Synopsis

TITLE OF TRIAL	Chemotherapy free treatment with venetoclax and obinutuzumab for relapsed primary CNS lymphoma patients (VENOBI-CNS study) – A phase IB study to assess the pharmacokinetics in the cerebrospinal fluid
SHORT TITLE	VENOBI-CNS
EUDRACT NO	2017-003690-33
PROTOCOL NUMBER/INTERNAL PROTOCOL NUMBER	Protocol Number: Version 2.0/2019-10-29 replaces Version 1.0/2019-05-16 Internal Protocol Number: ML40029
HEALTH CONDITION STUDIED	Primary central nervous system lymphoma (PCNSL)
PHASE	Phase IB
BACKGROUND	There is no standard treatment for relapsed or refractory PCNSL and strategies highly depend on previous treatments and clinical performance status. The most common genetic imbalance in PCNSL are gains of 18q21, which includes the BCL2 locus. Furthermore, the IELSG32 trial has established anti-CD20 directed therapy with rituximab in PCNSL. Obinutuzumab has additional pharmacodynamics features compared to rituximab, therefore it is consequent to test it in relapsed PCNSL as well. Based on data available, there are no additional concerning safety issues when combining venetoclax with obinutuzumab, of note, there is no evidence for higher risk of side effects with increased venetoclax doses. Therefore, we propose a single arm multicentre phase IB dose-escalation trial to investigate a chemotherapy free treatment of venetoclax in combination with fixed-dose obinutuzumab in relapsed immunocompetent PCNSL patients.
OBJECTIVE(S)	<u>Primary objective</u> • To investigate the pharmacokinetics (PK) of venetoclax and obinutuzumab in the cerebrospinal fluid (CSF) in patients with relapsed PCNSL <u>Secondary objectives</u> • To investigate preliminary clinical efficacy such as lymphoma response and event-free survival (We will use the standardized IPCG response criteria (1) to categorize the lymphoma response.) • Dose limiting toxicities (DLTs) during escalation of dosing groups as defined by CTCAE (version 5.0) and recommended phase II dose <u>Tertiary objectives</u> • To investigate frequency of gene alterations in DNA extracted from lymphoma tissue using the FoundationOneHeme platform. <u>Safety objectives</u> • To investigate safety and tolerability (dose limiting toxicity [DLT]) of venetoclax and obinutuzumab at different dosing levels

TREATMENT	All patients are planned to receive six cycles of induction treatment (combination of obinutuzumab and venetoclax, 18 weeks [six 3 weekly cycles]) and if at least stable disease without clinical deterioration has been achieved, patients will go on to maintenance treatment for 12 months (52 weeks) with venetoclax. During the combination induction phase, obinutuzumab at 1000mg will be given for 6 cycles (day 1, 8 & 15 [first cycle] and on day 1 in cycles 2 till 6; cycles repeated every 21 days) together with daily venetoclax (600mg [N=5], 800mg [N=5] or 1000mg [N=5]). Assignment to the respective dosing groups will be consecutively, starting at 800mg. Dose escalation will follow pre-specified rules according to the BOIN design. In brief: Only if zero or only 1 dose limiting toxicity (DLT) occurs in 5 patients and all patients fulfilled minimum safety evaluation requirements, the next cohort will be opened as planned. Patient recruitment will be stopped and not resumed until the safety assessment for the DLTs have been completed To assess lymphoma response, gadolinium enhanced MRI brain, as per local standards, has to be done at screening, on day 22, day 43, day 85, and at the end of induction treatment (day 127). During maintenance treatment, MRI brain is conducted every 8 weeks for the first 6 months and every 12 weeks thereafter. In case of disease progression or unacceptable toxicities, treatment will be stopped. Minimal follow-up per patient is 3 months after completing maintenance treatment.
INCLUSION CRITERIA	Inclusion criteria: 1. Age at inclusion ≥ 18 to 80 years, in case of ECOG 0 to 1 age up to 85 years 2. Eastern Cooperative Group performance status (ECOG) ≤ 3 3. Evaluable lymphoma manifestation in the CNS, either contrast-enhanced lesion in the brain parenchyma or measurable meningeal lesions. 4. Biopsy proven CD20 positive PCNSL at initial diagnosis or previous relapse (re-biopsy at study inclusion is not mandatory for inclusion, but strongly recommended if time in remission is longer than 24 months). 5. At least one prior HD-MTX containing chemotherapy application (MTX dosed at ≥ 1 g/m^2 body surface area) before progression or relapse. 6. Confirmed lymphoma relapse according to the IPCG response criteria. 7. Absolute neutrophil count (ANC) of at least 1’500/µl 8. Platelet count of at least 50’000/µl 9. Adequate liver (alanine aminotransferase [ALAT] and AST ≤ 3.0 x upper limit of normal [ULN] and total bilirubin ≤ 1.5 x ULN) and kidney function (estimated ≥ 30ml/min creatinine clearance according to Cockgroft-Gault formula) 10. Written informed consent 11. Recovery from toxicity from previous anti-lymphoma treatment to ≤ grade 2

EXCLUSION CRITERIA	Exclusion criteria: 1. Known allergy to venetoclax or other components of the formulation 2. Known allergy to obinutuzumab or other components of the formulation 3. Primary ocular lymphomas *without* brain parenchymal involvement 4. Lymphoma relapse outside the CNS; extra CNS relapse needs to be ruled out by body CT scans (neck till pelvis) or PET-CT scans. 5. Contraindications for lumbar puncture at the discretion of the clinical investigator 6. Prior exposure to obinutuzumab or venetoclax 7. Other additional anti-lymphoma treatment, e.g. chemotherapy or radiotherapy 8. Active hepatitis B or C 9. HIV seropositivity 10. Chronic use of immunosuppressive drugs, e.g. steroids for systemic autoimmune disease 11. Active infections requiring treatment 12. Other active malignancies (except non-melanoma skin cancer). Prior malignancies without evidence of disease for at least 5 years are allowed 13. Patient is pregnant or breastfeeding, or expecting to conceive or father children within one year of finishing venetoclax and 18 months for obinutuzumab. 14. Prior allogeneic haematopoietic stem cell or solid organ transplantation 15. Participation in any other interventional clinical trial within the last 30 days before the start of this trial; simultaneous participation in registry and diagnostic studies is allowed 16. Patient without legal capacity who is unable to understand the nature, significance and consequences of the trial 17. Known or persistent abuse of medication, drugs or alcohol 18. Person who is in a relationship of dependence/employment with the sponsor or the investigator 19. Administration of moderate or strong CYP3A inhibitors or inducers within 1 week of initiation of venetoclax dosing.

ENDPOINTS	Primary endpoint • PK of venetoclax and obinutuzumab expressed by the respective serum concentration and CSF concentration (µg/ml) measured within the first month since start of treatment on day 3, 15, and 28. We will calculate the ratio of the respective concentrations to investigate penetration into the CNS compartment. AUC will be calculated to express concentrations over time. Key secondary and tertiary endpoint(s): • Dose limiting toxicities (DLTs) during escalation of dosing groups within the first 6 weeks as defined by CTCAE (version 5.0) and recommended phase II dose level. DLT is defined as: - Trial therapy related death - Grade 4 neutropenia not resolved after 14 days despite growth factor support - Grade 3 to 4 febrile neutropenia - Grade 4 thrombocytopenia not resolved after 14 days - Grade 2 or higher bleeding associated with thrombocytopenia - Any other grade 3 or higher haematological or non-haematological adverse event related to one or both IMPs that does not resolve to at least grade 2 or to baseline value within 3 weeks since onset by complete drug discontinuation and supportive care if applicable *except*: o Alopecia o Nausea and diarrhoea adequately treated • Best lymphoma response achieved during induction (CR, PR, SD or PD). • Progression-free survival 1 (PFS1), which is defined as the time from the date of first dose until date of progression, relapse or death, whichever occurs first. Progression or relapse of the lymphoma will be evaluated by brain MRI as per schedule of assessment. In case of clinical suspicion of progression or relapse, brain MRI can be done as clinically indicated. • OS; this will be calculated from the date of first dose until death due to any cause. • Progression-free survival 2 (PFS2), which is defined as the time from the start of maintenance venetoclax treatment at week 12 until date of progression, relapse or death, whichever occurs first. Patients not reaching week 12 will be excluded from analysis of this endpoint. • Distribution and frequency (proportion) in which FoundationOne Heme® One analyses based on formalin fixed tissue identified genetic alterations in the lymphoma cells expressed as allelic frequency in total and stratified by responding and non-responding patients. Assessment of safety: • Adverse events and serious adverse events grading evaluated by CTCAE (version 5.0).

TRANSLATIONAL STUDIES	The objective of FMI testing (FoundationOne Heme® One platform, tertiary objectives) is to gain more insights into the mutational landscape of PCNSL and to investigate matched samples from lymphoma tissue (formalin-fixed), CSF, and peripheral blood (intra-patient validity) over time; an approach that has currently not been conducted in the field of PCNSL research. There will be no repeat brain biopsy unless clinically indicated. All samples will be pseudonymized. Results of analyses will be disclosed to the treating physician in a standardized report (BioPharma CLIA) as soon as each report from each individual sample has been issued. The treating physician will disclose results from FMI testing to the patient at latest at the time of lymphoma progression. At that time point, results from FMI testing may positively support further treatment decision making. However, if the patient asks for the results before lymphoma progression, the treating physician will have to disclose the results. In that case, it should be emphasized that the results should not alter the treatment plan if the patient tolerates current treatment and shows lymphoma response. This is because it is yet unclear to what extend FMI testing really helps to positively alter patient management.
TRIAL DESIGN	This is a non-randomized single arm open label dose-escalating (600mg, 800mg and 1000mg venetoclax always combined with 1000mg obinutuzumab) phase IB trial conducted at two German sites.
STATISTICAL ANALYSIS	15 patients will be enrolled into this study to investigate the PK of venetoclax and obinutuzumab (five for each dosing group). In case a patient is not assessable during DLT time (during the first two cycles) for whatever reason (e.g. death definitely unrelated to study drug, withdrawal of consent, lost to follow-up), we will replace the patient to guarantee that there are always five patients assessable for DLT in each of the three dosing groups. To assure patient's safety, we will follow the BOIN (Bayesian optimal interval) design to determine feasibility for dose escalation or de-escalation (2). For this, we set the target DLT at 30%. Further details on decision boundaries are described in the protocol. For the primary endpoint PK, all patients with at least one paired sample (CSF and peripheral blood [PB]) will be considered for analysis. We will describe the concentration of venetoclax and obinutuzumab in each patient in the serum and CSF at the respective time points (as outlined above). The median (range, interquartile range) of the concentration based on all evaluable patients at the respective time points will be computed separately for serum and CSF. To describe the CSF penetration of the respective compound, we will calculate the ratio of the CSF concentration / serum concentration. <u>Description of the primary analysis and population:</u> For the primary endpoint PK, all patients with at least one paired sample (CSF and PB) will be considered for analysis. We will conduct two analyses for efficacy. One is based on all registered patients in the denominator, irrespective whether treatment was applied, irrespective whether they refused or discontinued the treatment or whether other protocol violations are revealed (intention-to-treat principle). Second analysis will be based on all patients who have received at least one treatment application for sensitivity analyses (as treated analysis). Safety analyses will be performed in the safety population which includes all patients who have received at least one dose of trial treatment.

Safety:
The total number of AEs, the minimum, maximum and mean number of AEs per patient, the total number of follow-up days (number of days in the observation period), the number of AEs per follow-up day (total number of AEs divided by the total number of follow-up days), the number of patients who had at least one AE, and the number of patients who stopped treatment due to AE will be given. Same will be done for SAEs. We will use the CTCAE grading system to describe severity of any AE or SAE.

Secondary endpoints:
For all secondary endpoints, we will primarily present all data based on the 15 patients, but will also provide exploratory stratified analyses by dosing group. Patients with missing data regarding lymphoma response will be considered as non-responders. For time to event data (PFS, FFS, and OS), patients will be censored at last date of follow-up if they did not experience the event of interest beforehand. We will calculate respective survival probabilities at the 6, 9, and 12 months landmarks accompanied with 95% confidence intervals (CIs). Median survival times with 95% CIs will be calculated if reached. Again, because this study is entirely exploratory in nature, there will be no tests for hypothesis testing.

Safety analyses (DLT appraisal):

There will be two safety assessments for DLTs after the first cohort before preceding to cohort 2 and another one before preceding to cohort 3. DLT assessment will always take place 6 weeks after first drug application to the 5th patient of the respective cohort. The following rules based on the BOIN approach (2) (see 3.1 [Trial design]) apply to the safety analyses regarding DLTs (see 2.8.1 [Definition of dose limiting toxicities]):

Rule	**Target number of patients treated at each dose level (dose level of venetoclax)**		
	N=5 (600mg)	**N=5** (800mg)	**N=5** (1000mg)
Escalate if number of DLT is smaller or equal to:	1	1	1
De-escalate if number of DLT is larger or equal to:	2	2	2
Terminate study if number of DLT is larger or equal to:	4	4	4

SAMPLE SIZE	To be assessed for eligibility:	n = 20
	To be registered to trial:	n = 15
	To be analysed:	n = 15

	In case a patient is not assessable during DLT time (during the first two cycles) for whatever reason (e.g. death definitely unrelated to study drug, withdrawal of consent, lost to follow-up), we will replace the patient to guarantee that there are always five patients assessable for DLT in each of the three dosing groups.	
TRIAL DURATION	Recruitment period (months):	24 months
	First patient in to last patient out (months):	41 months
	Treatment duration per patient: 70 weeks (~16 months) (18 weeks induction, 52 weeks maintenance) or until disease progression or toxicities	16 months
	Follow up duration per patient (months) after completion maintenance treatment:	3 months
PLANNED DATES	Enrolment of first patient, first patient in (FPI)	3rd quarter 2019
	Enrolment of last patient, last patient in (LPI)	3rd quarter 2021
	End of trial defined as last patient last visit (LPLV)	1st quarter 2023
	Final analysis and study report	4th quarter 2023
	Planned interim analysis	NA
PARTICIPATING SITES	2 sites are planned in Germany (Stuttgart and Freiburg).	
SPONSOR	Klinikum Stuttgart, Stuttgart, Germany	
FUNDER(S)	Roche Pharma AG and AbbVie	