

## Protocol summary

<b>Protocol Number</b>	CJBH492A12101
<b>Full Title</b>	A phase I/Ib open-label, multi-center dose escalation study of JBH492 in patients with relapsed/refractory chronic lymphocytic leukemia (CLL) and Non-Hodgkin's Lymphoma (NHL)
<b>Objective(s)</b>	<p>Primary objective:</p> <ul style="list-style-type: none"> <li>To characterize safety, tolerability, and maximum tolerated dose (MTD) / recommended dose (RD) for expansion of JBH492 single agent in participants with relapsed/refractory (r/r) CLL and r/r NHL</li> </ul> <p>Secondary objectives:</p> <ul style="list-style-type: none"> <li>To evaluate the preliminary anti-tumor activity of single agent JBH492 in NHL</li> <li>To determine the pharmacokinetics (PK) of single agent JBH492, including total antibody (total Ab), total antibody-drug conjugate (ADC), DM4 (a maytansine-derived cytotoxic payload), and S-Methyl DM4</li> <li>To assess the immunogenicity of JBH492</li> </ul>
<b>Study Design / Methodology</b>	<p>This was a first-in-human, open-label, Phase I/Ib, multi-center study that investigated JBH492 as a single agent and consisted of a dose escalation part, followed by an expansion part (the expansion part was not performed due to early study termination and not due to any safety reasons). The escalation part was conducted in participants with r/r CLL and r/r NHL. The study consisted of the following periods:</p> <ul style="list-style-type: none"> <li>Pre-treatment period: From the day of participants' first informed consent to the day before first administration of study treatment (Day -28 to Day -1).</li> <li>On-treatment period: From the date of first administration of study treatment (Day 1) to 30 days after the date of last actual administration of any study treatment (including start and stop dates).</li> <li>Post-treatment safety follow-up period: Starting at Day 31 after last administration of study treatment. All participants had safety follow up assessments 30, 60, 90, 120 and 150 days (+7-day window) after the last dose of study treatment.</li> </ul>
<b>Centers</b>	8 centers in 7 countries: Germany (2), Korea, Republic of (1), Finland (1), Spain (1), Israel (1), Singapore (1), Japan (1)
<b>Study Population</b>	Patients with r/r CLL and r/r NHL
<b>Key Inclusion / Exclusion criteria</b>	<p>Inclusion Criteria:</p> <p>For patients with CLL:</p> <ul style="list-style-type: none"> <li>Confirmed diagnosis of CLL</li> </ul> <p>For patients with NHL:</p> <ul style="list-style-type: none"> <li>Histologically confirmed diagnosis of B- or T-cell NHL</li> <li>Must have a site of disease amenable to biopsy, and be suitable and willing to undergo study required biopsies at screening and during therapy</li> </ul> <p>Exclusion Criteria, applicable to both CLL and NHL:</p> <ul style="list-style-type: none"> <li>History of anaphylactic or other severe hypersensitivity/infusion reactions to ADCs, monoclonal antibodies (mAbs) and/or their excipients such that the patient is unable to tolerate immunoglobulin/monoclonal antibody administration</li> <li>Any prior history of treatment with maytansine (DM1 or DM4)-based ADC</li> <li>Known intolerance to a maytansinoid</li> <li>Patients with any active or chronic corneal disorders</li> <li>Patients who have any other condition that precludes monitoring of the retina or fundus</li> </ul>

	<ul style="list-style-type: none"> <li>• Patients with active Central Nervous System (CNS) involvement are excluded, except if the CNS involvement has been effectively treated and provided that local treatment was &gt; 4 weeks before first dose of study treatment. Patients that have been effectively treated for CNS disease and are stable under systemic therapy may be enrolled provided all other inclusion and exclusion criteria are met. Patients who received prophylactic intrathecal treatment are eligible, if treatment discontinued &gt; 5 half-lives prior to the first dose of study treatment</li> <li>• Impaired cardiac function or clinically significant cardiac disease</li> <li>• Known history of Human Immunodeficiency Virus infection</li> <li>• Active Hepatitis B Virus (HBV) or Hepatitis C Virus infection. Patients whose disease is controlled under antiviral therapy should not be excluded. Patients who are anti-HBcAb positive should be HBsAg negative and HBV-DNA negative to be eligible</li> </ul> <p>Other inclusion and exclusion criteria may apply.</p>
<b>Test Product(s), Dose(s), and Mode(s) of Administration</b>	Lyophilisate powder for intravenous injection every 3 weeks at 0.4, 0.8, 1.6, 2.4 or 3.6 mg/kg
<b>Key Assessments</b>	<p>Safety and tolerability: Incidence and severity of Dose Limiting Toxicities (DLTs), Adverse Events and Serious Adverse Events. Number of dose interruptions, reductions, dose intensity.</p> <p>PK: PK parameters (e.g. AUC, Cmax, Cmin, Tmax, T1/2) for four analytes (total Ab, total ADC, DM4, and sDM4)</p> <p>Efficacy: Overall response rate, Best overall response, Duration of Response, and Progression Free Survival</p> <p>Other: Incidence of anti-JBH492 antibodies</p>

<b>Statistical Methods</b>	<p><b>MTD/RD</b></p> <p><b>DLTs</b></p> <p>Estimation of the MTD of the treatment was planned to be based upon the estimation of the probability of DLT in Cycle 1 (i.e. the first 21 days) for participants in the Dose-Determining Set (DDS). An RD below the MTD could be identified based on other safety, clinical, PK, and pharmacodynamics (PD) data.</p> <p>Bayesian Hierarchical Logistic Regression Model (BHLRM) with Escalation With Overdose Control (EWOC) approach</p> <p>The relationship between dose and the probability of DLT was modeled using BHLRM for single-agent JBH492 based on the DDS. DLT data from two different disease areas, NHL and CLL, were combined using Bayesian hierarchical structure. BHLRM with EWOC principle was used to make dosing decisions. A dose could only be used for newly enrolled participants if the risk of excessive toxicity at that dose was less than 25%.</p> <p>Assessment of participant risk</p> <p>After each cohort of participants in dose escalation, the posterior distribution for the risk of DLT for new participants at doses of interest were evaluated. The posterior distributions were summarized to provide the posterior probability that the risk of DLT lies within the following intervals:</p> <ul style="list-style-type: none"><li>Under-dosing: [0, 0.16)</li><li>Targeted toxicity: [0.16, 0.33)</li><li>Excessive toxicity: [0.33, 1]</li></ul> <p>The MTD was defined as the highest dose estimated to have less than 25% risk of causing a DLT during the DLT evaluation period in more than 33% of treated participants.</p> <p>The MTD declaration was to occur when the following conditions were met:</p> <ul style="list-style-type: none"><li>• At least 6 treated participants at the dose to be determined as the MTD</li><li>• This dose satisfied one of the following conditions:<ol style="list-style-type: none"><li>1. The posterior probability of targeted toxicity at this dose exceeds 50% and was the highest among potential doses, or</li><li>2. Minimum of 21 treated participants on the trial if the escalation is always joint for NHL and CLL; minimum of 14 treated participants per disease area if the escalation is separated per the BHLRM model recommendation.</li></ol></li></ul> <p><b>Safety, tolerability, efficacy, and PK</b></p> <p>Data were summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant PK and PD measurements.</p>
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