4. Study population

This study will enroll adult subjects with aggressive or indolent forms of relapsed or refractory B-cell non-Hodgkin lymphoma (r/r NHL).

4.1 Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:
Note: changes in the inclusion criteria are highlighted as an x.1 version of the criterion. This is to indicate that there are updates compared to V2.0 of the protocol.

1. Signed informed consent form
2. Age ≥ 18 years

3.1 Histologically confirmed diagnosis of one of the following non-Hodgkin lymphoma subtypes:

a) Aggressive DLBCL, refer to Appendix 1 for all included subtypes defined by WHO 2016
b) Follicular lymphoma (FL) grade 1, 2 or 3A (FL grade 3B is considered under the subtypes of DLBCL)
c) Marginal zone lymphoma (MZL)
d) Mantle cell lymphoma (MCL)
e) Burkitt lymphoma (BL)
f) Primary central nervous system lymphoma (PCNSL)

4.1 Relapsed or refractory disease defined as one of the following:

a. DLBCL:
- Primary refractory disease, defined as patients failing to achieve CR or PR to first-line anti-CD20 and anthracycline-based chemoimmunotherapy and having either stable disease or primary progression
- Relapse within 12 months of completion of first line therapy and not eligible for transplant (Autologous Stem Cell Transplantation [ASCT]). Transplant ineligible subjects will include those who are deemed ineligible for high-dose chemotherapy and ASCT due to age, performance status or comorbidity, while having adequate organ function for CAR T-cell treatment
- No response to second or greater lines of therapy, defined as one of the following:
  - PD as best response to most recent therapy regimen
  - SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy
- Relapsed or refractory disease post-ASCT, defined as one of the following:
  - Disease progression or relapse post-ASCT (must have biopsy proven recurrence in relapsed subjects)
  - If salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy, as defined above

b. High-risk DLBCLwith IPI 3-5 or double/triple hit lymphoma (see Appendix 1: WHO):
   - Primary refractory disease, defined as subjects failing to achieve a CR to first-line anti-CD20 and anthracycline-based chemoimmunotherapy after at least 2 cycles at the interim disease assessment.

c. FL and MZL: Relapsed/refractory disease after at least 2 prior lines of therapy, unless all available therapies were administered in 1 line

d. MCL: Relapsed/refractory disease after at least 2 prior lines of therapy, , unless all available therapies were administered in 1 line

e. BL:
   - Primary refractory disease, defined as subjects failing to achieve CR or PR to first-line anthracycline-based chemoimmunotherapy and having either stable disease or primary progression
   - Histologically confirmed relapse after completion of at least one line of therapy
   - No complete response to second or greater lines of therapy

f. PCNSL:
   - Primary refractory disease, defined as subjects failing to achieve CR or PR to first-line treatment with high-dose methotrexate based chemotherapy or chemoimmunotherapy.
   - Relapse after first line of therapy, confirmed by either histological biopsy, positive CSF cytology as determined by flow cytometry, or by MRI imaging
   - No complete response to second or greater lines of therapy

Note: Induction with or without ASCT, consolidation and maintenance therapy is considered a single line of therapy

5.1 Measurable disease according to the Lugano Classification, or IPCG criteria for PCNSL [60]

6. ECOG performance status of 0 - 2 (subjects with ECOG 2 must have serum albumin ≥ 3.4 g/dL)

7.1 Adequate bone marrow function defined as:

- Absolute neutrophil count (ANC) ≥ 500/µL or ≥ 0.5 × 10^9/L (without G-CSF support within 7 days of the laboratory test or pegylated G-CSF support within 14 days of the laboratory test)
- Platelet count ≥ 50,000/µL or ≥ 50 x 10^9/L (without prior platelet transfusion within 7 days before the laboratory test)

  Note: For subjects receiving anticoagulant treatment, continuation of anticoagulant treatment should be discussed with the sponsor's medical monitor prior to enrollment in the study.

- Absolute lymphocyte count (ALC) ≥ 300/µL or ≥ 0.3 × 10^9/L
- Absolute number of CD3+ T cells ≥ 150/µL or ≥ 0.15 × 10^9/L

8. Adequate renal, hepatic and pulmonary function defined as:
   - Creatinine clearance (Cockcroft Gault) ≥ 45 mL/min
   - Aspartate aminotransferase (AST) ≤ 3 × upper limit of normal (ULN)
   - Alanine aminotransferase (ALT) ≤ 3 × ULN
   - Total bilirubin ≤ 2 x ULN, except in subjects with Gilbert's syndrome
   - No clinically significant pleural effusion
   - Baseline oxygen saturation > 92% on room air

9.1 Women of childbearing potential must have a negative serum pregnancy test at screening and prior to the first dose of conditioning chemotherapy

10.1 Women of childbearing potential and all male subjects must agree to use highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly) and agree to remain on a highly effective method of contraception from the time of signing the informed consent form until at least 12 months after GLPG5101 infusion. Subjects must agree to not donate eggs or sperm during this period. Refer to Appendix 4 for detailed information on definitions and contraceptive guidance.

4.2 Exclusion criteria

Each potential subject should not satisfy any of the following criteria to be enrolled in the study:
Note: changes in the inclusion criteria are highlighted as an x.1 version of the criterion. This is to indicate that there are updates compared to V2.0 of the protocol.

1.1 Richter's transformation

2.1 Prior treatment:

- Any anti-CD19 targeted therapy
- Salvage systemic therapy within 2 weeks or 5 half-lives (whichever is shorter) prior to leukapheresis,
- Bendamustine within 3 months prior to leukapheresis
- Allogeneic stem cell transplant within 6 months before leukapheresis. Subjects who received an allogeneic transplant must have stopped all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease. Subjects with active graft-versus-host disease are excluded
- Systemic corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) is not allowed for 7 days prior to leukapheresis and >72 hours prior to GLPG5101 infusion (if restarted).

  For subjects with PCNSL, higher dosages of corticosteroid therapy may be allowed after consultation with the sponsor's medical monitor

  Note: Topical and inhaled corticosteroids in standard doses and physiologic replacement for subjects with adrenal insufficiency are allowed.

3. History of another primary malignancy that requires intervention beyond surveillance or that has not been in remission for at least 3 years. The following are exempt from the 3-year limit:
   - Adequately treated non-melanoma skin cancer without evidence of disease
   - Curatively treated localized prostate cancer
   - Carcinoma in situ (e.g. cervix, bladder, breast) or a squamous intraepithelial lesion on Papanicolaou (PAP) smear

4.1 Toxicity from previous anticancer therapy that has not resolved to baseline levels or to Grade 1 or less

5.1 Active CNS involvement (with neurological changes) by disease under study, except if the CNS involvement has been effectively treated (i.e. subject is asymptomatic) and local treatment was > 4 weeks before screening. For subjects with PCNSL, any subject with active neurological symptoms (including seizures) should be discussed with the sponsor's medical monitor prior to inclusion in the study

6. Clinically significant cardiac disease within 12 months of screening such as:
   - Impaired cardiac function (LVEF < 45%) as assessed by echocardiogram performed ≤ 4 weeks prior to screening
   - Evidence of pericardial effusion as determined by echocardiogram
   - New York Heart Association Class III or IV congestive heart failure
   - Clinically significant arrhythmias
7. Primary immunodeficiency

8.1 Stroke or seizure within 6 months of screening. For subjects with PCNSL, any subject with seizures within 6 months prior to screening should be discussed with the sponsor's medical monitor as per inclusion criterion 4.1

9. History of autoimmune disease resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within 2 years prior to screening
10. Infection with HIV, hepatitis B or hepatitis C virus. A history of hepatitis B or C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing.
11. Uncontrolled infection at screening
12. Vaccinated with live attenuated vaccine ≤ 6 weeks prior to the start of lymphodepleting chemotherapy

13.1 Pregnant or nursing women, or planning to become pregnant within 12 months after GLPG5101 infusion

14. Major surgery ≤ 2 weeks prior to leukapheresis
15. Known allergy or hypersensitivity to tocilizumab

16.1 Presence of any medical condition that would, in the investigator's judgement, prevent the subject's participation in the clinical study due to safety concerns, or the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.