MAGNAZ

Inclusion criteria:

- Able to provide written informed consent and understand and comply with study requirements
- Age ≥18 years
- Demyelinating PNP defined by the European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of paraproteinemic demyelinating neuropathies
- Functional impairment; defined as an INCAT disability score of ≥2
- Diagnosis of IgM MGUS
- Presence of anti MAG antibodies ≥ 10.000 titer units, measured with the Bühlmann ELISA
- Adequate hematological, hepatic and renal function laboratory values
- Patients with hypertension can only be enrolled when blood pressure is adequately treated, defined as systolic blood pressure of <140 mmHg and diastolic blood pressure of <90 mmHg at screening
- No history of severe bleeding or bleeding disorder
- No previous treatment with intravenous immunoglobulins < 3 months before inclusion
- No previous treatment with an Anti CD20 monoclonal antibody (e.g., Rituximab) and/or cyclophosphamide < 6 months before inclusion. Patients without previous response to Rituximab >6 months before inclusion can be included.

Exclusion criteria:

- Hematological malignancy based on bone marrow analysis
- History of malignancy of any organ system (except basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or non-melanoma skin cancers, superficial bladder cancer or carcinoma in situ of cervix or breast), treated or untreated within the last 3 years
- History of ischemic stroke within 180 days before first dose of Zanubrutinib, history of central nervous system (CNS) hemorrhage, history of inherited or acquired hemorrhagic disorder
- Prior treatment with purine analogues (fludarabine or cladribine) or a BTK inhibitor
- Major surgery within 4 weeks of study treatment
- Participation in another interventional clinical trial
- Pregnant women, lactating women and women of child-bearing potential (WOCBP) not able or willing to prevent pregnancy. WOCBP will agree to use highly effective contraception for the duration of the trial treatment and for 12 months after Rituximab treatment stop or 120 days after Zanubrutinib treatment stop, whichever has a longer duration. Patients using hormonal contraceptives (e.g., birth control pills or devices) must use a barrier method of contraception (e.g., condoms) as well. Male participants will agree not to impregnate any woman and use a condom during the course of Zanubrutinib treatment and for a period of 120 days after the treatment is discontinued, when having sexual intercourse with WOCBP. Furthermore, they must refrain from donating sperm during this period.
- Other known concomitant causes of chronic (demyelinating) PNP
- Currently active, clinically significant cardiovascular disease or history of myocardial infarction within 6 months of screening
- A history of clinically significant ECG abnormalities (or certain ECG abnormalities at screening). Controlled atrial fibrillation is allowed
- Unable to swallow capsules or disease significantly affecting gastrointestinal function

- Uncontrolled active systemic infection, active tuberculosis or recent infection requiring parenteral anti-microbial therapy completed ≤ 14 days before the first dose of study drug
- Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C (patients with certain conditions in the blood reflecting a prior hepatitis C infection may be included)
- At time of study entry, taking any medications which are strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors or strong CYP3A inducers
- Intolerance to previous Rituximab treatment
- History of intolerance to the active ingredients or other ingredients of Zanubrutinib