SYNOPSIS

Name of sponsor	University Hospital Ulm (Germany), represented by the Chairman of the Board
Investigational medicinal product	Venetoclax, Rituximab
Title of study	Efficacy of Venetoclax in combination with Rituximab in Waldenström's Macroglobulinemia (VIWA-1)
Study design / phase	International phase II trial, explorative, multicenter, open label, and randomized
Primary study objective	To test whether Venetoclax/Rituximab increaes the rate of Complete Remission (CR) or Very Good Partial Remission (VGPR) 12 months after initiation of treatment using the response criteria updated at the Sixth IWWM[1] (CR/VGPR) compared to DRC.
Endpoints	<u>Primary endpoint:</u> • Rate of Complete Remission (CR) or Very Good Partial Remission (VGPR) 12 months after randomization (CR/VGPR). <u>Secondary endpoints:</u> • Response rate (CR, VGPR, PR, MR) and overall response rate (ORR: CR, VGPR, PR). • Best response. • Time to best response. • Time to first response. • Time to treatment failure (TTF). • Remission duration (RD). • Progression Free Survival (PFS). • Cause specific survival (CSS). • Overall survival (OS). • Safety • Quality of Life. • Comparison of response rates between CXCR4 mutated and CXCR4 wildtype patients. • MRD levels <u>Safety endpoints:</u> Safety variables will include AEs, SAEs, laboratory parameters, ECG and vital signs. The severity of AEs will be graded using the NCI-CTCAE version 5.0 dictionary. An AE is defined as any event arising or worsening after start of study drug administration until 110 days after the last study drug intake. Safety variables will be summarized by means of descriptive statistics and/or frequency tables as appropriate. All AEs, drug related AEs, serious AEs will be summarized by MedDRA classification and worst CTCAE grade.

Background	In Waldenström's macroglobulinemia (WM) chemotherapy induces only low CR/VGPR rates and response duration is limited. In addition, WM patients are often elderly, partly not tolerating chemotherapy related toxicities. Thus, innovative approaches are needed which combine excellent activity and tolerability in WM. Chemotherapy – free approaches are highly attractive for this patient group. Based on its high activity and favorable toxicity profile in indolent B-NHL such as CLL, Venetoclax was approved for the treatment of this diseases by the FDA and the European Medicines Agency (EMA). First data in relapsed/refractory WM have documented high activity and low toxicity of Venetoclax also in WM, including patients with prior Ibrutinib treatment or patients carrying CXCR4 mutations [2]. Ibrutinib itself has high activity and a relatively low toxicity profile in WM, but has also major disadvantages: the largest disadvantage is the need to apply this drug continuously. Furthermore, Ibrutinib efficacy depends largely on the genotype with a substantial drop in major responses and PFS in the presence of CXCR4 mutations and non-mutated MYD88 [3-5]. In particular the need of continuous treatment for Ibrutinib has prevented that Ibrutinib has become the standard of care outcompeting conventional Rituximab/chemotherapy. This is reflected in current guidelines such as the NCCN and the ESMO guidelines, which still see immunochemotherapy as a backbone of treatment, largely because of the advantage of a timely fixed application [6, 7]. Data in CLL in the relapsed as well as in the first line setting have convincingly shown that in contrast to Ibrutinib Venetoclax is highly efficient also when used in a timely defined application scheme over 12 months in combination with the anti-CD20 antibody Rituximab. Data documented deep responses including molecular responses and a highly significant advantage over immunochemotherapy in large international Phase III trials, changing the standard of care in this disease [8-10]. Based on this we hypothesize that timely fixed application of the combination of Venetoclax and Rituximab induces significantly superior treatment outcomes compared to chemotherapy and Rituximab (DRC) in patients with treatment naïve WM, regardless of the genotype. A confirmation of this assumption in the proposed trial will change the standard of care in WM.
Study Population - Inclusion criteria	• Each patient must meet all of the following inclusion criteria to be enrolled in this study: • Proven clinicopathological diagnosis of WM as defined by consensus panel one of the Sixth International Workshop on WM (IWWM)[1] diagnosed by a reference pathology center. Histopathology has to performed before randomization but within 4 months before start of therapy. In addition, pathological specimens have to be sent to the national pathological reference center for the determination of the mutational status of MYD88 and CXCR4 prior to randomization (if not already known). Immunophenotyping will be performed in each center and archived locally. • De novo WM independent of the genotype. • Patients must have at least one of the following criteria to start study treatment as partly defined by consensus panel criteria from the Seventh IWWM [11]: • Recurrent fever, night sweats, weight loss, fatigue (at least one of them).

	• Hyperviscosity. • Lymphadenopathy which is either symptomatic or bulky (≥ 5 cm in maximum diameter). • Symptomatic hepatomegaly and / or splenomegaly. • Symptomatic organomegaly and / or organ or tissue infiltration. • Peripheral neuropathy due to WM. • Symptomatic cryoglobulinemia. • Cold agglutinin anemia. • IgM related immune hemolytic anemia and/or thrombocytopenia. • Nephropathy related to WM. • Amyloidosis related to WM. • Hemoglobin ≤ 10 g/dL (patients should not have received red blood cells transfusions for at least 7 days prior to obtaining the screening hemoglobin). • Platelet count < 100 x 109/L (caused by bone marrow [BM] infiltration of the lymphoma). • Serum monoclonal protein > 5 g/dL, even with no overt clinical symptoms. • IgM serum concentration ≥ 5 g/dL. • and other WM associated relevant symptoms. Other criteria: • Subject must be ≥ 18 years of age. • Life expectancy > 3 months. • World Health Organization (WHO) / ECOG performance status ≤ 2. • Left ventricular ejection fraction ≥ 40% as assessed by transthoracic echocardiogram (TTE). • Baseline platelet count ≥ 50x109/L, absolute neutrophil count ≥ 0.75x109/L (if not due to BM infiltration by the lymphoma). • Adequate hepatic function per local laboratory reference range as follows: • Aspartate transaminase (AST) and alanine transaminase (ALT) < 3.0 x ULN. • Bilirubin <1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) • Subject must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min; calculated by the Cockcroft Gault formula or measured by 24 hours urine collection. • Females of childbearing potential (FCBP), i.e. fertile, following menarche and until becoming postmenopausal must have negative results for pregnancy test and must agree to use a highly effective method of birth control for the duration of the therapy up to 12 months after end of therapy). • Men must agree not to father a child for the duration of therapy and 12 months after and must agree to advice their female partner to use a highly effective method of birth control. Males must refrain from sperm donation for the duration of treatment and at least 12 months after the last dose of study medication. • Each patient must voluntarily date and sign an informed consent form in a language familiar to the patient indicating that he or she understands the purpose of and procedures required for the study and

	are willing to participate in the study. Patients must be willing and able to adhere to the prohibitions and restrictions specified in this protocol. • Affiliation to a social security scheme (relevant for France only).
Study Population - Exclusion criteria	The presence of the following criteria will exclude a patient from enrolment: • Serious medical or psychiatric illness (especially undergoing treatment) likely to interfere with participation in this clinical study. • Subject is known to be positive for HIV. • Active severe infection • Congenital or acquired severe immunodeficiency not attributed to lymphoma (clinical appearance: recurrent infections, necessity of immunoglobulin substitution therapy, patients after transplantation) • Evidence of other clinically significant uncontrolled condition(s) including, but not limited to: • Uncontrolled systemic infection (viral, bacterial or fungal). • Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection requiring treatment. Note: subjects with serologic evidence of prior vaccination to HBV (i.e. hepatitis B surface (HBs) antigen negative-, anti-HBs antibody positive and anti-hepatitis B core (HBc) antibody negative or positive anti-HBc antibody from intravenous immunoglobulins (IVIG) may participate (see protocol section 13.4.11). • adequate pulmonary function as demonstrated by DLCO ≤ 65% or FEV1 ≤ 65%. • Creatinine clearance ≥ 30 mL/min to < 45 ml/min • Uncontrolled diabetes mellitus (as indicated by metabolic derangements and / or severe diabetes mellitus related uncontrolled organ complications). • Uncontrolled hypertension. • Cardiac history of CHF requiring treatment or Ejection Fraction ≤ 50% or chronic stable angina. • Unstable angina pectoris, angioplasty, stenting, or myocardial infarction within 6 months prior start of therapy • Clinically significant cardiac arrhythmia that is symptomatic or requires treatment, or asymptomatic sustained ventricular tachycardia. • Subject has a cardiovascular disability status of New York Heart Association Class > 2. Class 2 is defined as cardiac disease in which patients are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain • Known pericardial disease. • History of stroke or intracranial haemorrhage within 6 month prior to randomization. • Known interstitial lung disease. • Infiltrative pulmonary disease, known pulmonary hypertension. • Prior history of malignancies unless the subject has been free of the disease for ≥ 3 years. Exceptions include the following: • Basal cell carcinoma of the skin, • Squamous cell carcinoma of the skin, • Carcinoma in situ of the cervix, • Carcinoma in situ of the breast, • Incidential histologic finding of prostate caner (TNM stage of T1a or T1b) • Primary amyloidosis.

	• Known cirrhosis (meeting child-pugh stage C). • Chemotherapy with approved or investigational anticancer therapeutic within 21 days prior to start of therapy • Glucocorticoid therapy within 14 days prior to therapy that exceeds a cumulative dose of 160mg of dexamethasone or equivalent dose of other corticosteroids given for anti-neoplastic intent. • Treatment with any of the following within 7 days prior to the first dose of study drug: • Moderate or strong cytochrome P450 3A (CYP3A) inhibitors (such as fluconazole, ketoconazole, and clarithromycin). • Moderate or strong CYP3A inducers (such as rifampin, carbamazepine, phenytoin, St. John's wort). • Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs. • Autologous stem cell transplant less than 90 days prior to start of therapy. • Allogeneic stem cell transplant less than 100 days prior to start of therapy . • Vaccination with live attenuated vaccines within 4 weeks prior to start of therapy . • History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or sponsor, if consulted, would pose a risk to subject safely or interfere with the study evaluation, procedures or completion. • Women who are pregnant as well as women who are breast-feeding and do not consent to discontinue breast-feeding. • Participation in another clinical trial within four weeks before start of therapy in this study. • No consent for registration, storage and processing of the individual disease-characteristics • Administration or consumption of any of the following within 3 days prior to the first dose of study drug: • grapefruit or grapefruit products. • Seville oranges (including marmalade containing Seville oranges). • star fruit. • Person of legal age who is incapable of comprehending the nature, significance and implications of the clinical trial and of determining his/her will in the light of these facts
Study design	The study will consist of an open labeled, stratified 1:1 randomization between Arm A and Arm B for de novo WM patients in need of treatment (phase II). Stratification factors are MYD88 and CXCR4 status (positive vs. negative). A stratified central block randomization will be used. The central randomization service will be used to avoid predictability of the treatment arm. The primary goal of this study is to explore the efficacy of Venetoclax plus Rituximab versus Dexamethasone/Cyclophosphamide/Rituximab in the treatment of de novo patients (Arm A vs. Arm B). In detail the study design will be as follows:

For all WM patients in need of treatment:

1:1 randomization between Arm A and Arm B

Arm A

Venetoclax* / Rituximab

Stepwise dose escalation in all patients with a target dose of 800 mg/d QD PO.

Cycle 1 (28-days cycle)

Venetoclax	200 mg/d QD PO	Day 1-7
	400 mg/d QD PO	Day 8-14
	800 mg/d QD PO	Day 15-28

Cycle 2 – 12

Rituximab	375 mg/m^2 i.v.	Day 1
Venetoclax	800 mg/d QD PO	Day 1-28

Arm B

DRC

Cycle 1-6

Dexamethasone	20 mg p.o.	Day 1
Rituximab	375 mg/m^2 i.v.	Day 1
Cyclophosphamide	100 mg/m^2 BID p.o.	Day 1-5

Cycle 7-12

Rituximab	375 mg/m^2 i.v.	Day 1

Follow-up Phase

All subjects who enter the trial will continue to be followed every 3 months for disease progression, subsequent treatment, and survival for five years after end of therapy.

Safety

Generally, safety evaluations include: adverse events, vital signs, physical examinations and clinical laboratory parameters. The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0 and will be documented in the eCRF. Adverse events that occur between the signing of the informed consent until 110 days after last intake of study drug will be collected.

Additionally, there will be a closer monitoring for treatment related toxicity comprising the first 6 patients included into arm A. For these 6 patients safety evaluations will be performed after they have completed 2 cycles of treatment and after they have completed 6 cycles of treatment.

	Data and Safety Monitoring Committee A Data and Safety Monitoring Committee (DSMC) will be installed and composed of 3 members, including a statistician, who are not involved in the execution of the trial. The DSMC will review data regarding safety as planned according to the DSMC Charter. ***Pathology Reference*** Archival lymph node or bone marrow biopsy specimen obtained at the time of initial diagnosis with representative stained slides, must be submitted to the national pathology of the participating study group for confirmation of WM. The investigative site must submit a bone marrow biopsy as well as aspirate slides and tumor/lymph node biopsy slides (if available) as part of the baseline screening (preferentially whole tumor blocks, and both unstained and HE stained slides). ***Minimal Residual Disease*** Minimal residual disease (MRD) will be determined by quantitative PCR using the $MYD88^{L265P}$ mutation as biomarker from peripheral blood samples (and if feasible in addition from bone marrow) of all study patients [12] . This approach allows determining MRD in around 90% of patients. MRD will be determined centrally. Peripheral blood and serum will be collected before start of treatment, in month 7 and 13, every 6 months during follow-up and at progression at any time of the study. This scientific program which will run in parallel to the clinical trial will allow correlating clinical responses to tumor burden under treatment and after stop of treatment. It will also permit to investigate whether increase in MRD predicts clinical relapse in WM. MRD status will not impact any clinical management of the patients in the trial.
Planned number of patients:	80 patients in two years will be recruited in total (see the statistical analysis plan below)
Number of study centers	30
Involved study groups	GLA, FILO
First Subject First Visit (FSFV)	Q4 2021
Duration of recruitment	approximately 24 months
Duration of the study for individual patient	1 year treatment plus 5 years follow-up (maximum of 6 years)
Duration of the entire study	maximum of 8 years after inclusion of the first patient
Investigational product	Venetoclax. Rituximab

Statistical Methods	The primary goal of this study is to explore the efficacy of Venetoclax in combination with Rituximab compared to DRC in the treatment of WM. **Sample size estimation:** RCT - Arms A and B: This study is an exploratory trial. The sample size is due to feasibility: It is assumed that 80 patients in total could be enrolled within 24 months in the involved 30 study centers. It is expected that the rate of withdrawal in the study is smaller than 10%. Thus, about 72 patients in total (36 per arm) will be analyzed at the end of the study. According to the literature the CR/VGPR rate in WM patients treated with DRC ranks between 10% to 5 % [13] [14, 15]. Thus, a CR/VGPR rate of 8% in patients treated with DRC (Arm B) is assumed. With a total number of 72 patients (2x36 patients per arm) a difference of 19% in the CR/VGPR rate (i.e. the CR/VGPR rate in Arm A is 27%) could be shown with a power of 80% at a one-sided type one error of 0.1 using the chi square test. **Statistical analysis:** All analyses in this study are exploratory. All results from statistical test have therefore to be interpreted as hypothesis generating and not as proof of efficacy. The primary study endpoint CR/VGPR rate will be evaluated in a full intention to treat way, so that only withdrawal of informed consent will make observations not evaluable for the primary study endpoint. Patients without CR/VGPR rate 12 months after randomization will be treated as 'failure', i.e. 'CR/VGPR =no'. The chi square test will be used for the analysis of the primary endpoint to test the CR/VGPR rate in the arms A and B at the 10% significance level (one-sided) in the ITT population. The corresponding set of null and alternative hypothesis is: H_0: $RR_A \leq RR_B$ H_A: $RR_A > RR_B$ where RR_B is the CR/VGPR rate in Arm B (DRC) and RR_A is the CR/VGPR rate in Arm A (Venetoclax/Rituximab). Additionally, the one-sided 90% confidence interval (CI) of the rate difference (RR_B-RR_A) will be calculated as effect estimator. Further analyses of the primary study endpoint encompass the Cochran-Mantel-Haenszel (CMH) test of rate difference adjusting for stratification factors (MYD88 and CXCR4 status). A CMH 90% stratified confidence interval (CI) of the rate difference (RR_B-RR_A) with each rate weighted by the number of subjects in each stratification factor combination will be calculated as an effect estimator. Additionally, logistic regression models will be used to investigate the influence of putative risk factors on the CR/VGPR rate. All secondary endpoints will also be analyzed exploratory. Group comparisons in binary endpoints will be performed two-sided using the chi square test or Fisher's exact test as appropriate at a 10% significance level. Additionally, 90% CIs will be calculated for group differences. Time to event endpoints will be analyzed using the Kaplan-Meier estimator incl. 90% CI. Furthermore, the Cox Proportional Hazard model will be used to investigate the influence of putative risk factors on time to event endpoints. Group comparison in

	quality of life (ordinal endpoint) will be performed using the Wilcoxon rank-sum test. For safety analysis of the RCT, all adverse events will be listed and the frequencies of the most frequent will be calculated. Group comparisons (A vs. B) of frequencies of AEs and SAEs will be performed using the chi square test or Fishers exact test as appropriate.