Document Name: GCT3009-01 Protocol Genmab

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**5 TRIAL POPULATION(S)**

**5.1 Inclusion Criteria**

Each potential subject must fulfill all of the following criteria to be enrolled in the trial.

1. Be at least 18 years of age.

2. Must sign an informed consent form (ICF) prior to any screening procedures indicating that

they understand the purpose of the trial, the procedures required for the trial, and are willing

to participate in the trial prior to any other trial-related assessments or procedures.

3. Criterion updated as per Amendment 1

3.1 Criterion updated as per Amendment 3

3.2 Has histologically or cytologically confirmed relapsed or refractory B-cell NHL with no

available standard therapy or is not a candidate for available standard therapy, and for whom,

in the opinion of the investigator, experimental therapy with GEN3009 may be beneficial. All

subjects must have received at least two prior lines of systemic therapy, and,

a. For all indolent NHL (FL, MZL, and SLL) as well as aggressive NHL (DLBCL,

HGBCL, and PMBCL), at least one of the two prior lines of treatment must have been

a CD20-containing chemotherapy regimen;

b. For MCL, subjects must have had or are otherwise ineligible for treatment with a BTK

inhibitor, and;

c. For CLL, subjects must have received at least one prior line of BTK inhibitor or BCL-

2 inhibitor.

Note: For B-cell NHL, “relapsed disease” is defined as the reappearance or growth of

lymphoma after at least 6 months duration of response. “Refractory disease” is defined as

failure to achieve response after at least 2 cycles of therapy or reappearance after a duration of

response of < 6 months.

For CLL, “relapsed disease” is defined as evidence of disease progression in a subject who has

previously achieved a CR or PR for ≥6 months. “Refractory disease” is defined as treatment

failure (not achieving a CR or PR) or as progression within 6 months from the last dose of

therapy.

4. Has 1 of the following B-cell NHL subtypes for the Dose Escalation:

a. DLBCL, *de novo* or histologically transformed

b. HGBCL (Swerdlow et al., 2016)

c. PMBCL

d. FL, with advanced symptomatic disease and with a need for treatment

e. MCL, without leukemic manifestation

f. MZL, either nodal, extranodal or mucosa associated, with a need for treatment

initiation based on symptoms and/or disease burden

g. SLL, with a need for treatment based on symptoms and/or disease burden

h. CLL, including all the following parameters:

i. Criterion updated as per Amendment 3

ia.B-cell count < 100109/L (100,000/μL) in the peripheral blood

ii. Presence of measurable lymphadenopathy and/or organomegaly

iii. Leukemic cells are small mature lymphocytes, and prolymphocytes must not

exceed 55% of the blood lymphocytes

iv. CLL cells on immunophenotype demonstrate a clonal B-cell population,

expressing the B-cell surface markers CD19 and CD20, as well as CD5.

Subjects with bright surface immunoglobulin expression or lack of CD23

expression in > 10% of cells must lack t(11;14) translocation by interphase

cytogenetics.

5. Has 1 of the following B-cell NHL subtypes for the Expansion:

a. DLBCL, *de novo* or histologically transformed

b. FL, with advanced symptomatic disease and with a need for treatment initiation

c. CLL, including all the following:

i. Criterion updated as per Amendment 3

ia.B-cell count < 100109/L (100,000/μL) in the peripheral blood

ii. Presence of measurable lymphadenopathy and/or organomegaly

iii. Leukemic cells are small mature lymphocytes, and prolymphocytes must not

exceed 55% of the blood lymphocytes

iv. CLL cells on immunophenotype demonstrate a clonal B-cell population,

expressing the B-cell surface markers CD19 and CD20, as well as CD5.

Subjects with bright surface immunoglobulin expression or lack of CD23

expression in > 10% of cells must lack t(11;14) translocation by interphase

cytogenetics.

6. Has measurable disease for B-cell NHL

a. A fluorodeoxyglucose (FDG)-positron emission tomography (PET) CT scan

demonstrating positive lesion compatible with CT (or MRI)-defined anatomical tumor

sites

***and***

b. A CT scan (or magnetic resonance imaging [MRI]) with involvement of ≥ 2 clearly

demarcated lesions/nodes with long axis > 1.5 cm and short axis > 1.0 cm or 1 clearly

demarcated lesion/node with a long axis > 2.0 cm and a short axis ≥ 1.0 cm.

7. Has active disease for CLL: Progressive or symptomatic disease with at least 1 of the following

criteria being met (Hallek et al., 2018):

a. Evidence of progressive marrow failure as manifested by the development of, or

worsening of, anemia and/or thrombocytopenia.

b. Massive (ie, ≥ 6 cm below the left costal margin) or progressive or symptomatic

splenomegaly.

c. Massive nodes (ie, ≥ 10 cm in longest diameter) or progressive or symptomatic

lymphadenopathy.

d. Progressive lymphocytosis with an increase of ≥ 50% over a 2-month period, or

lymphocyte doubling time (LDT) < 6 months.

e. Autoimmune complications including anemia or thrombocytopenia poorly responsive

to corticosteroids.

f. Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine).

g. Disease-related symptoms as defined by any of the following:

i. Unintentional weight loss ≥ 10% within the previous 6 months

ii. Significant fatigue

iii. Fevers ≥ 100.5°F or 38.0°C for 2 or more weeks without evidence of infection.

iv. Night sweats for ≥ 1 month without evidence of infection.

8. Has Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

9. Has acceptable laboratory parameters as follows:

**Parameter Result**

a. Creatinine clearance

> 50 mL/min (Cockcroft-Gault) or serum creatinine *≤* 1.5 X ULN

(refer to Appendix 1)

b. Serum alanine transaminase (ALT)

≤ 2.5  upper limit of normal (ULN)

*Note: If liver tumor/metastases are present, then ≤ 5*  *ULN is*

*allowed*

c. Serum aspartate transaminase (AST)

≤ 2.5  ULN

*Note: If liver tumor/metastases are present, then ≤ 5*  *ULN is*

*allowed*

d. Total Bilirubin

≤ 1.5  ULN

*Note: Subjects with Gilbert’s syndrome may be included if total*

*bilirubin is ≤ 3*  *ULN and direct bilirubin is ≤ 1.5*  *ULN*

e. Hemoglobin

≥ 5.6 mmol/L (9.0 g/dL)

*Note: Blood transfusion may be administered during screening to*

*meet this requirement*

f. Absolute neutrophil count

B-cell NHL: ≥ 1.010

9

/L (1,000/μL)

CLL: ≥ 1.0 x 10

9

/L (1,000/μL) unless due to bone marrow

involvement

*Note: G-CSF may be administered during screening to meet this*

*requirement*

g. Platelet count

B-cell NHL: ≥ 7510

9

/L (75,000/μL)

*Note: In presence of bone marrow involvement or splenomegaly,*

*platelets ≥ 50 × 109/L.*

CLL: ≥ 30 x 10

9

/L (30,000/μL)

*Note: Transfusion may be administered during screening to meet*

*this requirement*

h. Coagulation Status: PT/ INR/ aPTT

Prothrombin time (PT)/International normalized ratio (INR)/

Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN

10. Criterion updated as per Amendment 3

10.1 A woman of reproductive potential must agree to use adequate contraception during the

trial and for 12 months after the last GEN3009 administration. Adequate contraception is

defined as highly effective methods of contraception (refer to Appendix 12 for more

information). In countries where 2 highly effective methods of contraception are required, both

methods will be required for inclusion.

11. Criterion updated as per Amendment 3

11.1 A woman of childbearing potential must have a negative serum beta-human chorionic

gonadotropin (beta-hCG) at screening.

12. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted

reproduction during the trial and for 12 months after receiving the last dose of GEN3009.

13. A man who is sexually active with a woman of childbearing potential and has not had a

vasectomy must agree to use a barrier method of birth control, eg, either condom with

spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or

cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also

not donate sperm during the trial and for 12 months after receiving the last dose of GEN3009.

14. Must be willing and able to adhere to the requirements and restrictions specified in the ICF

and this protocol.

**5.2 Exclusion Criteria**

Any potential subject who meets any of the following criteria will be excluded from participating

in the trial.

1. Prior treatment with a CD37-targeting agent.

2. Prior allogeneic HSCT.

3. Autologous HSCT within 3 months before the first dose of GEN3009.

4. Treatment with an anti-cancer biologic including anti-CD20 therapy, radio-conjugated or

toxin-conjugated antibody or chimeric antigen receptor (CAR) T cell therapy within

4 weeks or 5 half-lives, whichever is shorter, before the first dose of GEN3009.

5. Chemotherapy or radiation therapy within 2 weeks of the first dose of GEN3009.

6. Treatment with an investigational drug or an invasive investigational medical device within

4 weeks or 5 half-lives, whichever is shorter, prior to the first dose of GEN3009.

7. Autoimmune disease or other diseases that require permanent or high-dose

immunosuppressive therapy.

8. Received a cumulative dose of corticosteroids more than the equivalent of 250 mg of

prednisone within the 2–week period before the first dose of GEN3009.

Note: Refer to Section 6.5.2 for steroid dosing limitations during study treatment period.

9. Has uncontrolled intercurrent illness, including but not limited to:

a. Ongoing or active infection requiring intravenous antibiotics treatment at the time

of enrollment or within the previous 2 weeks prior to the first dose of GEN3009.

b. Symptomatic congestive heart failure (grade III or IV as classified by the New York

Heart Association ([NYHA]), unstable angina pectoris or cardiac arrhythmia (refer

to Appendix 2).

c. Myocardial infarction, intracranial bleed, or stroke within the past 6 months.

d. Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia’s

formula (QTcF) >480 msec.

10. Toxicities from previous anti-cancer therapies have not resolved to baseline levels or to

Grade 1 or less except for alopecia and peripheral neuropathy.

11. Primary central nervous system (CNS) lymphoma or known CNS involvement at

screening.

12. Has known past or current malignancy other than inclusion diagnosis, except for:

a. Cervical carcinoma of Stage 1B or less.

b. Non-invasive basal cell or squamous cell skin carcinoma.

c. Non-invasive, superficial bladder cancer.

d. Prostate cancer with a current PSA level < 0.1 ng/mL.

e. Criterion deleted as per Amendment 3.

f. Any curable cancer with a CR of >2 years duration.

13. Intolerant to GEN3009 excipients (refer to the IB for more information).

14. Has had major surgery, (eg, requiring general anesthesia) within 3 weeks before screening

or will not have fully recovered from surgery, or has major surgery planned during the time

the subject is expected to participate in the trial (or within 4 weeks after the last dose of

GEN3009).

Note: Subjects with planned minor surgical procedures to be conducted under local

anesthesia may participate.

15. Has known history/positive serology for hepatitis B (unless immune due to vaccination or

resolved natural infection or unless passive immunization due to immunoglobulin therapy):

• Positive test for antibodies to the hepatitis B core antigen (anti-HBc)

**and**

• Negative test for antibodies to the hepatitis B surface antigen (anti-HBs).

16. Known medical history or ongoing hepatitis C infection that has not been cured.

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17. HIV tested positive at screening.

18. Is a woman who is pregnant or breast-feeding, or who is planning to become pregnant

while enrolled in this trial or within 12 months after the last dose of GEN3009.

19. Is a man who plans to father a child while enrolled in this trial or within 12 months after

the last dose of GEN3009.

20. Has any condition for which, in the opinion of the investigator, participation would not be

in the best interest of the subject (eg, compromise the well-being) or that could prevent,

limit, or confound the protocol-specified assessments.