, such as active HCV infections, diabetes- neuropathy, POEMS syndrome, CANOMAD syndrome, etc.
- Any co-existing medical or psychological condition that would preclude participation in the study or compromise the ability to give informed consent.
- History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention. Requires ongoing treatment with warfarin or warfarin derivatives. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug
- Any uncontrolled or clinically significant cardiovascular disease including the following:
- Myocardial infarction within 6 months before screening
- Unstable angina within 3 months before screening
- New York Heart Association class III or IV congestive heart failure
- History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)
- Active fungal, bacterial and/or viral infection requiring systemic therapy
- Known active infection with HIV, or serologic status reflecting active hepatitis B or C infection as follows:
- Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable (< 20 IU), and if they are willing to undergo monitoring every 4 weeks for HBV reactivation.
- Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable.
- Pregnant or lactating women.
- Vaccination or requirement for vaccination with a live vaccine within 28 days prior to the first dose of study drug or at any time during planned study treatment
- Ongoing alcohol or drug addiction or any psychiatric condition(s) which would compromise ability to comply with study procedures.
- Hypersensitivity to zanubrutinib or any of the other ingredients of the applicable study drugs.
- Active malignancy or systemic therapy for another malignancy within 3 years, which the except of adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, cervical carcinoma in situ without evidence of disease, localized prostate cancer without evidence of disease.

Discontinuation criteria
Zanubrutinib must be discontinued:
- after any grade intracranial hemorrhage;
- if toxicity cannot be treated to full resolution;
- if any toxicity recurs 4 times;
- and in cases of pregnancy.

5 Study design

This is a prospective phase IIA trial in which patients with polyneuropathy associated with antiMAG antibody will be treated with zanubrutinib. Patients with an hematological malignancies (waldenstrom macroglobulinemia, marginal zone lymphoma, chronic lymphocytic leukemia) that can be treated with zanubrutinib according to the Italian drugs agency (AIFA) approval and reimbursement criteria with be treated with zanubrutinib as per clinical practice and patients will

be followed prospectively. Instead, patients with MGUS (monoclonal gammopathy of undetermined significance) will be treated with zanubrutinib as an investigational medical product within this trial. In patients who will improve, defined as improvement of at least 1 point in 2 neurological scales (decrease of INCAT, ISS, ONLS, but increase for I-RODS and MRC), or in whom the neuropathy will not worse, defined as worse of at least 1 point in 2 neurological scales, zanubrutinib will be continued for additional 2 years.

Screening phase (28 day) - <u>Baseline</u> CBC and biochemistry ENG/EMG Hearth US, EKG anti-MAG antibody titer abdomen US bone marrow biopsy and aspirate cfDNA QoL, neurological assessment, pregnancy test	**<u>Start of therapy</u>** **<u>End of therapy</u>** **Response assessment** 

- ENG/EMG at upper and lower limbs at baseline and then every 6 months till month +54;
- Nerve ultrasound at upper and lower limbs at baseline, after 24 and 48 months of zanubrutinib, where available;
- CBC, biochemistry (hepatic and liver function, serum protein electrophoresis, IgG, IgA, IgM, free light chains, 24h-urine protein, Bence Jones protein, beta2microglobulin, LDH, albumin), anti-MAG titer every 3 months during the first year then every 6 months till month +54; Pregnancy test in childbearing potential at baseline, before 48 before of the first dose and then every 4 weeks till 8 weeks after the last dose of zanubrutinib, is needed.
- Neurological scales at baseline, every 6 months till months +24 and after for responding patients: MRC sum score, INCAT disability and INCAT sensory sum scores (ISS), Overall Neuropathy Limitations Scale (ONLS), I-RODS functional score, 10-meter walking time, 9-hole peg test, NRS;
- Bone marrow biopsy performed at baseline or within the last 3 months from study entry, after 24 and 48 months of zanubrutinib;
- Bone marrow aspirate at baseline, after 24 and 48 months of treatment;
- Abdomen US, Heart ultrasound and Electrocardiogram (ECG) at baseline, after 24 and 48 months.
- Plasma MYD88 L265P cell-free DNA at baseline and every 6 months till month +54;
- Quality of life will be assessed by FACT-GOG-NTX-13 QOL questionnaire every 3 months during the first year and then every 6 months.

Schedule of Activities

	Screening	Months of treatment											
Treatment cycles (28-day cycle)	-	**+1**	**+3**	**+6**	**+9**	**+12**	**+18**	**+24**	**+30**	**+36**	**+42**	**+48**	**+54**
Visit days +/- 7	**-28 to -1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**
Informed consent	x												
Review inclusion / exclusion criteria	x												
Demographic data	x												

Medical history	x												
Neuropathy diagnosis and treatment history	x												
Blood exams[3]		x	x	x	x	x	x	x	x	x	x	x	x
ENG/EMG[1]	x			x		x	x	x	x	x	x	x	x
Nerve ultrasound[2]	x							x				x	
Neurological exams[4]		x		x		x	x	x	x	x	x	x	x
Abdomen and heart US, ECG[6]	x							x				x	
Bone marrow biopsy and aspirate[5]	x							x				x	
cfDNA[7]		x		x		x	x	x	x	x	x	x	x
Quality of life		x	x	x	x	x	x	x	x	x	x	x	x
Response assessment[8]				x		x	x	x	x	x	x	x	x

1. electroneurography (ENG)/electromyography (EMG) at upper and lower limbs at baseline and then every 6 months till month +54;
2. Nerve ultrasound at upper and lower limbs at baseline, after 24 and 48 months of zanubrutinib, when available;
3. Complete blood count with differential, biochemistry (hepatic and liver function, serum protein electrophoresis, IgG, IgA, IgM, free light chains, 24h-urine protein, Bence Jones protein, beta2microglobulin, LDH, albumin), anti-MAG titer every 3 months during the first year then every 6 months till month +54; Pregnancy test in childbearing potential at baseline, before 48 before of the first dose and then every 4 weeks till 8 weeks after the last dose of zanubrutinib, is needed.
4. Neurological scales at baseline, every 6 months till months +24 and after for responding patients: MRC sum score, INCAT disability and INCAT sensory sum scores (ISS), Overall Neuropathy Limitations Scale (ONLS), I-RODS functional score, 10-meter walking time, 9-hole peg test, NRS;
5. Bone marrow biopsy performed at baseline or within the last 3 months from study entry, after 24 and 48 months of zanubrutinib. Bone marrow aspirate at baseline, after 24 and 48 months of treatment;
6. Abdomen US, Heart ultrasound and Electrocardiogram (ECG) at baseline, after 24 and 48 months.
7. Plasma MYD88 L265P cell-free DNA at baseline and every 6 months till month +54;
8. Quality of life will be assessed by FACT-GOG-NTX-13 QOL questionnaire every 3 months during the first year and then every 6 months.

6 Risks and benefits assessment

The therapeutic approach of the present study may be beneficial for patients with anti-MAG antibody neuropathy in terms of efficacy in comparison with an acceptable toxicity profile.

Risks to participating in the study

- Toxicity

Please refer to Appendix C: study drug toxicities.

- Psychosocial distress

Trial participation can entail psychological distress for patients beyond that caused by the illness itself: patients may experience depression, stress, uncertainty as a result of trial participation, loneliness and fear. Trial participation can also be a social burden for patients, straining on relationships with partners and on other social contacts.

7 Treatment

Patients with WM, MZL and CLL will be treated with zanubrutinib according to the Italian drug agency (AIFA) reimbursement criteria, while zanubrutinib will be provided by the sponsor for patients with MGUS or other low-grade lymphoproliferative diseases . All patients will receive zanubrutinib at 160mg bis-in-die orally or 320mg QD from day 1 of the first cycle for at least 2 years

and, if the patients have at least a stabilization of the disease, they will be treated for additional 2 years. After 4 years all patients will stop treatment. Therefore, although the treatment authorization differs, the conduct of the study does not differ, continuation of zanubrutinib for an additional two years is governed by the same predefined neurological response criteria. This ensures that treatment exposure, decision-making processes, and endpoints remain consistent across the study population. Both groups will be analyzed together for endpoints, given the identical assessment schedule, outcome measures, and longitudinal data collection

Drugs management

Zanubrutinib bottles will be stored at room temperature 15ºC to 30ºC (59°F to 86°F). Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Patients will take zanubrutinib with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Zanubrutinib capsules should not be opened, broken, or chewed at any time. Patients should be instructed that if a dose of zanubrutinib is not taken at the scheduled time, they should skip the study drug if the time to next dose is 8 hours or less,and return to normal dosing with the next dose. If a patient vomits after taking the zanubrutinib capsules, that dose should not be repeated.

Dose reductions and management and prophylaxis of Specific Adverse Events

Table 1. Guidelines for Management of Specific Adverse Events

HEMATOLOGIC TOXICITY	
Grade 3 or 4 neutropenia with/without fever and infection despite G-CSF	Hold zanubrutinib
	Administer G-CSF or growth factors for neutropenia as indicated
	When counts recover to ANC ≥ 1.5 × 10^9/L and/or platelets are ≥ 75 × 10^9/L resume treatment, and all signs of active infection are resolved (see next Section for the next dose).
Any grade intracranial hemorrhage	Discontinue zanubrutinib permanently
Severe thrombocytopenia, (platelets < 25 000/μL) and/or or presence of symptomatic bleeding	Hold treatment with zanubrutinib for severe thrombocytopenia (platelets < 25,000/μL) or presence of symptomatic bleeding until resolution of bleeding Platelets may be transfused at the discretion of the investigator

HEMATOLOGIC TOXICITY	
Grade 3 or 4 neutropenia with/without fever and infection despite G-CSF	Hold zanubrutinib
	Administer G-CSF or growth factors for neutropenia as indicated
	When counts recover to ANC ≥ 1.5 × 10^9/L and/or platelets are ≥ 75 × 10^9/L resume treatment, and all signs of active infection are resolved (see next Section for the next dose).

Severe thrombocytopenia, (platelets < 25 000/µL) and/or or presence of symptomatic bleeding	Hold treatment with zanubrutinib for severe thrombocytopenia (platelets < 25,000/µL) or presence of symptomatic bleeding until resolution of bleeding Platelets may be transfused at the discretion of the investigator
	In presence of any grade intracranial hemorrhage permanently discontinue zanubrutinib. When bleeding is resolved to grade 1, platelet level rises up to 50,000/µL without transfusion support for 5 consecutive days zanubrutinib at dose level (-1) If underlying condition cannot be treated to full resolution, permanently discontinue zanubrutinib.
OTHER TOXICITIES	
Atrial fibrillation (AF)	Hold until AF is controlled and anticoagulation introduced if required Re-start at either the original dose or dose level (-1), at the discretion of the treating investigator.
Inadequately controlled hypertension	Hold until hypertension to less than or equal to baseline. If baseline is greater than grade 1; hold until less than or equal to Grade 1 if BL is less than or equal to Grade 1. Re-start at the original dose level. If same event recurs at ≥ Grade 3, reduce dose by one level after recovery to BL or Grade 1.
Grade 3 or 4 non-hematologic events not specifically described above	Delay treatment with zanubrutinib for a maximum of 56 days.
	First event: if improvement to Grade ≤ 1 or baseline, resume treatment at the same dose For subsequent events: if improvement to Grade ≤ 1 or baseline, restart treatment at one dose level reduction.
Grade 1-2 non-hematologic toxicity	No dose reduction or delay.Delay treatment (zanubrutinib) for a maximum of 56 days until resolution to Grade ≤ 1 (or baseline status) After resolution, resume full dose of treatment
Grade 1 non-hematologic Toxicity	No dose reduction or delay.

G-CSF = granulocyte stimulating factor.

Zanubrutinib dose after treatment discontinuation

Treatment with zanubrutinib may be restarted upon resolution of toxicity and per investigator discretion if held **for a maximum of 56 consecutive days**.
If, in the investigator's opinion, it is in the patient's best interest to restart treatment after > 56 days, then written approval must be obtained from the sponsor's.

1) **First treatment interruption: once the toxicity has resolved to grade 1 or baseline level**,

therapy with zanubrutinib may be restarted **at the same dose.**

2) If the toxicity recurs, and for any subsequent occurrences, the dose of zanubrutinib should be reduced (Table 3). Based on patients' clinical characteristics, higher dose reduction may be considered at the discretion of the investigator.

Table 2. Zanubrutinib dose after treatment discontinuation

Toxicity occurrence	Zanubrutinib	
	Prior dose of zanubrutinib at interruption	**Restart zanubrutinib**
First	160 mg twice daily	Restart at 160 mg twice daily*
Second	160 mg twice daily	Restart at 80 mg twice daily
Third	80 mg twice daily	Restart at 80 mg once daily
Fourth	80 mg once daily	Discontinue zanubrutinib

*In patients with prior severe bleeding, re-start zanubrutinib at dose level (-1)

If the underlying condition cannot be treated to full resolution, permanently discontinue zanubrutinib. Dose modifications for hematological toxicity in patients with WM/CLL/MZL must consider the increased frequency of hematological compromise at the initiation of therapy. Therefore, the standard criteria used for solid tumors are difficult to be applied directly; many patients would be considered to have Grade II to IV hematological toxicity at baseline. The underlying disease, as well as adverse reactions to the therapy under study may further worse these cytopenias.

Concomitant surgery procedures, drugs and

Foods Surgery and Procedures

Susceptibility to bleeding has been observed with BTK inhibitors. Treatment with zanubrutinib should be held for 3 to 7 days before and after surgery, depending upon the type of surgery and the risk of bleeding.

Infection prophylaxis

Patients treated with BTK inhibitors such as zanubrutinib have an increased risk of Pneumocystis Carinii, also with atypical phenotype, fatal and non-fatal bacterial infections, but also herpes viral, cryptococcal, aspergillus infections and hepatitis B virus (HBV) reactivation. Therefore, prophylaxis with Bactrim is recommended. The use of azoles as anti-fungal prophylaxis or therapy should be discussed because of the potential drug–drug interactions. Immunoglobulins should be considered when clinically indicated in patients with hypogammaglobulinemia. Prophylactic antiviral therapy with lamivudine or entecavir or HBV-DNA monitoring (every 3 months), is recommended in patients with negative HBsAg and HBV-DNA but positive HBcAb (regardless of HBsAb status).

Prophylaxis of neutropenia

Use of neutrophil growth factors is permitted per the ASCO guidelines.

Live viral vaccines

Live viral vaccines to patients should not be administered. The safety of immunization with vaccines following zanubrutinib therapy has not been studied.

Skin cancer

Since, the most frequent second primary malignancy associated with the use of zanubrutinib in patients with B-cell malignancies was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin). Patients should be advised to use sun protection.

Prohibited Food
Use of the following foods is prohibited during study treatment and for at least 3 days prior to initiation of study treatment:
- Grapefruit
- Grapefruit products
- Seville oranges (including marmalade containing Seville oranges)
- Star fruits

Drugs not allowed during the study
The use of warfarin and other vitamin K antagonists is not allowed during this study. The investigator should evaluate the use of other anticoagulation therapies, such as apixaban/dabigatran or low-molecular weight heparin. Steroid therapy for anti-neoplastic intent with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids are allowed only for 10 days during the study at any time.

Drug–Drug Interaction

It has been shown that co-administration of zanubrutinib with the strong CYP3A inducer rifampin decreased AUC0-∞ of zanubrutinib by 13.5-fold in healthy subjects. Co-administration of zanubrutinib with strong CYP3A inhibitor itraconazole increased AUC0-∞ of zanubrutinib by 3.8-fold (refer to Section 1.3.2.3). These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib. Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (see Table 5 for a list of these medications) and grapefruit juice and Seville oranges should be used with caution as they may affect the metabolism of zanubrutinib (APPENDIX D). If possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and should consider using alternative agents. If these agents will be used, follow the dose modification table in Table 8. The medical monitor should be consulted in these situations. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

Table 3. Dose Modification for zanubrutinib when Co-Administered with Strong/Moderate CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended use
Inhibition	Strong CYP3A inhibitor (eg. ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole)	80 mg once daily
	Moderate CYP3A inhibitor (eg. erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit products)	80 mg twice daily
Induction	Strong CYP3A inducer (e.g. carbamazepine, phenytoin, rifampin, St. John's wort)	Avoid concomitant use; Consider alternative agents with less induction potential.

	Moderate CYP3A inducer (eg. bosentan, efavirenz, etravirine, modafinil, nafcillin)	160 mg twice daily, use with caution; Monitor for potential lack of efficacy.

8 Pregnancy and contraception

Adult subjects of childbearing potential (ACBP) must:

- Understand the potential teratogenic risk to the unborn child and the need for effective contraception.
- Be capable of complying with effective contraceptive measures.
- Be informed and understand the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy.
- Understand the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test.
- Understand the need and accept to undergo pregnancy testing based on the frequency outlined in this protocol.

ACBP enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) while participating in the study; 2) in case of dose interruptions; and 3) after the last dose of study drug.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. ACBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception

Highly effective methods:

- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy.

Additional effective methods:

- Male condom
- Diaphragm (not recommended in patients with low platelets count)
- Cervical cap.

Pregnancy tests

Pre-menopausal women who are not surgically sterile must agree to have pregnancy tests:

1. One serum test at baseline
2. One serum test within 48 hours prior treatment with zanubrutinib start
3. One serum test every 4 weeks during treatment period with zanubrutinib combination.
4. After zanubrutinib discontinuation:

a) one serum test after 4 and 8 weeks from the last dose.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (>/= 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Mullerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

The reliability of sexual abstinence should be evaluated in relation duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. Willingness to not donate sperm or oocytes during the entire study treatment period

and after treatment discontinuation for 90 days after the last dose of zanubrutinib.

9 Duration of the study

Definition of the ending of the study: the last visit of the last subject in the last clinical trial site involved in the study.

Estimated starting date: Q4 2025

Ending date: Q1 2031

Recruitment duration: 18 months

10 Discontinuation of study treatment

Completion
A subject will be considered to have completed the study if he or she has not died before the end of the study, has not been lost to follow-up, or has not withdrawn consent before the end of study.

Discontinuation of treatment
Treatment should be discontinued if any of the following occurs:

- The subject experiences disease progression or relapse
- The subject becomes pregnant
- The subject refuses further treatment with the study drug
- The investigator believes that for safety reasons (e.g. AE) it is in the best interest of the subject to stop treatment.
- Any grade intracranial hemorrhage;
- Any toxicity recurs 4 times
- In case a toxicity cannot be treated to resolution;

Withdrawal from the study
A subject will be withdrawn from the study for any of the following reasons:

1. Withdrawal of consent
2. Lost to follow-up
3. Death
4. The sponsor discontinues the study for one of the following reasons:
    a. Evidence of lack of therapeutic effect or disease progression
    b. Toxicity and/or any SAEs that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug
    c. Major violation of the study protocol.

If a subject is lost to the follow-up, then every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken up must be documented. When a subject withdraws before completing the study, the reason for the withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

10.1 Study Discontinuation Criteria

In accordance with ICH E6(R3) Good Clinical Practice and Regulation (EU) 536/2014, the Sponsor may temporarily halt or permanently discontinue the clinical trial if new information arises that results in an unfavourable risk–benefit assessment or compromises participant safety, trial integrity, or regulatory

compliance.

The clinical trial may be discontinued under any of the following circumstances (non-exhaustive list):

- **Identification of unacceptable risks to participants**, including adverse events or reactions whose nature, severity, or frequency is new, unexpected, or inconsistent with the known safety profile of the investigational medicinal product.
- **Emergence of relevant toxicity or other safety concerns** that cannot be adequately managed within the framework of the study and that modify the risk–benefit balance.
- **Receipt of new safety information** from other clinical trials, non-clinical studies, pharmacovigilance activities, or post-marketing data indicating potential harm or a negative change in the risk–benefit profile.
- **A recommendation from Regulatory Authorities and Ethics Committees** to suspend or terminate the study for safety, ethical, or scientific reasons.
- **Major non-compliance** with the protocol, ICH GCP, or applicable regulatory requirements that may compromise participant protection or the scientific value of the trial.
- **Any other situation** that, in the judgement of the Sponsor, renders continuation of the study unjustifiable, unsafe, or non-compliant with the applicable regulatory framework.
- If the study is temporarily halted or permanently discontinued, the Sponsor will fulfil all obligations established by Regulation (EU) 536/2014, including timely notification to the Member States concerned via CTIS, the relevant Ethics Committee(s), and all investigators. The Sponsor will ensure that all trial participants are appropriately informed and managed in accordance with ethical standards and regulatory requirements.

11 Drug supply Accountability

Zanubrutinib for WM, MZL and CLL will be used according to the Italian drug agency, while for MGUS or other low-grade lymphomas will be supplied by the Sponsor.

The investigator and the trial site are responsible for investigational product accountability. To this end, it is assumed that all clinical trial supplies will be delivered to and by the responsibility of a suitably qualified and authorized person such as a hospital pharmacist, who will document drug disposition and accountability for the duration of the trial.

Packaging, labelling and storage

Packaging and labelling will be in accordance with Good Manufacturing Practice (GMP) for clinical trials. They must not be employed for any other trial or for any other clinical use.

Drug reconciliation procedures

The drug formulation, dose, number of bottles/capsules dispensed, received, and returned must be recorded. The investigator must maintain an accurate record of the shipment and dispensing of the study drugs in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each patient must be available for inspection at any time. All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any drug labels, or any partly used or unused drug supply. At the conclusion of the study, and, as appropriate during the course of the study, each local site will destroy all used and unused drug containers by providing to the Sponsor with a certificate of destruction.

12 Criteria of evaluation of response

Efficacy evaluations will be performed as specified in the Time and Events Schedule and will include the following examinations:

- Neurological improvement is defined by an improvement of at least 1 point in 2 different neurological scales such as a decrease for the ONLS, INCAT disability, INCAT sensory sum scores (ISS), but an increase of MRC sum and I-RODS functional score;
- Neurophysiology, EMG/ENG and nerve ultrasound (where available)
- Disease-related symptoms, physical examination and patient-reported outcome and quality of life.
- Physical examinations will focus on examination of lymph nodes, liver and spleen.
- CBC with measurement of data including absolute lymphocyte count hemoglobin, platelet, monoclonal protein, IgM levels, anti-MAG antibody titer.
- Overall response rate (ORR), defined as the proportion of subjects with measurable disease achieving a best overall response of either complete remission (CR), very good partial response (VGPR) and partial response (PR).

Efficacy Outcome Measures

- Disease relapse will be defined by as worsening of at least 1 point in 2 different neurological scales such as increase of ONLS, INCAT disability, INCAT sensory sum scores (ISS), but a decrease of MRC sum score, I-RODS functional score after the nadir;
- ORR (defined as rate of a clinical response of CR, VGPR or PR) after 12, 24 and 48 months of zanubrutinib treatment
- Plasma cell free DNA

Neurophysiology recommendation

Neurophysiological examination is assessed at baseline, and every 6 months for 24 months. For responding or stabilized patients, continuing receiving zanubrutinib, EMG/ENG is continued till month +54. Other assessments take place if clinically necessary.
Neurophysiological evaluation is performed, using a standard proper machine. For electroneurographic (ENG) study a standard method with surface electrodes for stimulation and recording, a stimulus duration of 0,1 ms, and a signal bandwidth 20 Hz-10 kHz are used. The following nerves are studied: median nerve, by recording from abductor pollicis brevis muscle and from index finger; ulnar nerve, by recording from abductor digiti minimi muscle and little finger; radial nerve, by recording from skin over the extensor tendons to the thumb; peroneal nerve, by recording from extensor digitorum brevis muscle; tibial nerve, by recording from abductor hallucis brevis muscle; sural nerves, by recording posterior to the lateral malleolus; superficial peroneal nerve, by recording between the tibialis anterior tendon and lateral malleolus. Ulnar and tibial nerve F wave latency is included in the electrodiagnostic evaluation. ENG parameters analyzed are: distal motor latency (DML), compound action muscle potential (CMAP) amplitude, negative peak duration of distal CMAP, motor conduction velocity (MCV), sensory nerve action potential (SNAP) amplitude and sensory conduction velocity (SCV). Distance between the distal stimulation site and the recording motor site is measured in order to ensure correct interpretation of DML change during follow up and to obtain the Terminal Latency Index (TLI) [(distance between distal stimulus site and the recording surface) / (MCV × DML)].
Electromyography with a coaxial needle electrode was performed recording spontaneous and voluntary activity from some muscles of upper and lower limb (at least from first dorsal interosseus, biceps brachii, vastus medialis, tibialis anterior and gastrocnemius), to evaluate axonal damage.

Evaluation of toxicity Safety Outcome Measures

Data from all subjects who receive zanubrutinib will be included in the safety analyses. Subjects who entered the study and did not take zanubrutinib and had this confirmed, will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v5.0.

The safety outcome measures for this study are as follows:
• Nature, frequency, and severity of adverse events and serious adverse events
• Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment
• Premature withdrawals

Time to event analysis

Event free survival will be calculated as time from the start of therapy to relapse or death or start of a new therapy (event) or last known follow-up (censured), whichever is first reported. Patients still alive without signs of worsening of neurological symptoms nor new treatment will be censored on the last date a subject is known to be alive or lost to follow-up. Time to ~~relapse~~ progression will be calculated as time from the start of therapy to the worsening of neurological symptoms defined as worsening of least 1 point in at least 2 neurological scales such as Overall Neuropathy Limitations Scale (ONLS), INCAT disability, INCAT sensory sum scores (ISS), MRC sum score, I-RODS functional score after the nadir. Overall survival (OS) will be calculated as time from the start of therapy to death (event) or last known follow-up (censured). Survival time of living subjects will be censored on the last date a subject is known to be alive or lost to follow-up.

13 Statistical considerations

Size of study population s.

The reference population derives from the II phase NCT00050245 trial which has been published in Annals of Neurology 2009;65:286-293. Twenty-six patients with antiMAG neuropathy were randomized to four weekly infusions of 375mg/m2 rituximab or placebo. The primary endpoint was an increase of at least 1 point of the INCAT leg disability scores at month 8. Thirteen patients were randomized to rituximab and 13 to placebo. Randomization was balanced for age, electrophysiology, disease duration, disability scores, and baseline B cells. After 8 months, by intention to treat, 4 of 13 rituximab-treated patients improved by 1 INCAT score compared with 0 of 13 patients taking placebo (p=0.096). However, excluding 1 rituximab-randomized patient who had normal INCAT score at entry, and thus could not improve, the results were significant (p= 0.036). The time to 10m walk was significantly reduced in the rituximab group (p=0.042) (intention to treat). Clinically, walking improved in 7 of 13 rituximab-treated patients.
Considering the refenreced proportion $p0 \approx 0.323$, a one-sided z test for one-sample proportion, a level of significance (α) of 5%, a power of the study (1-β) equal to 80%, and assuming that the proportion of patients with improvement of at least 1 point in 2 neurological scales (INCAT or ISS or ONLS or I-RODS or MRC) after 12 months of zanubrutinib is 50% (p1=0.50), the number of patients needed to be studied is 45 (https://www.trialdesign.org/). Hypothesizing a study withdrawal of 5% the number of patients to enroll should be at least 47 patients. We plan to screen 50 patients from 9 medical centers.

Efficacy Analysis Populations

The All-Subjects-as-Treated (ASaT) population, which consists of all enrolled subjects who receive at least one dose of study medication, will serve as the primary population for the analyses of efficacy data in this trial. Details on the approach to handling missing data for efficacy analyses are provided in Statistical method section. Only screen failures and patients who refuse before the treatment start would be excluded from the statistical analysis.

Safety Analysis Populations

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Statistical methods

Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Sample Size Section.

The primary endpoint will be summarized by the observed proportion and associated confidence intervals. The one-sided 95% lower confidence bound will be used for the primary hypothesis test (reject H0 if the lower bound exceeds p0). Two-sided 95% intervals will be reported for descriptive purposes.

Secondary endpoints will be analyzed descriptively and inferentially according to their measurement scale. The proportions of patients with neurological improvement at 24 and 48 months and the proportions achieving ENG/EMG improvement at 12, 24 and 48 months will be summarized with the observed proportion and 95% confidence intervals. Continuous laboratory markers (monoclonal protein, IgM, and anti-MAG antibody titers) will be summarized at each timepoint and 95% CIs and analyzed using Wilcoxon or students' t test. Adverse events, serious adverse events and adverse events of special interest will be presented by type, frequency and severity in the safety population. Overall response rate (CR, CRi, VGPR, PR) will be reported as proportions with 95% CIs, and duration- and time-to-response will be described using Kaplan–Meier methods. Event-free survival, time to progression, and overall survival will be analyzed using Kaplan–Meier estimators with medians and 95% CIs.

Key efficacy analyses for primary and secondary endpoints in this study have been summarized

Endpoints/Variables (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary endpoint			
proportion of neurological improvement (defined as improvement of at least 1 point in at least 2 neurological scales decrease for ONLS, INCAT disability, INCAT sensory sum scores (ISS) scale, but increase for MRC sum and I-RODS functional score) (12 months)	observed estimate, one-sided and two-sided 95% Confidence Interval	ASaT	Patients without neurological response will be considered as non-responder
Secondary endpoints			
Proportion of neurological improvement after 24 and 48 months of zanubrutinib	observed estimate, one-sided and two-sided 95% Confidence Interval	ASaT	Patients without neurological response will be considered as non-responder
Proportion of patients with ENG/EMG improvement since the baseline (decrease of distal motor latency, increase of terminal latency index, increase of sensory nerve action potential amplitude at upper limbs) after zanubrutinib treatment at 12, 24 and 48 months	observed estimate, two-sided 95% Confidence Interval	ASaT	Patients in no EMG/ENG assessment will be considered as not responder
Levels of monoclonal protein, IgM and of anti-MAG antibody titers at 12, 24 and 48 months.	means of quartile. Mann-Whitney and Kruskal-Wallis tests in case of continuous variables	ASaT	Patients with missing data will be considered as not responder
Overall response rate, defined as the proportion of patients achieving complete response (CR), complete response rate with incomplete bone marrow recovery (CRi), very good partial response (VGPR), partial response according to guidelines;	Point estimates and 95% Confidence Intervals	ASaT	Patients with missing data will be considered as not responder
Event free survival	Summary statistics using Kaplan-Meier Method	ASaT	Censored at last assessment. Subjects without efficacy evaluation data or without survival data will be censored at Day 1.
Time to progression	Summary statistics using Kaplan-Meier Method	ASaT	Censored at last assessment. Subjects without efficacy evaluation data or without survival data

The baseline characteristics, hematological and neurological responses will be compared according to the MYD88 mutation (present vs wild-type), MGUS vs overt lymphoma with the Wilcoxon or students' t test, Fisher exact test, Chi-square test when appropriated. Survival curves will be plotted with Kaplan-Meier methods and compared with Log-rank test in univariable analysis and by means of Cox regression m\odel in multivariable analysis, after assessment of proportionality of hazards. Comparison between the primary endpoint with the historical control will be based on a one-sided

5% test level. All the other tests will be 2-sided, accepting p<0.05 as indicating a statistically significant difference and confidence intervals will be calculated at 95% level. The number and percentage of subjects screened, treated, primary reasons for screening failure, and discontinuation will be displayed.
All analysis will be performed using R software (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

The study is powered as a one-sample one-sided test of proportion vs historical control ($\alpha = 0.05$ one-sided, power = 80%). We assume the true responder proportion with zanubrutinib p1=0.50 and a historical control responder proportion p0≈0.323 (source: Dalakas et al., Ann Neurol 2009;65:286-293), which yields an approximate required sample size of 45 evaluable patients using the standard normal approximation for proportions. Allowing for a 5% non-evaluable/withdrawal rate increases planned enrolment to 47 patients; therefore we plan to screen up to 50 patients at 9 clinical centers.

Sample-size calculations were performed with the formula $n = \frac{(z_{1-\alpha}\sqrt{p_0(1-p_0)} + z_{1-\beta}\sqrt{p_1(1-p}}{(p_1 - p_0)^2}$ and confirmed by [trialdesign.org].

Statistical Methods for Safety Analyses

All adverse events (AEs) will be tabulated, safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences, laboratory tests, and vital signs within drug cohort and total. Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoint as appropriate. The incidence rate of Grade 3 or higher adverse events and the incidence rate of Grade 5 AEs will be provided as appropriate.

Interim analysis

No formal interim analysis will be performed. However, a safety assessment will be made in the first 20 enrolled patients by the study coordinator and co-coordinators. Toxicity will be considere unacceptable if 25% or more patients discontinue treatment permanently due to an AE.

14 Independent data monitoring committee

No independent clinical data monitoring committee has been appointed for this study.

15 Quality of life assessment

FACT-GOG-NTX-13 QOL questionnaire every 3 months during the first year and then every 6 months (https://www.facit.org/measures/FACT-GOG-NTX-13).

16 Translational research Rationale

A relevant number of patients with anti-MAG neuropathy harbor *MYD88*^{L265P} mutation, being present in almost all patients with associated Waldenstrom macroglobulinemia and less common in patients with MGUS. *MYD88*^{L265P} mutation is rare in patients with CLL or MZL.

Objective

To define the biologic characteristics of patients with anti-MAG neuropathy cells in terms of *MYD88*^{L265P} and *CXCR4*$^{Whim\text{-}like}$ mutations.

Samples collection and schedule

Peripheral blood samples will be collected at baseline and every 6 months (Appendix E).

Methods

gDNA extraction from WBC cells and cfDNA extraction from plasma will be performed according to the manufacturer by Maxwell® RSC Blood DNA and by Maxwell® RSC LV ccfDNA kit, respectively. MYD88 (L265P) mutation levels will be assessed by a custom dual labelled MYD88 (L265P) probe assay, designed for ddPCR and validated by the OUT, on gDNA extracted from BM and on cfDNA

extracted from plasma as previously reported[25]. ddPCR will be performed on QX200 system (Bio-Rad). MYD88 (L265P) ddPCR cut-off is settled based on the background level defined from a group of control samples including samples from multiple myeloma patients and the healthy samples. Furthermore, similar ddPCR approaches will be used for CXCR4 from bone marrow samples.

17 List of recruiting Italian centers

See attached file "Elenco centri partecipanti_studio Mazinga_v1.0 del 10/07/2025"

18 Adverse Events Definition

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product. and which does not necessarily have a causal relationship with this treatment [Dir 2001/20/EC Art 2(m)]. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (GVP Annex IV, ICH-E2D Guideline). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities (GVP Annex 1 – European directive 2001/20/EC).

Adverse Reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. [DIR 2001/83/EC Art 1(11)]. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out. (Annex IV, ICH-E2A Guideline). Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure (European directive 2001/83/EC Art 101(1)). Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious Adverse Event or Serious Adverse Reaction

A serious AE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

For reports of hospitalization, it is the sign, symptom or diagnosis, which led to hospitalization that is the serious event for which details must be provided. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

• hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).

• surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse

events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
• disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.
• a standard procedure for protocol therapy administration will not be reported as a serious adverse event. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event.
• the administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
• a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
• prolonged hospitalization for technical, practical, or social reasons in the absence of an adverse event.

Unlisted (Unexpected) AE/Reference Safety Information
An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information.

Causality of adverse event
The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE. An adverse event is considered not associated with the use of the treatment if the attribution is not related or doubtful according to the definitions listed below:
Not Related: an AE that is not related to the use of the drug.
Doubtful: an AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
An adverse event is considered associated with the use of the treatment if the attribution is possible, probable, or definitely according to the definitions listed below:
Possible: an AE that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
Probable: an AE that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).
Very Likely: an AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

Classification of severity of adverse event
For both AE and SAE, the investigator(s) must assess the severity of the event.
The severity of adverse events (AE) will be graded on a scale of 1 to 5 according to the Common Terminology Criteria for Adverse Events v 5 (CTCAE):
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

If a specific event is not included in the NCI CTCAE toxicity scale, the following scale should be used to grade the event:

Grade	Definition
1	**Mild** Awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities

2	**Moderate** Discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic manoeuvres
3	**Severe** is Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Living.
4	**Life-threatening** Immediate risk of death; requires hospitalization and clinical intervention.
5	**Death**

Reporting Procedures

Adverse Event

All AEs, whether serious or non-serious and pregnancy exposures and/or pregnancy in partners, will be recorded by the physician from the time the patient signs the informed consent for study participation until a minimum of up to 6 months after the last dose or to the end of the follow-up period whichever is longer.

If a subject starts other therapies, then SAEs will no longer be required to be reported.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. The causality will be assessed for each study drug separately. A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should be recorded only once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious). The Adverse Event eCRF should be updated by changing the event from “non-serious” to “serious,” providing the date that the event became serious, and completing all data fields related to serious adverse events."

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities.

Serious Adverse Event

All events that meet the definition of a serious adverse event will also be reported by e-mail to andrea.visentin@unipd.it and sonia.faoro@aopd.veneto.it within 24 hours of them becoming aware, using a CIOMS Report Form or a Pregnancy Questionnaire form. This timeframe also applies to additional new information (follow-up) on previously reported SAEs.

All serious AEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- the event resolves
- the event stabilizes
- the event returns to baseline, if a baseline value/status is available
- the event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious

AE. The cause of death of a subject in a study, whether or not the event is expected or associated with the product under study, is considered a serious adverse event.
The investigator will decide if these events are related to the protocol treatment (i.e. not related, doubtful, possible, probable, very likely) and the decision will be recorded on the form, if necessary with the reasoning of the investigator.

Pregnancies

Pregnancies occurring while subjects are on study drug or within 26 weeks after a subject's last dose of study drug or pregnancy of the partner are considered events to be reported immediately to Sponsor. If the subject is on study drug, the study drug is to be discontinued immediately and the subject is to be instructed to return any unused portion of the study drug to the Investigator. The pregnancy must be reported to Sponsor using a Pregnancy Questionnaire Form.
The Investigator will follow the subject until completion of the pregnancy, and must notify the Sponsor of the outcome within 5 days or as specified below. The Investigator will provide this information as a follow-up to the initial pregnancy report. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted foetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAE. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAE. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to the study drug should also be reported. In the case of a live "normal" birth, the Sponsor should be advised as soon as the information is available. Any suspected fetal exposure must be reported to Sponsor within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counselling.

Adverse Event of Special Interest (AESI)

Specific AEs or groups of AEs will be followed as part of standard safety monitoring activities. These events will be reported to the Sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and non-serious AEs) following the procedure described above for serious AEs and will require enhanced data collection.
Within this trial these adverse events of any grade will be considered AESI: hypertension, atrial fibrillation, atrial arrhythmia, ventricular arrhythmia, bleeding, any cardiovascular event, sudden death, infections.

Other Malignancies

In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for OS.

All forms must be as complete as possible and written in English, including details of the current illness and serious adverse event and an assessment of the causal relationship between the event and the investigational product. The information not available at the time of the initial report must be documented on a follow-up form.
The Investigator, in case of death, has to communicate the event also to his local Ethics Committee.
Information about SUSAR will be forwarded by the Sponsor directly into the Eudravigilance database. Any question concerning SAE reporting can be directed to sponsor:
Dr. Andrea Visentin
e-mail address: andrea.visentin@aopd.veneto.it
Phone: 0039 049 821 2298

Addition Pharmacovigilance procedures

The Investigator Sponsor is responsible for all pharmacovigilance activities in the Study, including, but not limited to, submitting all safety reports arising out of the Study to the applicable regulatory

authorities and the appropriate ethics committee(s), as required by the Study protocol, any applicable Institutional policy, or applicable laws and/or regulations, within the requisite, applicable timeframes. In addition, Investigator Sponsor shall send all SAEs (including both initial and follow-up) following the treatment of Study Drug to BeiGene within agreed timeline. Safety reports of pregnancy exposures and special situations, as defined in the Protocol, shall be reported to BeiGene in the same manner as for SAEs.
Reporting SUSARs

SAE reported to the sponsor that is evaluated by the Investigator as related to the IMP and unexpected will be reported to the regulatory authorities (EMA Eudravigilance) and the ethics committee by the Promotor (QPPV) within the reporting timelines:

- Fatal or life threatening SUSARs: not later than 7 days after the sponsor has information that the case fulfills the criteria for a fatal or life threatening SUSAR, and any follow up information within a further 8 days.
- All other SUSARs: not later than 15 days after the sponsor for pharmacovigilance has information that the case fulfils the criteria for a SUSAR.

SUSARs will be reported to the Qualified Person for Pharmacovigilance (QPPV) of Azienda Ospedale – Università di Padova with 24 hours according to the relevant Pharmacovigilant SOP of promoter.
The QPPV is Dr Sonia Faoro, of the Pharmacy Unit.
The CIOMS report form must be sent to sonia.faoro@aopd.veneto.it and andrea.visentin@aopd.veneto.it
Phone: 049 821 1888.

Study drugs quality complaint handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. Any suspected any quality defect in zanubrutinib or its packaging, labelling will be reported to the Sponsor within 24 hours.

19. Quality assurance Control of data consistency

Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered on the master database. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

On-site quality control

In order to ensure that the study is conducted according to Good Clinical Practice (GCP), the sponsor will send to every single center an Investigator's File, will organize Training Meetings in which principal investigators as well as collaborative investigators will be involved. In these meetings the following issues will be addressed:

1. Regulatory procedures.
2. Compulsory documents to be sent to the sponsor in order to be authorized to enroll patients.
3. Study documents archive system.
4. Patient information sheet and informed consent: how to approach the patient and where to archive the document.
5. Biological samples centralization system.
6. Patient selection criteria and registration procedure.
7. CRFs, queries management.
8. SAEs/SUSARs
9. Main source documents to be sent to the sponsor

During the first Training Meeting, different operative procedures will be distributed and explained, procedures concerning patient selection criteria and registration procedures, CRFs and SAEs/SUSARs. All these will be in the Investigator's File as well. During general meetings, a report concerning the conduction of the study will be distributed. In this report, up to date data can be found concerning not only accrual but also SAEs/SUSARs, list of participating centers and particular situations that may have arisen during the conduction of the trial. This report constitutes an important working tool for the Investigator and is also an up to date report to be periodically presented to the Ethics Committee. Furthermore, the statistical design and the precise accrual will be a method to select data that need to be verified.

Central review procedures

All samples are sent to a single laboratory (within 24 hours). Samples are then processed and distributed to different laboratories in order that the various analyses are carried out uniformly and using internationally recognized standards. This type of organizations allows a highly defined standard of diagnosis, as well as a uniform diagnostic work-up for all enrolled cases, and a closely monitored census of the illness during the course of the study. Besides, this system provides the same standard for all patients, otherwise not possible.

20 Ethical considerations and Patient protection, Regulatory and legal obligations

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) (APPENDIX F) or the laws and regulations of the country, whichever provides the greatest protection to the patient. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The protocol will be approved by the Local, Regional or National Ethics Committees.

Subject identification

The name of the patient will not be asked for nor recorded at the sponsor. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms.
A subject identification list should be archived in each site in the Investigator Site File.

Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix G to this protocol. It is the responsibility of the individual investigator to translate the enclosed informed consent document. The translated version should be dated and version controlled. The translated informed consent form is part of the documents to be submitted to the ethics committee for approval. The competent ethics committee for each institution must validate local informed consent documents before the center can join the study. It is the responsibility of the Local Ethical Committee to guarantee that the translation is conforming to the ICH-GCP guidelines. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered at the Sponsor. This must be done in accordance with the national and local regulatory requirements. For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice.

21 Administrative responsibilities The Study Principal Investigators

The principal investigator (in cooperation with the Data Center) will be responsible for writing the

protocol, reviewing all case report forms and documenting their review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. They will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

Study Principal Investigators:
Dr. Andrea Visentin
Azienda Ospedale Università Padova
UOC Ematologia
andrea.visentin@aopd.veneto.it

Prof. Livio Trentin
Azienda Ospedale Università Padova
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Principal Investigators for neurological assessment:
Prof. Chiara Briani
Azienda Ospedale Università
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chiara.briani@unipd.it

Dr. Bruno Ferrero
AOU Città della Salute e della Scienza di Torino
ferrerobruno_neuro@yahoo.it

Principal Investigator for translation studies
Dr. Simone Ferrero
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simone.ferrero@unito.it

22. Trial sponsorship and financing

The promoter of the study is Azienda Ospedale - University Padova, which has also signed an agreement with BeOne medicine (formerly BeiGene) for the supply of study drugs free-of-charge and for a financial contribution to the study.

23. Trial insurance

The Sponsor has signed an insurance contract according to the "Decreto Ministeriale 14 luglio 2009 - Requisiti minimi per le polizze assicurative a tutela dei soggetti partecipanti alle sperimentazioni cliniche dei medicinali".

24. Publication policy, study report and archiving of study documentation

Once the trial has been closed and the Writing Committee has presented the main study publication, any participating center may, eventually, use its own data (data generated in its own center) for educational purposes, publications and presentations. These may be sent to Sponsor 30 days before the submision. The investigator is due to include sponsor's name in any final publication.

Authorship
Authorship will be based on the ICMJE criteria. In details, the study coordinator and the sponsor will be responsible for substantial contributions to the conception or design of the work, the acquisition, analysis, interpretation of data for the work, drafting the work or revising it critically, agreement for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, approval of the final version of the manuscript. As a result, the final publication of the trial, results will be written by the study investigators on the

basis of the final analysis performed by the Sponsor. A draft of the manuscript will be submitted for review. Authors of the manuscript will be the investigators who have included at least 1 evaluable patient in the trial (by order of inclusion). Unless further agreement is made by investigators and the sponsor, all other participants or representatives of the sponsor who have contributed to the trial will be mentioned in the acknowledgment section of the manuscript.

Responsibility for publication
The manuscript will be sent to a major scientific journal after revision by the coordinator of the trial. The manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, as well as supporting bodies. The Study Coordinator and Co-Coordinators must approve all publications, abstracts and presentations based on patients included in this study. This is applicable to any individual patient registered/randomized in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomized treatment arms nor an analysis of any of the study end-points unless the final results of the trial have already been published by the Study Coordinator.

Study report
An ICH-compliant integrated clinical and statistical report will be prepared upon completion of the study and data analysis.

Archiving of study documentation
Essential records, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations. The Sponsor will notify the investigators/institutions when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol.

Essential documents include for example:
- IRB/EC approvals for the study protocol and all amendments
- All source documents and laboratory records
- Patients' informed consent forms (with study number and title of trial)
- Any other pertinent study document.

25. Investigator authorization procedure
Investigators will be authorized to register and enroll patients in this trial only when they have returned to Azienda Ospedale - Università Padova:
- The (updated) list of the normal ranges, in their own institution, of all laboratory data required by the protocol, preferably signed and dated by the head of the laboratory.
- A signed conflict of interest disclosure form.
- A copy of the favorable opinion of their local or national (whichever is applicable) ethics committee mentioning the documents that have been reviewed (incl. version number and date of documents) and indicating the list of the ethics committee members.
- A copy of the translated, if applicable, and adapted, if changed by the Ethics Committee, (according to all national requirements), Informed Consent, clearly mentioning the version number and the date.
- The coordinator of the pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided)
- List of co-investigators who are authorized to work for this study

The center specific applicable list of required documents will be included in the protocol activation package, with proper instructions as required.

26. Patient registration procedure

Patient registration will only be accepted from authorized investigators (see "Authorization procedure"). A patient can be registered after verification of eligibility criteria. A patient who has not been registered before the first treatment administration will not be accepted in the study at a later date. An exhaustive list of questions to be answered during the registration procedure is included in the registration check-list, which is part of the case report forms. This check-list should be completed by the responsible investigator before the patient is registered.

27. Forms and procedures for collecting data

Case report forms and schedule for completion

Data will be collected using e-CRFs, in REDCap, managed by Azienda Ospedale - Università Padova. The system allows for audit trails, logging all user activity and all pages viewed by every user. Only the data requested by the protocol will be gathered.

Data flow

In all cases, it remains the responsibility of the investigator to check that e-CRFs are sent to the Azienda Ospedale - Università Padova as soon as possible and that they are completely and correctly filled out. Azienda Ospedale - Università Padova will perform extensive consistency checks and issue electronic Query Forms in case of inconsistent data. The investigator (or an authorized staff member) will electronically answer these queries and sign the query forms. The Azienda Ospedale - Università Padova will subsequently verify the modifications. If an investigator (or an authorized staff member) needs to modify a CRF after the e-form has been sent to the Azienda Ospedale - Università Padova, he/she should notify the Data Center in creating a query.

28 Monitoring procedures during the study

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. The sponsor expects that during site visits the relevant investigational staff will be available, the source documentation will be available and a suitable environment will be provided for review of study-related documents.

In accordance with regulatory guidelines, audits may be carried out for this study. The investigator is required to facilitate an audit by means of a site visit. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected. Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

APPENDIX A: REFERENCES

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APPENDIX B: NEUROLOGICAL SCALES

Overall Neuropathy Limitations Scale (ONLS)

Instruction: the examiner should question **and** observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms e.g. tingling, numbness or weakness? **(if "no", please go to "legs" section)**	Yes	No

Is the patient affected in their ability to	**Not affected**	**Affected but not Prevented**	**Prevented**
Wash and brush their hair			
Turn a key in a lock			
Use a knife and fork together (or spoon, if knife and fork not used)			
Do or undo buttons or zips			
Dress the upper part of their body excluding buttons or zips			

If all these functions are prevented can the patients make purposeful movements with their hands or arms?	Yes	No	Not applicable

Arm Grade
0 = Normal
1= Minor symptoms in one or both arms but not affecting any of the functions listed
2= Disability in one or both arms affecting but not preventing any of the functions listed 3= Disability in one or both arms preventing at least one but not all functions listed
4= Disability in both arms preventing all functions listed but purposeful movement still possible 5= Disability in both arms preventing all purposeful movements

SCORE=____

LEG SCALE

	Yes	**No**	**Not applicable**
Does the patient have difficulty running or climbing stairs?			
Does the patient have difficulty with walking?			
Does their gait look abnormal?			
How do they mobilise for about 10 metres (i.e. 33 feet)?			
Without aid			
With one stick or crutch or holding to someone's arm			
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame			
With a wheelchair			
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?			
If they cannot walk as above are they able to make some purposeful movements of their legs e.g. reposition legs in bed?			
Does the patient use ankle-foot orthoses/braces ?(please circle) If yes: (**please circle**)		**Right / left**	

Leg Grade

0= Walking/climbing stairs/running not affected
1= Walking/climbing stairs/running is affected, but gait does not look abnormal 2= Walks independently but gait looks abnormal
3= Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4= Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm, frame)
5= Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person 6= Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7= Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

SCORE: _____

Overall Neuropathy Limitation Scale = arm scale (range 0-5) + leg scale (range 0-7); [range: 0 (no disability) to 12 (maximum disability)]

TOTAL SCORE=____

Is there any disorder, other than peripheral neuropathy, which affects the above functions	***Yes***	***No***
If **yes** please describe:		

Inflammatory Neuropathy Cause and Treatment (INCAT) Disability

Scale Arm disability

0 = No upper limb problems

1 = Symptoms, in one or both arms, not affecting the ability to perform any of the following functions: doing all zips and buttons; washing or brushing hair; using a knife and fork together; handling small coins

2 = Symptoms, in one arm or both arms, affecting but not preventing any of the above mentioned functions

3 = Symptoms, in one arm or both arms, preventing one or two of the above mentioned functions

4 = Symptoms, in one arm or both arms, preventing three or all of the functions listed, but some purposeful movements still possible

Leg disability

0 = Walking not affected

1 = Walking affected, but walks independently outdoors

2 = Usually uses unilateral support (stick, single crutch, one arm) to walk outdoors

3 = Usually uses bilateral support (sticks, crutches, frame, two arms) to walk outdoors

4 = Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps

5 = Restricted to wheelchair, unable to stand and walk a few steps with help

Overall disability = Sum of arm and leg disability

INCAT Sensory Sum Score (ISS).

The ISS ranges from 0 (normal sensation) to 20 (most severe sensory deficit) and is composed of the summation of the following sensation qualities:

- Pinprick arm grade (range 0-4)
- Vibration arm grade (range 0-4)
- Pinprick leg grade (range 0-4)
- Vibration leg grade (range 0-4)
- Two-point discrimination grade (range 0-4)

Pinprick is tested with the sharp end of an esthesiometer, subjects indicate normal or abnormal. Paresthesia, dysesthesia or hyperesthesia are to be scored as abnormal. Normal reference point: face.
Vibration sense is tested using the graduated Rydel-Seiffer tuning fork, measures obtained are compared with the reported normative threshold values.
Pinprick and vibration sense examination take place distal to proximal and only the highest extension of dysfunction of the most affected arm and leg are recorded separately for both qualities.

Pinprick sensation (sites of examination and corresponding grades)		Vibration sensation (sites of examination and corresponding grades)		Two-point discrimination (sites of examination and corresponding grades)
Arms →	Legs →	Arms →	Legs →	Index finger[K]
Normal sense 0, at index finger[A]	Normal sense 0, at hallux[F]	Normal sense 0, at index finger[A]	Normal sense 0, at hallux[F]	Normal sense 0, < 4 mm
Abnormal sense →	Abnormal sense →	Abnormal sense →	Abnormal sense →	Abnormal sense
1, at index finger[B] →	1, at hallux[G] →	1, at index finger[B] →	1, at hallux[G] →	1, 5-9 mm
2, at wrist[C] →	2, at ankle[H] →	2, at wrist[C] →	2, at ankle[H] →	2, 10-14 mm
3, at elbow[D] →	3, at knee[I] →	3, at elbow[D] →	3, at knee[I] →	3, 15-19 mm
4, at shoulder[E] →	4, at groin[J] →	4, at shoulder[E] →	4, at groin[J] →	4, > 20 mm

A,B: index finger (dorsum distal interphalangeal joint); C: ulnar styloid process; D: medial humerus epicondyle; E: acromioclavicular joint; F,G: hallux (dorsum inter-phalangeal joint); H: medial malleolus; I: patella; J: anterior superior iliac spine; K: index finger (ventral side: distal phalanx)

Inflammatory Rasch-built Overall Disability Scale (I-RODS)

I-RODS is a 24-item scale, with each item representing a common, daily activity.

The items range in difficulty from very easy ("reading a newspaper/book" and "eating") to very difficult ("standing for hours" and "running")

The patient assigns a score between 0 and 2 to each item as follows:
0 = impossible to perform
1 = performed with difficulty
2 = easily performed

List of Daily Activities

1. Reading
2. Eating
3. Brushing teeth
4. Washing upper body
5. Sitting on toilet
6. Making sandwich
7. Dressing upper body
8. Washing lower body
9. Moving chair
10. Turning key in lock
11. Going to general practitioner
12. Taking shower
13. Doing dishes
14. Doing shopping
15. Catching object (e.g., ball)
16. Bending and picking up object
17. Walking one flight of stairs
18. Travelling by public transportation
19. Walk while avoiding obstacles
20. Walking up to 1 km outside
21. Able to carry and put down heavy object (about 10 kg)
22. Dancing
23. Standing for hours
24. Running

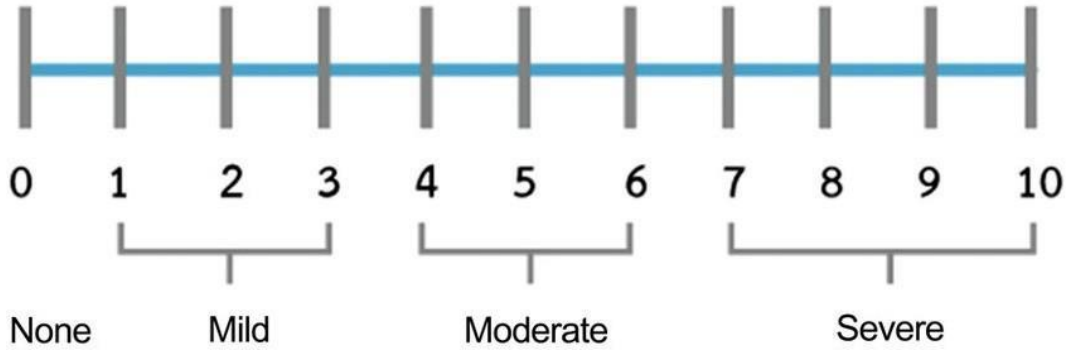
Medical Research Council (MRC) muscle scale

The muscle scale grades muscle power on a scale of 0 to 5 in relation to the maximum expected for that muscle.

Score	Description
0	No contraction
1	Flicker or trace of contraction
2	Active movement, with gravity eliminated
3	Active movement against gravity
4	Active movement against gravity and resistance
5	Normal power

Numeric Rating Scale (NRS)

The Numeric Rating Scale (NRS) is the simplest and most commonly used numeric scale in which the child rates the pain from 0 (no pain) to 10 (worst pain).



9-hole peg test

It is used to measure finger dexterity in patients with various neurological diagnoses

APPENDIX C: STUDY DRUGS TOXICITIES

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 the Table below. This section outlines expected serious adverse reactions for regulatory purposes and the information within the RSI section does not represent a comprehensive overview of the zanubrutinib safety profile. Fatal and life- threatening events are considered unexpected.

Expected Adverse Drug Reactions

Table 79: Expected Serious Adverse Drug Reactions (Occurring in > 1 Patient): All BGB-3111 Monotherapy Studies (Safety Analysis Set)

	Number of subjects exposed (N = 1962)
System Organ Class Preferred Term	**All Zanubrutinib SARs n (%)**
Infections and infestations	
Pneumonia	141 (7.2)
COVID-19 pneumonia	65 (3.3)
Urinary tract infection	32 (1.6)
Lower respiratory tract infection	13 (0.7)
Upper respiratory tract infection	13 (0.7)
Bronchitis	9 (0.5)
Pneumonia fungal	5 (0.3)
Pneumonia cryptococcal	4 (0.2)
Organising pneumonia	3 (0.2)
Pneumonia bacterial	3 (0.2)
Atypical pneumonia	2 (0.1)
Pneumocystis jirovecii pneumonia	2 (0.1)
Pneumonia klebsiella	2 (0.1)
Pneumonia pneumococcal	2 (0.1)
Pneumonia viral	2 (0.1)
Viral upper respiratory tract infection	2 (0.1)
Vascular disorders	
Haematuria	12 (0.6)
Hypertension	7 (0.4)
Subdural haematoma	6 (0.3)
Post procedural haemorrhage	5 (0.3)
Upper gastrointestinal haemorrhage	5 (0.3)
Cerebral haemorrhage	4 (0.2)
Gastrointestinal haemorrhage	3 (0.2)
Haemorrhage intracranial	3 (0.2)
Subdural haemorrhage	3 (0.2)
Traumatic intracranial haemorrhage	3 (0.2)
Contusion	2 (0.1)
Periorbital haematoma	2 (0.1)
Purpura	2 (0.1)
Rectal haemorrhage	2 (0.1)
Traumatic haematoma	2 (0.1)
Tumour haemorrhage	2 (0.1)
Blood and lymphatic system disorders	
Anaemia	27 (1.4)
Febrile neutropenia	19 (1.0)
Neutropenia	11 (0.6)
Platelet count decreased	10 (0.5)
Neutrophil count decreased	8 (0.4)
Thrombocytopenia	6 (0.3)
Cardiac Disorder	
Atrial fibrillation	27 (1.4)
Atrial flutter	4 (0.2)
Musculoskeletal and connective tissue disorders	
Back pain	9 (0.5)
Arthralgia	4 (0.2)
Musculoskeletal pain	2 (0.1)
Myalgia	2 (0.1)
General disorders and administration site conditions	
Fatigue	6 (0.3)
Asthenia	2 (0.1)
Oedema peripheral	2 (0.1)
Gastrointestinal disorders	
Diarrhoea	8 (0.4)
Constipation	2 (0.1)
Nervous system disorder	
Vertigo	4 (0.2)
Dizziness	3 (0.2)
Metabolism and nutrition disorders	
Tumour lysis syndrome	4 (0.2)

Source: ADSL, ADAE.
Data cut-off date: 3-May-2021 (BGB-3111-AU003), 16-Oct-2020 (BGB-3111-1002),10-May-2022 (BGB-3111-111), 05-Apr-2022(BGB-3111-113), 20-Oct-2020 (BGB-3111-205), 11-Nov-2020 (BGB-3111-206), 16-Oct-2020 (BGB-3111-207), 4-Feb-2021 (BGB-3111-210), 31-May-2022 (BGB-3111-214), 1-Sep-2022 (BGB-3111-215), 16-Nov-2021(BGB-3111-216), 30-Nov-2022 (BGB-3111-218), 21-Jun-2022(BGB-3111-302), 31-Oct-2022 (BGB-3111-304), 8-Aug-2022 (BGB-3111-305), 17-Oct-2022 (BGB-3111-LTE1).
Overall column includes monotherapy studies: BGB-3111-AU-003, BGB-3111-1002, BGB-3111-111, BGB-3111-113, BGB-3111-205, BGB-3111-206, BGB-3111-207, BGB-3111-210, BGB-3111-214, BGB-3111-215, BGB-3111-216, BGB-3111-218, BGB-3111-302 [Cohort 1 zanubrutinib arm + Cohort 2], BGB-3111-304 [Cohort 1/1a zanubrutinib arms + Cohort 2 + Cohort 3], BGB-3111-305, BGB-3111-LTE1.

Source: zanubrutinib IB, 14April 2023

APPENDIX D: Interaction with other medicinal products and other forms of interaction

Clinical drug-drug interaction study with zanubrutinib showed that co-administration of zanubrutinib with the strong CYP3A inducer rifampin decreased AUC0-∞ of zanubrutinib by 13.5-fold in healthy subjects. Co- administration of zanubrutinib with strong CYP3A inhibitor itraconazole increased AUC0-∞ of zanubrutinib by 3.8-fold. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib.

Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers and grapefruit juice and Seville oranges should be used with caution as they may affect the metabolism of zanubrutinib.

If all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and should consider using alternative agents. If these agents will be used, follow the dose modification table in Table 3. The medical monitor should be consulted in these situations. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

Dose Modification Table for zanubrutinib when Co-Administered with Strong/Moderate CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended use
Inhibition	Strong CYP3A inhibitor (eg. ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole)	80 mg once daily
	Moderate CYP3A inhibitor (eg. erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit products)	80 mg twice daily
Induction	Strong CYP3A inducer (eg. carbamazepine, phenytoin, rifampin, St. John's wort)	Avoid concomitant use; Consider alternative agents with less induction potential.
	Moderate CYP3A inducer (eg. bosentan, efavirenz, etravirine, modafinil, nafcillin)	160 mg twice daily, use with caution; Monitor for potential lack of efficacy.

CYP3A INHIBITORS AND INDUCERS

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole, clotrimazole

Protease inhibitors: amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib
Food products: grapefruit juice (*citrus paradisi* juice)
Herbal medications: Schisandra sphenanthera
Others: amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam
Strong/Moderate CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum), enzalutamide, mitotane, bosentan, efavirenz, etravirine, modafinil

Abbreviation: CYP: cytochrome P450.
Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.
Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. http://medicine.iupui.edu/flockhart/table.htm

SENSITIVE CYP2C8, CYP2C9, AND CYP2C19 SUBSTRATES OR CYP2C8, CYP2C9, AND CYP2C19 SUBSTRATES WITH A NARROW THERAPEUTIC INDEX

CYP2C8 Substrates	**CYP2C9 Substrates**	**CYPC19 Substrates**
repaglinide[1]	celecoxib	**Anti-epileptics:**
paclitaxel	phenytoin[2]	S-mephenytoin[1,2]
	warfarin[2]	
		Proton-Pump Inhibitors
		lansoprazole[1]
		omeprazole[1]

Abbreviations: AUC, area under the plasma concentration time curve; CYP, cytochrome P450; NTI, narrow therapeutic index.

[1] Sensitive substrates: Drugs that exhibit an area under the plasma concentration time curve (AUC) ratio (AUCi/AUC) of 5-fold or more when coadministered with a known potent inhibitor.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).
Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for drug interaction information or contact the medical monitor of the protocol.
Source: Food and Drug Administration Center for Drug Evaluation Research (CDER). FDA Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations. 2012.

APPENDIX E: CENTRALIZATION OF SAMPLES TO PADOVA LABORATORY

cfDNA samples will be collected at each of the participating sites and centralized to the unit of Padova and analyzed in the laboratory of Padova or of Torino.

Padova address: Dr.ssa Federica Frezzato Campus biomedico Pietro d'Abano - laboratorio Ematologia Via G. Orus 2b 35131 Padova – Italy Phone: +39-049-821 7729 study coordinator +39-049-821 7809	TURIN address: Prof. Simone Ferrero/Dr.ssa Daniela Drandi Laboratorio Biologia Molecolare c/o laboratorio Ematologia Universitaria 1 AOU Città della Salute e della Scienza di Torino, Via Genova 3, (Piano Terra) 10126 Torino – Italy Phone: +39-011-633/6884/4251/4220

Samples collection

PB collected as per clinical practice are to be centralized to the assigned central laboratory according to the below reported scheme:

Time-points	Peripheral Blood
Baseline (T0)	10 ml x 2 in cell-free DNA BCT tubes
Every 6 months till month +24 or till month 48 for responding patients	10 ml x 2 in cell-free DNA BCT tubes
month +24	10 ml x 2 in cell-free DNA BCT tubes
month +48	10 ml x 2 in cell-free DNA BCT tubes

All samples must be stored at room temperature and centralized as soon as possible to the central laboratory.

Operative considerations for plasma and WBC cells collection

PB samples for molecular analyses on cfDNA of diagnostic materials should be collected in 2 Cell-Free DNA BCT tubes [Streck's black/baige vacutainers].

1) **20 ml of PB** will be collected in 2 Cell-Free DNA BCT tubes (Streck's, 10 ml each).

Cell-Free DNA BCT is a direct draw whole blood collection tube intended for collection, stabilization and transportation of plasmatic circulating tumor DNA (ctDNA). The formaldehyde-free preservative reagent contained in Cell-Free DNA BCT stabilizes nucleated blood cells, preventing the release of cellular genomic DNA, and inhibits nuclease-mediated degradation of ctDNA, contributing to the overall stabilization of ctDNA. Samples collected in Cell-Free DNA BCT tubes are stable for up to 14 days at room temperatures, allowing convenient sample collection, transport and storage (Fig1).

Fig1. Cell-Free DNA BCT specification

Cell-Free DNA BCT specification	
Blood Draw Volume	10.0 ml
Anticoagulant	K_3EDTA
Additive	Proprietary Stabilizing Agent
Storage Prior to use	Room Temperature
Shipment temperature	Room Temperature

Since Cell-Free DNA BCT CE contains chemical additives, it is important to avoid possible backflow from the tube. To guard against backflow, observe the following precautions:

2) keep patient's arm in the downward position during the collection procedure;
3) hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection;
4) release tourniquet once blood starts to flow in the tube, or within 2 minutes of application. Fill tube completely.
5) remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results. One inversion is a complete turn of the wrist, 180 degrees, and back (Fig 2).

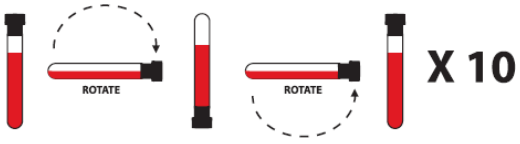


Fig2. Cell-Free DNA BCT tubes after PB recovering

When stored at 18°C - 30°C, unused Cell-Free DNA BCT is stable through expiration date. Do not freeze unfilled Cell-Free DNA BCT.
Do not refrigerate or freeze Blood collected in Cell-Free DNA BCT.

Operative procedures for samples storage

Plasma selection/collection from BCT or EDTA tubes.

6) Centrifuge tubes at 1.300xg for 13 minutes at room temperature.
7) Collect Plasma in separate 15 ml tube and centrifuge again at 1800xg for 10 minutes at room temperature.

8) Store plasma at -80°C in 1ml aliquots.

B-CELLS collection from BM EDTA and PB leftover after plasma collection

Resuspend the BM sample in erythrocytes lysis buffer (NH4Cl) (1:5 dilution) and the leftover blood (after plasma recovery) from BCT in erythrocytes lysis buffer (NH4Cl) (1:2 dilution). Leave 15 minutes at room temperature (lying flat at dark) then centrifuge 15 minutes at 450xg at room temperature. Discard the supernatant, resuspend the pellet in 10-15 ml of NH4Cl and centrifuge 10 minutes at 450xg at room temperature. Remove supernatant, resuspend in PBS or 0.9% NaCl (q.s.). Dispense 5-10x10^6 cells in each tube, centrifuge 1 minute at 13000xg and discard supernatant. Cells can now be stored indefinitely, as dried pellets, at -80°C for further DNA extraction

ddPCR for MYD88 L265P

Mutation detection assay is reported in Drandi D et al.[25]. A single set of primers is combined with two competitive probes in two assays, one for *MYD88^{L265P}* labeled with FAM, and one for *MYD88^{WT}* labeled with HEX.

In the Pre-PCR zone, prepare the 20X primer and probe mix and the ddPCR reaction mix. One ddPCR master mix must be created for each assay to perform 3 replicates per sample. Each reaction must include at least 2 replicates of POSITIVE CONTROL; 3 replicates of each samples; 3 replicates of WT control sample; 3 replicates of no template control (NTC). Prepare the ddPCR mix for a volume increased by 10% (for one replicate: 22ul instead of 20ul) to be sure to have enough reaction mix volume for each replicate. Dispense the reaction mix in one well, based on the number of technical replicates needed. In the DNA zone, load the amount of gDNA (20ng/ul), for 3 replicates 49.5ul (16.5x3) of mix add 16.5lzl (5.5x3) of gDNA. Vortex, spin-down and then pipet the sample few times before add the gDNA to the mix. Seal carefully the plate or the strips with optical adhesive film or caps, mix and spin down briefly. From this well, 20ul of mix will be taken for, droplet generation, for each replicate. Proceed with droplets generation, loading 20ul of reaction mix and 60ul of droplet generation oil into the proper DG8 cartridge wells. Transfer the plate to a thermocycler and start the amplification using the following thermal protocol: 95 °C for 10 min; then 40 cycles of 94 °C for 30 s, 55 °C for 1 min; 98 °C for 10 min. Load the post-PCR 96- wells plate into a QX200 droplet reader according to the manufacturer instruction. Perform the analysis by QuantaSoft Analysis Pro 1.0.596 (Bio-Rad Inc.). For ddPCR analysis the following criteria should be met: a) only replicates with ≥ 9000 droplets must be considered for the analysis; b) a threshold, determined for positive control and WT, should be used for the unknown samples and should be similar in different plates; c) positive control samples should show a reproducible ratio between experiments. Results can be expressed as MUT/WT (a/b) ratio. Cut-off ratio for positivity results is referred to the highest *MYD88^{L265P}* level detected within the control group of healthy subject samples or MM patients (*MYD88^{WT}*). Cut-off value should always be indicated. (i.e. MUT/WT ratio 3.4E-4 as cut off for negativity).

APPENDIX F: World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

World Medical Association
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, *"The health of my patient will be my first consideration"*, and the International Code of Medical Ethics declares that, *"A physician shall act in the patient's best interest when providing medical care"*.

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional

affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious AEs. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only

minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention andt he patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the

completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded.