Safety and Efficacy of GEN3009 (DuoHexaBody®-CD37) in Relapsed or Refractory B-cell Non-Hodgkin Lymphoma - A First-in-Human, Open-label, Phase I/IIa Dose Escalation Trial with Dose Expansion Cohorts

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Dose Escalation (GEN3009 for R/R B-cell NHL Including CLL/SLL):- Determine the MTD with and/or determine the RP2D of GEN3009- Evaluate safety and tolerability of GEN3009Expansion (GEN3009 for R/R, DLBCL, FL, and CLL Cohorts):-Evaluate (preliminary)...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON56143

Source
ToetsingOnline

Brief title
GCT3009-01

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
B-cell Non-Hodgkin Lymphoma, B-cell Non-Hodgkin Lymphoma cancer

Research involving

Human

Sponsors and support

Primary sponsor: Genmab
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Gen3009, Open-label, Phase 1/11a, Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma

Outcome measures

Primary outcome

Dose Escalation (GEN3009 for R/R B-cell NHL Including CLL/SLL):

• Rate of DLTs

• Frequency and severity of adverse events (AEs)/AESIs/SAEs

• Changes in laboratory parameters

• Changes in vital signs

• Frequency of dose interruptions, dose delays, and dose intensity

Expansion(GEN3009 for R/R, DLBCL, FL, and CLL Cohorts):

• ORR

Expansion (GEN3009 + GEN3013 Safety Run-in for R/R B-NHL):

• Rate of DLTs

• Frequency and severity of AEs/AESIs/SAEs

• Changes in laboratory parameters

• Changes in vital signs

• Frequency of dose interruptions, dose delays, and dose intensity

Expansion (GEN3009 + GEN3013 for R/R DLBCL):

• CR rate

Secondary outcome

Dose Escalation (GEN3009 for R/R B-cell NHL Including CLL/SLL):

• PK parameters: clearance, volume of distribution and area under the curve (AUC) at different time points (AUC7days, AUClast and AUCinf), maximum concentration (Cmax), time to Cmax (Tmax), predose trough concentrations (Ctrough), and half-life (T1/2)

• Incidence of neutralizing anti-GEN3009 antibodies (ie, ADAs)

• Objective response rate (ORR)

• Complete response rate (CR)

• Duration of response (DoR)

• Time to response (TTR)

• Progression-free survival (PFS)

• Overall survival (OS)

Expansion (GEN3009 for R/R, DLBCL, FL, and CLL Cohorts):

• PK parameters: CL, AUC7days, AUClast, Cmax, Tmax, Ctrough, and T1/2

• Frequency and severity of AEs/AESIs/SAEs

• Changes in laboratory parameters

• Changes in vital signs

• Frequency of dose interruptions, dose delays, and dose intensity

• CR rate

• DoR

• TTR

• PFS

• OS

• Incidence of neutralizing anti-GEN3009 antibodies (ie, ADAs)

Expansion (GEN3009 + GEN3013 Safety Run-in for R/R B-NHL):

• PK parameters: CL, AUC7days, AUClast, Cmax, Tmax, Ctrough, and T1/2

• Incidence of neutralizing ADAs to GEN3009

• Incidence of neutralizing ADAs to GEN3013

• CR rate

• ORR

• DoR

• TTR

• PFS

• OS

Expansion (GEN3009 + GEN3013 for R/R DLBCL):

• ORR

• DOR

• TTR

• PFS

• OS

• Rate and duration of MRD negativity

• Frequency and severity of AEs/AESIs/SAEs

• Changes in laboratory parameters

• Changes in vital signs

• Frequency of dose interruptions, dose delays, and dose intensity

• PK parameters: CL, AUC7days, AUClast, Cmax, Tmax, Ctrough, and T1/2

• Incidence of neutralizing ADAs to GEN3009

• Incidence of neutralizing ADAs to GEN3013

Study description

Background summary

GEN3009 (DuoHexaBody®-CD37) is a bispecific antibody with a hexamerization-enhancing mutation that targets 2 different epitopes of the CD37 antigen. GEN3009 was designed to induce highly potent cytotoxicity towards B cells in a variety of B-cell malignancies through enhanced complement-dependent cytotoxicity (CDC) and by Fc*R-mediated effector functions including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cell-mediated phagocytosis (ADCP).
The bispecific antibody is generated using the DuoBody® technology, resulting in an asymmetric bispecific antibody with a regular IgG1 structure containing 2 different CD37-binding arms. Introduction of an E430G mutation results in enhanced Fc-Fc-mediated antibody hexamerization on the cell surface (HexaBody® technology) upon CD37 binding, while retaining monomeric properties in solution. Moreover, GEN3009 has CMC properties comparable to regular human IgG1 and the HexaBody mutation was shown to have no meaningful impact on nonclinical pharmacokinetic (PK) behavior in absence of target.

GEN3013 is a bispecific antibody recognizing the T-cell antigen CD3 and the B-cell antigen CD20. GEN3013 triggers potent T-cell-mediated killing of CD20-expressing cells.

Study objective

Dose Escalation (GEN3009 for R/R B-cell NHL Including CLL/SLL):
- Determine the MTD with and/or determine the RP2D of GEN3009
- Evaluate safety and tolerability of GEN3009

Expansion (GEN3009 for R/R, DLBCL, FL, and CLL Cohorts):
-Evaluate (preliminary) anti-tumor efficacy of GEN3009

Expansion (GEN3009 + GEN3013 Safety Run-in for R/R B-NHL):
-Identify the RP2D of GEN3009 + GEN3013 combination
-Evaluate safety and tolerability of GEN3009 + GEN3013 combination

Expansion (GEN3009 + GEN3013 for R/R DLBCL):
-Assess preliminary anti-tumor activity of GEN3009 + GEN3013 combination

Study design

This trial is a FIH, open-label, multicenter trial to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity, and preliminary efficacy of GEN3009 and GEN3013 in R/R B-cell NHL.

Intervention

GEN3009 will be administered intravenously in 4-weeks cycles (ie, 28 days), with a schedule of weekly dosing in Cycles 1 through 3, every second week in Cycles 4 through 9, and every 4 weeks in Cycle 10 until disease progression, unacceptable toxicity, death or end of trial. A starting dose of 20 mg is proposed for this FIH clinical trial of GEN3009. Six dose levels will be tested. Additional/intermediate dose levels may also be explored based upon emerging data.
In the Expansion, the RP2D determined by the Dose Escalation will be investigated.

GEN3013 will be administered during treatment cycle 1 once per week starting from day 8, cycles 2 to 3 once per week, cycles 4 to 12 once every 4 weeks, cycles 13 until end of trial GEN3013 once every 4 weeks.

Study burden and risks

GCT3009-01 is a FIH trial of GEN3009. No clinical data on DuoHexaBody CD37 exists and the safety profile for GEN3009 is yet to be established. The trial population is limited to subjects with relapsed or refractory B-cell NHL who have exhausted standard therapies or are ineligible for standard therapies. The risk to subjects in this trial should be minimized by compliance with the eligibility criteria, trial procedures, close monitoring, and proper/prompt management of treatment-emergent adverse events (TEAEs). Most common risks:
• Infusion-related reactions (that are most frequent) such as fever and/or shaking chills, flushing and/or itching, changes in heart rate and blood pressure, dyspnea (shortness of breath) or chest discomfort, back or abdominal pain, nausea, vomiting, and/or diarrhea, and skin rashes. Therefore, premedication with corticosteroids, antihistamines and antipyretics is mandatory 30 120 minutes prior to the first 4 administrations of GEN3009. These medications will help prevent or reduce the severity of potential side effects

of GEN3009. Patients will be observed for at least 4 hours after each of the first 4 administrations of GEN3009.
• Clinical tumor lysis syndrome during treatment- the release of toxic substances in the blood upon destruction of a large number of cancerous cells by the study drug. The toxic substances can damage the kidneys, the heart and nervous system.
• Radiation risks PET, CT and MRI scans.
• Discomforts after tests: pain/bruising after bone marrow biopsy, blood draw.
In summary, this trial explores GEN3009 in subjects with R/R B-cell NHL who have limited treatment options. Based on nonclinical data of GEN3009 and clinical data from other CD37-targeting compounds, GEN3009 has the potential to address the highly unmet medical need in this patient population. With safety precautions and close monitoring plan in place, the described risks are outweighed by the potential benefit subjects might receive from GEN3009.

Treatment with epcoritamab involves subcutaneous injection (the first 4 visits followed by hospitalization and premedication). Risks associated with participation are side effects, among which tumor lysis syndrome, cytokine release syndrome and neurological symptoms (ICANS). The risk to subjects in this trial should be minimized by compliance with the eligibility criteria, trial procedures, close monitoring, and proper/prompt management of TEAEs.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Each potential subject must fulfill all of the following criteria to be enrolled in the trial.
- Be at least 18 years of age.
- Must sign an informed consent form (ICF) prior to any screening procedures.
- Has histologically or cytologically confirmed relapsed or refractory Bcell NHL
o For the dose escalation: with no available standard therapy or is not a candidate for available standard therapy. All subjects must have received at least 2 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 1 of the 2 prior lines of treatment must have been a CD20-containing systemic 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 1 prior line of BTK inhibitor or BCL-2 inhibitor.
o For the expansion (including Safety Run-in): All subjects must have received at least 2 prior lines of systemic therapy, and,
a. For FL and DLBCL, at least 1 of the 2 prior lines of treatment must have been a CD20-containing systemic regimen;
b. For CLL, subjects must have received at least one prior line of BTK inhibitor or BCL-2 inhibitor.
- Has 1 of the following B-cell NHL subtypes for the Dose Escalation:
o DLBCL, de novo or histologically transformed
o HGBCL
o PMBCL
o FL, with advanced symptomatic disease and with a need for treatment
o MCL, without leukemic manifestation
o MZL, either nodal, extranodal, or mucosa associated, with a need for treatment initiation based on symptoms and/or disease burden
o SLL, with a need for treatment based on symptoms and/or disease burden
o CLL with active disease that needs treatment based on the International Workshop on Chronic Lymphocytic Leukemia [iwCLL] criteria) and the following

B-cell NHL subtypes for the Expansion (including safety run-in):
o DLBCL, de novo or histologically transformed
o FL Grade 1, 2 and 3a, with advanced symptomatic disease and with a need for treatment initiation
o CLL, must have active disease that needs treatment with at least 1 of the following criteria being met:
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
o GEN3009 + GEN3013 combination cohort only: Documented CD20+DLBCL or FL based on representative pathology report
- Has measurable disease for B-cell NHL or for CLL.
- Has ECOG performance status of 0 or 1.
- Has acceptable laboratory parameters.
- A woman of reproductive potential must agree to use adequate contraception during the trial and for 12 months after the last GEN3009 and/or GEN3013 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.
- A woman of childbearing potential must have a negative serum betahCG at screening.
- 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 and all men must also not donate sperm during the trial and for 12 months after receiving the last dose of GEN3009 and/or GEN3013.

Exclusion criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the trial.
- Prior treatment with a CD37-targeting agent.
- For the Expansion (including safety run-in): GEN3009 + GEN3013 combination cohort only: Prior treatment with a CD3 × CD20 bispecific antibody.
- Prior allogeneic HSCT.
- Autologous HSCT within 3 months before the first dose of GEN3009.
- For the Expansion (including safety run-in): Lymphomas leukemia phase: high absolute lymphocyte count or the presence of abnormal cells in the peripheral blood indicating circulating lymphoma cells
- 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. Treatment with small molecules such as BTK inhibitors, BCL2 inhibitors, or PI3K inhibitors within 5 half-lives prior to the first dose of GEN3009.
- Chemotherapy or radiation therapy within 2 weeks of the first dose of GEN3009.
- 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, and at any time during the study treatment period.
- 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.
- Has uncontrolled intercurrent illness (refer to Protocol Section 5.2 for details).
- For the Expansion (including safety run-in): GEN3009 + GEN3013 combination cohort only: Seizure disorder requiring therapy (such as steroids or anti-epileptics)
- Toxicities from previous anti-cancer therapies have not resolved to baseline levels or to Grade 1 or less except for alopecia and peripheral neuropathy.
- Primary central nervous system (CNS) lymphoma or known CNS involvement at screening.
- Has known past or current malignancy other than inclusion diagnosis (refer to Section 5.2 for details).
- Had allergic reactions to anti-CD20 or anti-CD37 monoclonal antibody treatment or intolerant to GEN3009 excipients (refer to the GEN3009 IB for more information).
- For the Expansion (including safety run-in): Intolerant to GEN3013 excipients (refer to the GEN3013 IB for more information).
- Has had major surgery, (eg, requiring general anesthesia) within 4 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 and/or GEN3013).
- Has known history/positive serology for hepatitis B.
- Known medical history or ongoing hepatitis C infection that has not been cured.
- Known history of seropositivity for HIV infection.
- 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 and/or GEN3013.
- Is a man who plans to father a child while enrolled in this trial or within 12 months after the last dose of GEN3009 and/or GEN3013.
- 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. Additionally, vulnerable subjects or subjects under guardianship, curatorship, judicial protection or deprived of liberty), are excluded from participation in this trial.
- Prior treatment with live, attenuated vaccines within 4 weeks prior to initiation of GEN3009. 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 nonauthorized SARS-CoV-2 vaccinations are not allowed.
- Dose escalation only: Lymphomas leukemia phase: high absolute lymphocyte count or the presence of abnormal cells in the peripheral blood indicating circulating lymphoma cells.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-01-2021
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DuoBody®-CD3 x CD20
Generic name:	Epcoritamab
Product type:	Medicine
Brand name:	DuoHexaBody®-CD37
Generic name:	NA

Ethics review

Approved WMO

Date:	04-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-002752-16-NL

Register	ID
CCMO	NL72025.056.20