5.1.2 Inclusion Criteria – Expansion Part A (GEN3014 Single Cohorts)

Each potential subject must fulfill all of the following criteria to be eligible for inclusion in the Expansion Part A of the trial:

1. Must be at least 18 years of age.
2. Must sign an ICF prior to any Screening procedures. Where required by local or country specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (DNA and RNA).
3. ECOG PS score 0, 1, or 2 for MM and AML; ECOG PS 0 or 1 for DLBCL.
4. Must have fresh bone marrow samples collected at Screening.
5. Criterion modified per Amendment 2.

   5.1 Has acceptable laboratory test results during the Screening period, as follows:

Parameter		**Result**
a.	Creatinine clearance (Clcr) or serum creatinine	Clcr ≥50 mL/min estimated by Cockcroft-Gault (see Appendix 10.5) or serum creatinine ≤1.5 × upper limit of normal (ULN)
b.	Serum alanine aminotransferase (ALT)	≤2.5 × ULN
c.	Serum aspartate aminotransferase (AST)	≤2.5 × ULN
d.	Total bilirubin	≤2 × ULN *Note: A subject with Gilbert's syndrome may be included if total bilirubin is ≤3×ULN and direct bilirubin is ≤1.5 × ULN*
e.	Hemoglobin	≥8 g/dL (≥80 g/L or ≥5 mmol/L) *Note: Red blood cell transfusion may be administered during Screening to meet this requirement*
f.	Absolute neutrophil count	>1.0 × 10^9/L (>1,000/μL) *Note: G-CSF may be administered during Screening to meet this requirement*
g.	Platelet count	>50 × 10^9/L (>50,000/μL) *Note: Platelet transfusion may be administered during Screening to meet this requirement*
h.	Coagulation Status: Prothrombin time (PT), International normalized ratio (INR), activated partial thromboplastin time (aPTT)	PT/INR/aPTT ≤1.5 × ULN

6. A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3014 administration. Adequate contraception is defined as highly effective methods of contraception (refer to Appendix 10.4 for more information). In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.

7. A woman of childbearing potential must have a negative serum β-hCG at Screening.
8. 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 GEN3014.
9. 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 GEN3014.

Specific Inclusion Criteria for RRMM:

10. Criterion modified per Amendment 1.

    10.1 Must have documented multiple myeloma as defined by the criteria below and have evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:

    - Prior documentation of monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven plasmacytoma.

    and

    - Measurable disease at baseline as defined by any of the following:
        - IgG, IgA, IgD, or IgM myeloma: Serum M-protein level ≥0.5 g/dL (≥5 g/L) or urine M-protein level ≥200 mg/24 hours;

        or

        - Light chain myeloma: Serum Ig free light chain (FLC) ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.

    Note: Subjects with RRMM must have exhausted standard therapies, at the investigator's discretion.

11. Criterion modified per Amendment 3.

    11.1 For anti-CD38 mAb-naive RRMM Cohort: Subject received at least 3 prior lines of therapy including a PI and an IMiD in any order, or who is double refractory to a PI and an IMiD; or subject received at least 2 prior lines of therapy if 1 of those lines included a combination of PI and IMiD. Note: Subjects should not have received any anti-CD38 antibody (eg, daratumumab, isatuximab).

12. Criterion modified per Amendment 2.

    12.1 Criterion modified per Amendment 3.

    12.2 For anti-CD38 mAb-refractory RRMM Cohort: Prior to trial entry, subject received daratumumab or a daratumumab-containing regimen or an isatuximab-containing regimen and had evidence of progressive disease (PD) during the treatment or within 90 days of treatment cessation.

13. Criterion modified per Amendment 2.

    13.1 Criterion modified per Amendment 3.

13.2 Potassium level ≥3.0 mEq/L (≥3.0 mmol/L); and corrected serum calcium ≤14.0 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (see formula for corrected serum calcium in Appendix 10.7).

Specific Inclusion Criteria for R/R DLBCL:

14. Criterion modified per Amendment 1.

14.1 Relapsed or refractory DLBCL, both de novo or histologically transformed. Note: Relapsed disease is defined as the reappearance or growth of lymphoma after at least 6 months duration of response (DOR). Refractory disease is defined as failure to achieve response after at least 2 cycles of therapy or reappearance after a DOR of <6 months. Subjects with R/R DLBCL must have exhausted standard therapies, at the investigator's discretion.

15. Received at least 2 prior lines of systemic therapy, with 1 being a CD20-containing chemoimmunotherapy.

16. Have at least 1 measurable site of disease:

- A fluorodeoxyglucose (FDG)-positron emission tomography (PET) computed tomography (CT) scan demonstrating positive lesion compatible with CT (or magnetic resonance imaging [MRI])-defined anatomical tumor sites.

and

- A CT scan (or 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.

17. Must have available archival or fresh tumor tissue or both to submit to a central laboratory for CD38 assay.

Specific Inclusion Criteria for R/R AML:

18. Criterion modified per Amendment 1.

18.1 Relapsed or refractory AML, both de novo or secondary; must have failed all conventional therapy. Acute promyelocytic leukemia (APL) is excluded from this trial. Note: Relapse is defined by BM blasts ≥5% in patients who have been in complete remission (CR) previously, or reappearance of blasts in the blood, or development of extramedullary AML. Refractory is defined as not being able to achieve a CR after the initial therapy.

19. Subject with relapsed AML who received at least 2 prior therapies for AML with the exception of hydroxyurea.

20. Subject with refractory AML who received at least 1 prior line of therapy for AML with the exception of hydroxyurea.

21. Subject's life expectancy at Screening is judged to be at least 3 months.

5.1.3 Inclusion Criteria – Expansion Part B (Randomized H2H)

Each potential subject must fulfill all of the following criteria to be eligible for inclusion in the Expansion Part B of the trial:

1. Must be at least 18 years of age.
2. Must sign an ICF prior to any Screening procedures. Where required by local or country specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (DNA and RNA).
3. ECOG PS score 0, 1, or 2.
4. Must have fresh bone marrow samples collected at Screening.
5. Has acceptable laboratory test results during the Screening period, as follows:

Parameter		**Result**
a.	Creatinine clearance (Clcr) or serum creatinine	Clcr ≥20 mL/min (Cockcroft-Gault formula [see Appendix 10.5] or EGFR [MDRD] or CKD-epi)
b.	Serum alanine aminotransferase (ALT)	≤2.5 × ULN
c.	Serum aspartate aminotransferase (AST)	≤2.5 × ULN
d.	Total bilirubin	≤2 × ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 × ULN)
e.	Hemoglobin	≥7.5 g/dL (≥4.65 mmol/L) *Note: Red blood cell transfusions are not permitted within 7 days before the laboratory test for eligibility review; recombinant human erythropoietin use is permitted*
f.	Absolute neutrophil count	>1.0 × 10^9/L (>1,000/μL) *Note: (Granulocyte colony stimulating factor [G-CSF] use is permitted)*
g.	Platelet count	>50 × 10^9/L (>50,000/μL) if bone marrow is >50% involved in myeloma. Otherwise ≥75 × 10^9/L *Note: Platelet transfusions are not permitted within 7 days before the laboratory test for eligibility review*
h.	Coagulation Status: Prothrombin time (PT), International normalized ratio (INR), activated partial thromboplastin time (aPTT)	PT/INR/aPTT ≤1.5 × ULN

6. A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3014 or daratumumab SC administration. Adequate contraception is defined as highly effective methods of contraception (refer to Appendix 10.4 for more information). In countries where 2 highly effective methods of contraception are required, both methods will be required for inclusion.
7. A woman of childbearing potential must have a negative serum β-hCG at Screening and within 72 hours of the first dose of study treatment prior to dosing.
8. 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 GEN3014 or daratumumab SC.

9. 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 GEN3014 or daratumumab SC.
10. Must have documented multiple myeloma as defined by the criteria below and have evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:
    - Prior documentation of monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven plasmacytoma.

      and

    - Measurable disease at baseline as defined by any of the following:
      - IgG, IgA, IgD, or IgM myeloma: Serum M-protein level ≥0.5 g/dL (≥5 g/L) or urine M-protein level ≥200 mg/24 hours;

      or

      - Light chain myeloma: Serum Ig free light chain (FLC) ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.
11. Subject received at least 3 prior lines of therapy including a PI and an IMiD in any order, or who is double refractory to a PI and an IMiD; or subject received at least 2 prior lines of therapy if 1 of those lines included a combination of PI and IMiD. Note: Subjects should not have received any anti-CD38 antibody (eg, daratumumab, isatuximab).
12. Potassium level ≥3.0 mEq/L (≥3.0 mmol/L); and corrected serum calcium ≤14.0 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (see formula for corrected serum calcium in Appendix 10.7).

5.2 Exclusion Criteria

5.2.1 Exclusion Criteria – Dose Escalation and Expansion Part A (GEN3014 Single Cohorts)

Any potential subject who meets any of the following criteria will be excluded from being treated in the Dose Escalation and/or Expansion Part A (GEN3014 Single Cohorts) of the trial.

1. Criterion modified per Amendment 3.

   1.1 Prior treatment with any CD38-directed therapies (eg, daratumumab, isatuximab, CD38 CAR-T, bispecific Ab) in anti-CD38 mAb-naive RRMM Cohort. Note: Prior daratumumab or isatuximab exposure is allowed for anti-CD38 mAb-treated RRMM subjects in the Dose Escalation and anti-CD38 mAb-refractory RRMM Cohort in the Expansion Part A.
2. Treatment with an anti-cancer agent (eg, small molecule, antibody, CAR-T cell therapy), chemotherapy, radiation therapy, or major surgery within 2 weeks prior to the first dose of GEN3014.

   2CZ. Czech Republic: See Appendix 10.15 for requirements as per local health authorities.

3. Treatment with an investigational drug within 4 weeks or 5 half-lives, whichever is shorter, prior to the first dose of GEN3014.
4. Cumulative dose of corticosteroids more than the equivalent of ≥140 mg of prednisone within 2-week period before the first dose of GEN3014.
5. Criterion modified per Amendment 3

   5.1 Has clinically significant cardiac disease, including:

   - Myocardial infarction within 1 year prior to the first dose of GEN3014, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV [see Appendix 10.6]) uncontrolled cardiac arrhythmia (CTCAE v5.0 grade 2 or higher) or clinically significant electrocardiogram (ECG) abnormalities.
   - Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >480 msec.
6. Toxicities from previous anti-cancer therapies have not resolved to baseline levels or to Grade 1 or less except for alopecia and peripheral neuropathy.
7. Primary central nervous system (CNS) tumor or known CNS involvement at Screening.
8. Criterion modified per Amendment 3

   - 8.1 Has known history/positive serology for hepatitis B (unless immune due to vaccination or unless passive immunization due to Ig 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).
9. Known medical history or ongoing hepatitis C infection that has not been cured.
10. Known history of seropositivity of human immunodeficiency virus (HIV).
11. Currently receiving any other investigational agents.
12. 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 GEN3014.
13. A man who plans to father a child while enrolled in this trial or within 12 months after the last dose of GEN3014.

Specific Exclusion Criteria for RRMM:

14. Prior allogeneic HSCT.
15. Autologous HSCT within 3 months of the first dose of GEN3014.

Specific Exclusion Criteria for R/R AML:

16. <5% blasts in blood or bone marrow at Screening.
17. Prior autologous HSCT.
18. Allogenic HSCT within 3 months of the first dose of GEN3014.
19. Criterion modified per Amendment 1.

19.1 Active graft-versus-host-disease requiring immunosuppressive treatment. Any immunosuppressive medication (eg, calcineurin inhibitors) must be stopped ≥4 weeks prior to the first dose of GEN3014.

Additional Exclusion Criteria for All Subjects:

20. Criterion modified per Amendment 2.

20.1 Criterion modified per Amendment 1_DK-1.

20.2 Criterion modified per Protocol Amendment ES-1.

20.3 Criterion modified per Protocol Amendment FR-1.

20.4 History of allergic reactions attributed to compounds of similar active substance or excipients.

21. Criterion added per Amendment 2.

21.1 Criterion modified per Amendment 3

21.2 Has known past (within 3 years) 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. Any curable cancer with a CR of >2 years duration.

22. Prior treatment with live, attenuated vaccines within 28 days prior to initiation of trial drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Experimental and/or non authorized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations are not allowed.

23. Any concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the trial procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this trial.

Additional Exclusion Criterion for RRMM:

24. Known allergies, hypersensitivity, or intolerance to mAbs, human proteins, hyaluronidase, or excipients (refer to GEN3014 IB and daratumumab IB).

5.2.2 Exclusion Criteria – Expansion Part B (Randomized H2H)

Any potential subject who meets any of the following criteria will be excluded from being treated in the Expansion Part B (Randomized H2H) of the trial.

1. Prior or concurrent treatment with any CD38-directed therapies (eg, daratumumab, isatuximab, CD38 CAR-T, bispecific Ab) for RRMM.
2. Treatment with an anti-cancer agent (eg, small molecule, antibody, CAR-T cell therapy), chemotherapy, radiation therapy, or major surgery within 2 weeks prior to randomization.