**Clinical Trial Protocol BYON4228.001**

**Protocol title: A first-in-human dose escalation and expansion study with the SIRPα-directed monoclonal antibody BYON4228 alone and in combination with rituximab to evaluate the safety, pharmacokinetics, pharmacodynamics and efficacy in patients with relapsed/refractory CD20 positive B-cell Non-Hodgkin's Lymphoma (NHL)**

**Inclusion Criteria**

1. Male or female, age ≥ 18 years at the time of signing informed consent;

2. Patient with:

a. Part 1 only: B-cell NHL expressing CD20 by immunohistochemistry (IHC) or flow cytometry, R/R to at least 2 prior lines of therapy or autologous CAR-T cell therapy;

b. Part 2 cohort A only: Histologically confirmed DLBCL expressing CD20 by IHC or flow cytometry, R/R to frontline therapy, or second line salvage regimens or autologous hematopoietic cell transplantation, or autologous CAR-T therapy;

c. Part 2 cohort B only: Histologically confirmed marginal zone or follicular lymphoma (Grade 1-3a) expressing CD20 by IHC or flow cytometry, R/R to at least 2 prior lines of therapy or autologous CAR-T cell therapy;

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1;

4. Disease that is measurable or assessable for response per Lugano Classification for lymphomas;

5. Laboratory measurements, blood counts:

a. Hemoglobin ≥ 9.5 g/dL (> 5.9 mmol/L);

b. Absolute neutrophil count (ANC) ≥ 1.0 × 109 /mL;

c. Platelet counts ≥ 50 × 109 /mL;

6. Laboratory measurements, hepatic function:

a. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 5 × upper limit of normal (ULN);

b. Total bilirubin ≤ 1.5 × ULN or 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or a genetic equivalent;

7. Laboratory measurements, renal function: Serum creatinine ≤ 1.5 × ULN or calculated glomerular filtration rate (GFR) 60 mL/min/1.73 m2 (calculated with CKD-EPI formula);

8. Females of childbearing potential must be willing to use a highly effective method of

contraception during the study and for 12 months after the last dose of rituximab or for 2 months after the last dose of BYON4228, whichever takes longer;

9. Part 1: Willing to consent to 1 pre-treatment tumor biopsy. If a recent (≤ 2 months) archival tumor biopsy sample is available prior to signing the ICF and the patient did not have anticancer treatment (including steroids) since the biopsy was performed, this could be used as the pretreatment tumor biopsy;

10. Part 2: Willing to consent to 1 pre-treatment and 1 on-treatment tumor biopsy. If a recent (≤ 2 months) archival tumor biopsy sample is available prior to signing the ICF and the patient did not have anticancer treatment (including steroids) since the biopsy was performed, this could be used as the pre-treatment tumor biopsy.

**Exclusion Criteria**

1. Having been treated with:

a. CD47 or SIRPα targeting agents at any time;

b. Other anticancer therapy including chemotherapy or immunotherapy within 4 weeks prior to start of BYON4228 treatment, targeted therapy or investigational agents within 2 weeks prior to start of BYON4228 treatment or within 5 times the elimination half-life of the therapy whichever is longer (max 4 weeks). Note: treatment with hormonal therapy with LHRH agonists for localized prostate cancer, and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion;

c. Steroid treatment within 1 week prior to start of BYON4228 treatment. Note: intermittent use of bronchodilators, topical steroids or local steroid injections is allowed. Patients who have been stabilized to 10 mg prednisone (or equivalent) orally once daily or less within 1 week prior to start BYON4228 treatment may be enrolled;

d. Radiotherapy within 4 weeks prior to start of BYON4228 treatment, or within 1 week for palliative pain care;

In addition, the patient must have sufficiently recovered from any treatment-related toxicities or CTCAE Grade ≤ 1 or baseline, except for toxicities not considered a safety risk for the patient at the investigator's discretion;

2. History of hypersensitivity or allergic reaction to any of the excipients of BYON4228 or rituximab

which led to permanent discontinuation of the treatment;

3. Symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, or treatment for brain metastases within 4 weeks prior to start of BYON4228 treatment;

4. Burkitt's lymphoma;

5. Known active or chronic hepatitis B, C or E infection or human immunodeficiency virus (HIV);

6. Red blood cell (RBC) transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to screening. RBC transfusions are permitted during screening to meet the hemoglobin inclusion criteria, RBC transfusion within 2 weeks prior to start of BYON4228 treatment is not allowed;

7. Patients with active graft versus host disease (GVHD) or ongoing immunosuppression for GVHD;

8. History of autoimmune hemolytic anemia or autoimmune thrombocytopenia;

9. History of active autoimmune disorders (including but not limited to: Crohn's disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Grave's disease) or other conditions that compromise or impair the immune system (except for hypogammaglobulinemia);

10. Second malignancy, other than the one treated in this trial, in the last 3 years before signing ICF. Except appropriately treated basal cell or localized squamous skin carcinomas, localized prostate cancer, localized cervical cancer or other malignancy for which patients are not on active anticancer therapy as defined in Exclusion Criterion 1;

11. History (within 6 months prior to start of BYON4228 treatment) or presence of clinically significant cardiovascular disease such as unstable angina, congestive heart failure, myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication;

12. Severe active infection or other severe uncontrolled systemic disease (e.g. advanced renal disease,

pulmonary, uncontrolled diabetes mellitus, severely immunocompromised state, or metabolic disease) at screening;

13. Major surgery within 4 weeks prior to start of BYON4228 treatment;

14. Pregnancy or active breastfeeding;

15. Other condition that in the investigator's opinion is likely to jeopardize patient safety or interfere with the patient's ability to comply with trial requirements.