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 or x.2 version of the criterion. This is to indicate that there are updates compared to the previous version of the protocol.

1. Signed informed consent form

2.1 Age ≥ 18 years at the time of signing informed consent form

3.2 One of the following NHL subtypes (histology must have been confirmed within 12 months of screening):

- DLBCL (see Appendix 1 for all included subtypes defined by WHO 2016)
- FL Grade 1, 2 or 3A (FL Grade 3B is considered under the subtypes of DLBCL)
- MZL
- MCL
- BL
- PCNSL
- DLBCL-RT
- High-Grade B-cell Lymphoma (HGBL)

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

- DLBCL 2L+ (Cohort 1a):
    - Primary refractory disease[13], defined as subjects failing to achieve CR to first-line anti-CD20 and anthracycline-based chemoimmunotherapy
    - Relapse after completion of first-line therapy per NCCN, ESMO, or other defined treatment guideline, including those not eligible for transplant (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 (see Appendix 10 for detailed criteria on transplant ineligible status)
    - Treatment failure after second or greater lines of therapy[14]
    - 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

[13] ***Primary refractory disease defined as no CR to first-line therapy***
- Subjects who are intolerant to first-line therapy are excluded
- Progressive disease (PD) as best response to first-line therapy (per NCCN, ESMO, or other appropriate local guidelines)
- Stable disease (SD) as best response after at least 4 cycles (DLBCL) or majority of cycles (BL, PCNSL) of first-line therapy (per NCCN, ESMO, or other defined treatment guidelines)
- Partial response (PR) as best response after at least 6 cycles (DLBCL) or all cycles (BL, PCNSL) of first-line therapy (per NCCN, ESMO, or other defined treatment guidelines)

[14] ***Treatment failure after 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 (SD duration no longer than 6 months from last dose of therapy)
- PR as best response after completion of second or greater line of therapy. Subjects enrolling with a PR after completion of 2L+ therapy require a tumor biopsy at screening

- Subjects with DLBCL transformed from indolent lymphoma (FL, MZL, LPL) are eligible if they have received at least one line of prior therapy that is typically utilized to treat aggressive lymphoma even if it was during the indolent phase
- Subjects with DLBCL transformed from CLL (Richter Transformation; DLBCL-RT) are excluded from this cohort.

- DLBCL 2L+ with SCNSL (Cohort 1b)
  - As outlined for DLBCL 2L+ with CNS involvement
  - Referred to throughout as SCNSL
- High-risk First-Line DLBCL(Cohort 2)
  - Including DLBCL NOS or HGBL NOS with IPI 3-5, or HGBL with MYC and BCL2 rearrangements (double-hit lymphoma) or with MYC, BCL2, and BCL6 rearrangement (triple-hit lymphoma) (see Appendix 1)
  - Defined as subjects failing to achieve a CR on PET after 2 or 3 cycles of first-line anti-CD20 and anthracycline-based chemoimmunotherapy. Subjects must have a positive PET per Lugano classification (Cheson et al., 2014) (Deauville PET score of 4 or 5 and an overall response of PR/stable disease [SD]) after 2 or 3 cycles of frontline chemotherapy-induced therapy
  - Subjects with DLBCL transformed from CLL (Richter Transformation; DLBCL-RT) are excluded from this cohort.
- FL and MZL 3L+ (Cohort 3):
  - Relapsed/refractory disease after at least 2 prior lines of therapy, unless all available therapies were administered in the first line
- MCL 2L+ (Cohort 4):
  - Relapsed/refractory disease after at least 2 prior lines of therapy[14], or 1 prior line of therapy if a BTK inhibitor was administered in the first line
- BL 2L+ (Cohort 5):
  - Primary refractory disease[13], defined as subjects failing to achieve CR to first-line anthracycline-based chemoimmunotherapy
  - Histologically confirmed relapse after completion of at least one line of therapy
  - Treatment failure after second or greater lines of therapy[14]
  - Presence of typical Burkitt translocations including t(8;14), t(2;8) or t(8;22) is required. Burkitt-like lymphoma or HGBL with 11q aberration is not allowed in this cohort

- PCNSL 2L+ (Cohort 6a):
    - Primary refractory disease[13], defined as subjects failing to achieve CR to first-line[15] treatment with high-dose methotrexate-based chemotherapy or chemoimmunotherapy
    - Relapse after completion of first- or greater-line[15] therapy, confirmed by either histological biopsy, positive CSF cytology as determined by flow cytometry, or by (magnetic resonance imaging) MRI imaging[16]
    - Treatment failure after second or greater lines[15] of therapy[14]
- PCNSL First-Line Consolidation (Cohort 6b):
    - First-line subjects, ineligible for consolidation with ASCT after induction therapy
    - Subjects should have CR or PR after first-line induction with a high-dose methotrexate-based therapy and meet one of the transplant ineligible criteria in Appendix 10
- DLBCL-RT 2L+ (Cohort 7):
    - Confirmed diagnosis of CLL based on iwCLL 2018 criteria (Hallek et al., 2018) with histologically confirmed Richter Transformation to DLBCL subtype (DLBCL-RT)
    - Primary refractory disease[13] defined as subjects failing to achieve CR to first-line therapy for Richter Transformation
    - Relapse after completion of first- or greater-line of therapy for Richter Transformation
    - Treatment failure after second or greater lines of therapy[14] for Richter Transformation

5.2 Presence of at least one measurable lesion (for nodal lesions longest diameter [LDi] > 1.5 cm; for extranodal lesions including brain lesions: >1 cm) or a PET positive (Deauville 4 or 5) lesion according to the Lugano Classification (except for PCNSL subjects ineligible for ASCT after induction therapy, Cohort 6b) (Lauren E Abrey et al., 2005)

- Lesions that have been previously irradiated will only be considered evaluable if they have shown progression

[15] Induction therapy with or without ASCT, consolidation and maintenance therapy is considered a single line of therapy. Line of therapy is defined in Appendix 9
[16] For PCNSL histological confirmation by re-biopsy or CSF cytology at relapse is recommended if feasible. However, subjects will be eligible without re-biopsy/CSF cytology provided the initial diagnostic material/report (if cytology) is available and current MRI imaging findings are consistent with PCNSL by neuroradiology review.

- Subjects without a measurable lesion or a PET positive lesion will be eligible if they have splenomegaly and bone marrow infiltration with lymphoma

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

7.3 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). Platelet count ≥ 30,000/µL or ≥ 30 x 10^9/L (without prior platelet transfusion within 7 days before the laboratory test) if attributed to the study indication such as for subjects with significant bone marrow infiltration and/or splenomegaly due to lymphoma.
- Absolute lymphocyte count (ALC) ≥ 300/µL or ≥ 0.3 × 10^9/L

8.1 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. For subjects with Gilbert's syndrome total bilirubin must be ≤ 3 x ULN
- No clinically significant pleural effusion
- Baseline oxygen saturation > 92% on room air. Subjects with dyspnea are eligible if their dyspnea is Grade <2, according to CTCAE

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 5 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 exclusion criteria are highlighted as an x.1 and x.2 version of the criterion. This is to indicate that there are updates compared to the previous version of the protocol.

1.1 This exclusion criterion was removed per protocol version 7

2.3 Prior treatment:

- Any anti-CD19 targeted therapy
- Systemic cytotoxic therapy, within 2 weeks or 5 half-lives whichever is shorter before leukapheresis
- Systemic lymphotoxic agents (cyclophosphamide, ifosfamide, methotrexate) within 2 weeks before leukapheresis
- Intrathecal therapy with single agent or combinations of cytarabine, methotrexate or hydrocortisone within 1 week before leukapheresis
- Bendamustine, fludarabine or cladribine within 3 months before leukapheresis
- T cell engagers e.g. bi-specific CD3xCD20 antibodies within 3 months before leukapheresis (except for subjects with DLBCL-RT [Cohort 7])
- Radiation therapy within 2 weeks prior to leukapheresis or if to the pelvis, large intra-abdominal or retroperitoneal lesions within 4 weeks 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
- Systemic corticosteroid therapy at a pharmacologic dose (> 30 mg/day of hydrocortisone or equivalent doses of other corticosteroids) is not allowed for 7 days before leukapheresis and within 72 hours before GLPG5101 infusion (if restarted). For cohorts 5, 6a and 6b only, subjects with PCNSL, SCNSL, or BL with brain involvement, should receive an adequate dose of corticosteroids to control neurological symptoms during screening. When the subject is stable, and no later than 72 hours before leukapheresis, the dose of corticosteroids should be reduced to the minimum required to control the symptoms, and should not be higher than dexamethasone 4 mg twice a day (or an equivalent dose of other corticosteroids). If there is a clinically significant neurological deterioration, the subject should not undergo leukapheresis at that time. Post leukapheresis, corticosteroids should be continued at a sufficient dose and duration to prevent neurological deterioration, tapering off as clinically indicated. Subjects that require an increase in the dose of corticosteroids within 72 hours of leukapheresis (higher than the stable dose received in screening) a repeat MRI scan of the brain is required to establish a new baseline prior to lymphodepletion.

  Note: Topical and inhaled corticosteroids in standard doses and physiologic replacement for subjects with adrenal insufficiency at a maximum of 30 mg/day hydrocortisone or equivalent doses of other corticosteroids are allowed at all times.

3.2 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 (as per primary tumor [T], regional lymph nodes [N], distant metastases [M] TNM staging) without evidence of disease
- Carcinoma in situ (e.g. cervix, bladder, breast) or a squamous intraepithelial lesion on Papanicolaou (PAP) smear without evidence of disease
- CLL for subjects with DLBCL-RT (Cohort 7)

4.2 Toxicity from previous anticancer therapy that has not resolved to baseline levels or to ≤ Grade 2 (according to CTCAE v5.0), except for peripheral neuropathy, alopecia, and cytopenias which are allowed if the inclusion criteria are met

5.3 Active CNS involvement (lesion on contrast-enhanced CT/MRI brain, malignant B cells in CSF) by disease under study, except if the CNS involvement has been effectively treated (i.e. subject is asymptomatic and CSF is clear of lymphoma cells or brain imaging is clear of lymphoma) and local treatment was ≥ 4 weeks before screening. This exclusion criterion is not applicable for subjects in Cohorts 1b, 5, 6a or 6b. For subjects with CNS involvement, any subject with active neurological symptoms (including seizures) should be discussed with the sponsor's medical monitor before inclusion in the study

6.1 Clinically significant cardiac disease such as:

- Impaired cardiac function (LVEF < 45%) as assessed by 2D echocardiogram or multigated acquisition (MUGA) performed ≤ 4 weeks before screening
- Clinically significant and/or symptomatic pericardial effusion
- Myocardial infarction or coronary artery bypass graft within 6 months of screening
- History of New York Heart Association Class III or IV congestive heart failure (see Appendix 7)
- Clinically significant ventricular arrhythmia
- Unexplained syncope, not believed to be vasovagal in nature or due to dehydration within 12 months of screening
- Non-ischemic cardiomyopathy
- Other severe/clinically significant cardiac disease within 12 months of screening

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 4.3

9.1 History of autoimmune disease requiring systemic immunosuppression or disease modifying treatment within 28 days before 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. 1 Systemic fungal, bacterial, viral, or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement despite appropriate antibiotics or other treatment)

12. 1 Vaccinated with live attenuated vaccine ≤ 6 weeks before the start of lymphodepleting chemotherapy

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

14. 1 Major surgery ≤ 2 weeks before leukapheresis

15.1 Known allergy or hypersensitivity to any product (including its excipients) to be given to the subject as per study protocol (e.g.tocilizumab, conditioning chemotherapy, etc.)

16.1 Presence of any medical condition that would, in the investigator‘s judgment, 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.

17. Subjects who have had a venous thrombo-embolic event requiring anticoagulation and who meet any of the following criteria:

- Have been on a stable dose of anticoagulation for <1 month
- Have had Grade ≥ 2 hemorrhage in the past 6 weeks

Note: Any subject who is on a therapeutic dosage of anticoagulant treatment should be discussed with the sponsor's medical monitor before inclusion in the clinical study

18. Any serious underlying medical or psychiatric condition likely to interfere with study visits or procedures

19. Subjects with bleeding diathesis and coagulopathies

20. Subjects with aggressive, rapidly progressive disease who would be unable to proceed with infusion of GLPG5101, 7 days after leukapheresis without receiving bridging therapy

21. Subjects with active graft-versus-host disease.

22. Subjects with no archival tumor sample or report (if CSF cytology) within 12 months before screening, and without a repeated tumor biopsy. Except for subjects with

relapsed PCNSL 2L+ (Cohort 6a) in whom a biopsy is deemed not feasible and have MRI imaging findings at screening that are consistent with PCNSL by neuroradiology review

23. Subjects with a body weight less than 50 kg.