SYNOPSIS

Sponsor	Genmab US, Inc.
Investigational Product	Epcoritamab (GEN3013); DuoBody®-CD3xCD20
Trial Registration ID Number: NCT04542824	**IND Number:** 135659 **Japic CTI No.:** JapicCTI-205408

Title of Trial
Safety and Preliminary Efficacy of Epcoritamab (GEN3013; DuoBody®-CD3xCD20) in Japanese Subjects With Relapsed or Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL) – A Phase 1/2, Open-Label, Dose-Escalation Trial With Expansion Cohorts

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Trial Sites
Dose Escalation Part: 6 sites in Japan
Diffuse large B-cell lymphoma (DLBCL) Cohort, Monotherapy Expansion Part: 15 sites in Japan

Publications
No publications were available at the time of finalization of this clinical study report (CSR).

Trial Period	**Development Phase**
Initiation date (Dose Escalation Part): 20 Aug 2020 Initiation date (Monotherapy Expansion Part): 06 Jan 2021 Completion date: Trial is ongoing	Phase 1/2

Data Cutoff Dates
Pharmacokinetics (PK) and anti-drug antibody (ADA) data: 27 Feb 2023
Other data: 21 Apr 2023

Objectives and Endpoints

Dose Escalation Part

Primary Objective

- Determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D)

Secondary Objectives

- Establish tolerability of epcoritamab
- Establish PK profile after single and multiple doses
- Evaluate immunogenicity
- Evaluate preliminary anti-lymphoma efficacy as determined by Lugano criteria
- Evaluate preliminary anti-lymphoma efficacy as determined by LYmphoma Response to Immunomodulatory therapy Criteria (LYRIC)
- Evaluate preliminary anti-lymphoma efficacy

Exploratory Objectives

- Evaluate biomarkers predictive of clinical response to epcoritamab
- Evaluate the effect of anti-cytokine therapy on cytokine release syndrome (CRS)

Primary Endpoints

- Dose-limiting toxicities (DLTs)
- Adverse events (AEs)

Secondary Endpoints

- Cytokine measures
- Laboratory parameters (biochemistry, hematology)
- PK parameters (clearance, volume of distribution, area under the concentration-time curve from time zero to the last measurable concentration [$AUC_{0\text{-last}}$] and from time zero extrapolated to infinity [$AUC_{0\text{-}\infty}$], maximum concentration [C_{max}], time of C_{max} [t_{max}], predose concentrations, and elimination half-life [$t_{½}$])

- Incidence of ADAs to epcoritamab
- Overall response rate (ORR) as determined by Lugano criteria as assessed by investigator
- Complete response (CR) rate as determined by Lugano criteria as assessed by investigator
- Duration of response (DOR) as determined by Lugano criteria as assessed by investigator
- Progression-free survival (PFS) as determined by Lugano criteria as assessed by investigator
- ORR as determined by LYRIC as assessed by investigator
- CR rate as determined by LYRIC as assessed by investigator
- DOR as determined by LYRIC as assessed by investigator
- PFS as determined by LYRIC as assessed by investigator
- Time to next anti-lymphoma therapy (TTNT)
- Overall survival (OS)

Exploratory Endpoints
- Expression of CD3, CD20, and other molecular markers in tumor biopsies pre-treatment
- Evaluation of the overall impact (efficacy and safety) of anti-cytokine therapies on CRS

Monotherapy Expansion Part

Primary Objective
- Evaluate anti-lymphoma efficacy as determined by Lugano criteria

Secondary Objectives
- Further evaluate anti-lymphoma efficacy as determined by Lugano criteria
- Further evaluate anti-lymphoma efficacy as determined by LYRIC
- Further evaluate anti-lymphoma efficacy
- Evaluate safety and tolerability of epcoritamab
- Evaluate PK and immunogenicity of epcoritamab
- Further assess the preliminary antitumor activity of epcoritamab

Exploratory Objectives
- Evaluate biomarkers predictive of clinical response to epcoritamab
- Evaluate the effect of anti-cytokine therapy on CRS

Primary Endpoint
- ORR as determined by Lugano criteria as assessed by Independent Review Committee (IRC)

Secondary Endpoints
- CR rate as determined by Lugano criteria as assessed by IRC
- DOR as determined by Lugano criteria as assessed by IRC
- PFS as determined by Lugano criteria as assessed by IRC
- Duration of complete response (DOCR) determined by Lugano criteria, as assessed by IRC
- Time to complete response (TTCR) determined by Lugano criteria, as assessed by IRC
- Time to response (TTR) determined by Lugano criteria, as assessed by IRC
- ORR as determined by LYRIC, as assessed by IRC
- CR rate as determined by LYRIC, as assessed by IRC
- DOR as determined by LYRIC, as assessed by IRC
- PFS as determined by LYRIC, as assessed by IRC
- DOCR determined by LYRIC, as assessed by IRC
- TTCR determined by LYRIC, as assessed by IRC
- TTR determined by LYRIC, as assessed by IRC
- TTNT
- OS
- Safety (ie, AEs, laboratory parameters, and cytokine measures)
- PK parameters (clearance, volume of distribution, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, predose concentrations, and $t_{½}$), and incidence of ADAs to epcoritamab
- Rate and duration of minimal residual disease (MRD) negativity

Exploratory Endpoints

- Expression of CD3, CD20, and other molecular markers in tumor biopsies pre-treatment
- Evaluation of the overall impact (efficacy and safety) of anti-cytokine therapies on CRS

Methodology

This is an open-label, single-country, interventional, multicohort, phase 1/2 trial in Japanese subjects with R/R B-NHL. The trial includes 2 parts: a Dose Escalation Part and an Expansion Part comprising a Monotherapy Part and a Combination Therapy Part.

Epcoritamab was administered by subcutaneous (SC) injection in treatment cycles of 28 days. The epcoritamab dosing regimen in the trial included an initial priming dose of 0.16 mg on Cycle 1 Day 1 (C1D1), an intermediate dose of 0.8 mg on Cycle 1 Day 8 (C1D8), and a full dose of epcoritamab on Cycle 1 Day 15 (C1D15), Cycle 1 Day 22 (C1D22), and thereafter, administered according to the following schedule:

- Cycles 1 to 3: Days 1, 8, 15, and 22 (once weekly [QW])
- Cycles 4 to 9: Days 1 and 15 (once every 2 weeks [Q2W])
- Cycles 10 and beyond until unacceptable toxicity, progressive disease, or end of trial: Day 1 (once every 4 weeks [Q4W])

The step-up dosing method was used to mitigate the incidence and severity of CRS. CRS prophylaxis with corticosteroids and premedication with antihistamines and antipyretics was mandatory during Cycle 1 in both parts of the trial.

The Dose Escalation Part of the trial was performed using a modified 3+3 design to determine the MTD and full dose level of epcoritamab in Japanese subjects for the RP2D regimen. Full doses of 24 mg and 48 mg epcoritamab were evaluated and were administered on C1D15, C1D22, and thereafter. None of the subjects experienced DLTs, and an MTD was not reached. Selection of 48 mg as the full dose level of epcoritamab for the RP2D regimen was based on PK/pharmacodynamic modeling and supported by all available data (PK, pharmacodynamics, safety, and efficacy) from the Dose Escalation Part of GCT3013-04 and from GCT3013-01.

The Monotherapy Expansion Part of the trial was conducted in 2 cohorts of subjects with R/R DLBCL or grade 1-3A follicular lymphoma (FL) to further examine the efficacy, PK, and safety of the RP2D regimen (0.16 mg priming dose, 0.8 mg intermediate dose, and 48 mg full dose).

Adverse events of special interest (AESIs) for this trial included CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), and clinical tumor lysis syndrome (CTLS), all of which may be considered on-target toxicities. In addition, other safety topics of interest were defined.

Primary analysis of results from the Dose Escalation Part and the DLBCL cohort of the Monotherapy Expansion Part (hereafter referred to as the DLBCL expansion cohort) of the trial were previously reported in a CSR using a clinical data cutoff of 31 Jan 2022. This report presents updated analysis results from the Dose Escalation Part and the DLBCL expansion cohort using a clinical data cutoff of 21 Apr 2023. Results from the FL expansion cohort are presented in a separate CSR. Results from the combination therapy cohorts in the Expansion Part of this trial will be reported separately at a future date.

Number of Subjects Planned and Analyzed

A sample size of up to 18 DLT-evaluable subjects was planned for the Dose Escalation Part of the trial. A total of 9 subjects were treated with epcoritamab full doses of 24 mg (n=3) or 48 mg (n=6).

A sample size of 35 subjects was planned for the DLBCL expansion cohort. A total of 36 subjects received the epcoritamab regimen of 0.16 mg priming dose, 0.8 mg intermediate dose, and 48 mg full dose.

Diagnosis and Main Criteria for Inclusion

Subjects enrolled in both the Dose Escalation and Monotherapy Expansion Parts of the trial were ≥20 years old, of Asian race and Japanese ethnicity, had documented evidence of CD20-positive mature B-cell neoplasm according to World Health Organization (WHO) classification 2016 (Swerdlow et al., 2016) or WHO classification 2008 based on a representative pathology report, and were previously treated with ≥2 lines of systemic antineoplastic therapy including ≥1 anti-CD20 monoclonal antibody-containing therapy. Subjects had measurable disease with involvement of ≥2 clearly demarcated lesions/nodes with a 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 short axis ≥1.0 cm, based on computed tomography or magnetic resonance imaging. Subjects were required to meet a predefined per-protocol washout period from prior antineoplastic agent(s) and have a life expectancy >3 months on standard of care treatment. Subjects with DLBCL who also failed prior high-dose therapy (HDT) autologous stem cell transplant (ASCT) or were ineligible for

HDT-ASCT due to age, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, and/or insufficient response to prior treatment were also eligible.

In the Dose Escalation Part of the trial, subjects had been diagnosed with 1 of the following: DLBCL (de novo or histologically transformed), high grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma, FL, marginal zone lymphoma (nodal, extranodal of mucosa-associated lymphoid tissue, or splenic), or small lymphocytic lymphoma.

In the Monotherapy Expansion Part of the trial, subjects had been diagnosed with 1 of the following: DLBCL, not otherwise specified (according to the WHO 2016 classification) including histologically transformed from indolent lymphomas except chronic lymphocytic leukemia and Waldenstrom macroglobulinemia; or double-hit or triple-hit DLBCL.

Subjects were excluded from participating in both parts of the trial if they had primary central nervous system (CNS) lymphoma or known CNS involvement, past or current malignancy (other than noted in the protocol), aspartate transaminase and/or alanine transaminase >3× the upper limit of normal (ULN), total bilirubin >1.5× ULN, creatinine clearance <45 mL/min/1.73 m^2, clinically significant cardiac disease, acute infections, chronic ongoing infectious diseases requiring treatment, diseases or treatments resulting in immunosuppression, seizure disorders requiring therapy, or a history of confirmed progressive multifocal leukoencephalopathy. Subjects were also excluded if they had prior ASCT within 100 days before first epcoritamab administration, any prior allogeneic stem cell transplantation or solid organ transplantation, or prior therapy with an investigational bispecific antibody targeting CD3 and CD20. In the Monotherapy Expansion Part only, subjects with a positive test result for human T-cell lymphotropic virus type 1 were also excluded.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Numbers

The epcoritamab drug product was provided as a concentrate for solution in 2 concentrations: 5 mg/mL and 60 mg/mL. Diluted doses were prepared using a diluent as applicable at the site pharmacy.

In both parts of the trial, a priming dose of 0.16 mg was administered on C1D1, followed by an intermediate dose of 0.8 mg on C1D8. In the Dose Escalation Part, a full dose of 24 mg or 48 mg epcoritamab was administered on C1D15, C1D22, and thereafter. In the Monotherapy Expansion Part, subjects received the 48 mg full dose level of epcoritamab on C1D15, C1D22, and thereafter, as determined by the Dose Escalation Part.

Epcoritamab was administered by SC injection.

The following batch numbers were released for use during the Dose Escalation Part and for the DLBCL expansion cohort:

- Epcoritamab 5 mg/mL: B3323, B3576, B3782, B4087
- Epcoritamab 60 mg/mL: B3324, B3409, B3441, B3705, B3718, B3719, B4043

Reference Therapy, Dose, and Mode of Administration, Batch Numbers

Not applicable.

Duration of Treatment

For each subject, the treatment period continued until disease progression unless the subject fulfilled 1 of the discontinuation criteria. The trial will run for a maximum of 3 years after the last subject's first dose.

Statistical Methods

No formal hypothesis testing was performed in either the Dose Escalation Part or the DLBCL Monotherapy Expansion Part of the trial. Analyses of trial participants and efficacy were performed using the full analysis set (FAS), defined as all subjects who had been exposed to ≥1 dose of epcoritamab. Analysis of safety was performed using the safety analysis set, which was identical to the FAS.

Sample Size

Up to 18 DLT-evaluable subjects were planned in the Dose Escalation Part of the trial to evaluate DLTs and determine the full dose level of epcoritamab for the RP2D dosing regimen. Sample size calculations for the Monotherapy Expansion Part were based on showing consistent results in Japanese subjects, as had been shown in prior studies of non-Japanese subjects.

The ORR for non-Japanese subjects was estimated at 45% for subjects with DLBCL, based on the GCT3013-01 trial. A response rate greater than 35% for Japanese subjects with DLBCL was considered indicative of both clinical relevance and consistency with earlier results. A sample size of 35 subjects was selected for the DLBCL expansion cohort. Therefore, at least 13/35 (37%) subjects would need to respond to treatment, to have the desired ORR of greater than 35%. The probability of observing at least 13 responders, under the assumption that the true ORR is 45%, is 87%.

Efficacy and Safety

In the Monotherapy Expansion Part, response to trial treatment and disease progression was centrally reviewed by an IRC, in addition to investigator evaluation, determined by Lugano criteria and LYRIC. Only investigator evaluation was used in the Dose Escalation Part.

Continuous data were summarized using descriptive statistics such as mean, standard deviation, median, and range. Categorical data were summarized using frequency count as well as 95% confidence interval (CI), if applicable. For time-to-event data, the Kaplan-Meier method was used for descriptive summaries. Sensitivity analyses were performed for the DLBCL expansion cohort using additional predefined analysis populations.

Changes from Originally Planned Analysis

Due to missing baseline tumor biopsies, subject consent preference, and/or unevaluable assay results, all exploratory MRD analyses were performed using the MRD-evaluable set, defined as all subjects in the FAS who had at least 1 on-treatment MRD sample. In addition, exploratory MRD analysis was performed using circulating tumor DNA (ctDNA) instead of peripheral blood mononuclear cell (PBMC) results due to inadequate sensitivity of the PBMC assay.

Neutralizing antibodies against epcoritamab were not evaluated due to the low incidence of ADA at the proposed dose. Flow cytometry assays were not performed due to logistical challenges.

RESULTS

Baseline Characteristics of Trial Population

Dose Escalation Part (N=9)

As of the data cutoff date of 21 Apr 2023, a total of 9 subjects were enrolled and received ≥1 dose of epcoritamab in the Dose Escalation Part. These 9 subjects included 7 subjects with DLBCL (all de novo) and 1 subject each with HGBCL or FL. Of the 9 treated subjects, 6 (66.7%) discontinued epcoritamab treatment as of the data cutoff date, all due to progressive disease. Five (55.6%) of the 9 subjects permanently discontinued the trial, all due to death, and of the 4 (44.4%) subjects remaining on trial as of the data cutoff date, 3 (33.3%) continued to receive epcoritamab treatment, and 1 (11.1%) remained in survival follow-up.

All subjects were of Asian race and Japanese ethnicity as required per protocol, and almost all subjects were male (88.9%). The median age was 64.0 years (range: 42, 74). Subjects had a baseline ECOG performance status of 0 (55.6%) or 1 (44.4%). Subjects with DLBCL (n=7) were required to be ineligible for ASCT; reasons for ineligibility included age (42.9%), prior transplant (14.3%), and other (42.9%; ie, primary refractory disease, resistant to chemotherapy, and bone marrow invasion).

The median number of prior lines of anti-lymphoma therapy was 3.0 (range: 2, 5), with 44.4% of subjects having received ≥4 prior lines of therapy. Four (44.4%) subjects had received prior radiotherapy, 2 (22.2%) subjects had received prior chimeric antigen receptor (CAR) T-cell therapy, and 1 subject received a prior ASCT. Six (66.7%) subjects had primary refractory disease, 8 (88.9%) subjects were refractory to ≥2 consecutive prior lines of anti-lymphoma therapy, and all subjects were refractory to their last line of antineoplastic therapy.

Monotherapy Expansion Part – DLBCL Cohort (N =36)

As of the data cutoff date of 21 Apr 2023, a total of 36 subjects were enrolled and received ≥1 dose of epcoritamab in the DLBCL expansion cohort. Of the 36 subjects, 83.3% had de novo disease and 16.7% had transformed disease (all with FL at initial diagnosis). Twenty-eight (77.8%) subjects discontinued epcoritamab treatment as of the data cutoff date, mainly due to progressive disease (23 [63.9%] subjects). A total of 8 (22.2%) subjects continued to receive epcoritamab treatment as of the data cutoff date.

All subjects were of Asian race and Japanese ethnicity as required per protocol, and 19 (52.8%) subjects were female. The median age was 68.5 years (range: 44, 89). Most subjects had a baseline ECOG performance status of 0 (58.3%) or 1 (36.1%). Subjects were required to be ineligible for ASCT; reasons for ineligibility included age (66.7%), ECOG performance status (2.8%), prior transplant (16.7%), and other (13.9%; ie, lymphoma in peripheral blood, refractory, resistant or refractory to chemotherapy, and not applicable).

The median number of prior lines of anti-lymphoma therapy was 3.0 (range: 2, 8), with 30.6% having received ≥4 prior lines of therapy. Overall, 38.9% of subjects had received prior radiotherapy, 19.4% had a prior ASCT, and none had received prior CAR T-cell therapy. More than half of the subjects had primary refractory disease (55.6%), and a similar proportion were refractory to ≥2 consecutive prior lines of anti-lymphoma therapy (58.3%). Most subjects (80.6%) were refractory to their last line of antineoplastic therapy.

Efficacy Results

Dose Escalation Part (N=9)

Selection of 48 mg as the full dose level of epcoritamab for the RP2D regimen was based on PK/pharmacodynamic modeling and supported by all available data (PK, pharmacodynamics, safety, and efficacy) from the Dose Escalation Part of GCT3013-04 and from GCT3013-01.

The RP2D regimen of epcoritamab included step-up dosing and comprised a priming dose of 0.16 mg (C1D1), an intermediate dose of 0.8 mg (C1D8), and full doses of 48 mg (C1D15, C1D22, and thereafter) in 28-day treatment cycles QW for Cycles 1 to 3, Q2W for Cycles 4 to 9, and Q4W for Cycle 10+ until 1 of the discontinuation criteria was met.

Based on investigator assessment determined by Lugano criteria, the ORR (CR + partial response [PR]) for subjects in the Dose Escalation Part of the trial (N=9, including subjects with DLBCL, HGBCL, and FL) was 55.6% (95% CI: 21.2, 86.3) with 4 (44.4%) subjects and 1 (11.1%) subject achieving best response of CR and PR, respectively. The CR rate was 44.4% (95% CI: 13.7, 78.8).

No subjects were ADA positive at baseline. On treatment, 1 (11.1%) subject was ADA positive with a titer value ≥1. The presence of ADA did not appear to impact efficacy or safety in this subject.

Monotherapy Expansion Part – DLBCL Cohort (N =36)

As of the data cutoff date of 21 Apr 2023, the median duration of follow up was 22.1 months (range: 21.2, 24.6) for the DLBCL expansion cohort.

Based on IRC assessment determined by Lugano criteria, the ORR (CR + PR) was 55.6% (95% CI: 38.1, 72.1) with 17 (47.2%) subjects and 3 (8.3%) subjects achieving best response of CR and PR, respectively. The CR rate was 47.2% (95% CI: 30.4, 64.5), representing clinically meaningful efficacy in this patient population with a high unmet need. The ORR was generally consistent across the prespecified subgroups.

Based on IRC assessment, the median DOR was 15.2 months (95% CI: 4.2, not reached [NR]). The estimated percentage of subjects remaining in response at 12 and 18 months was 65.0% and 45.0%, respectively, for all responders, and 64.7% and 52.9%, respectively, for complete responders.

The median TTR and TTCR were 1.4 and 2.7 months, respectively.

The median PFS was 4.1 months (95% CI: 1.2, 14.8). For subjects who achieved a CR (n=8) the median PFS was not reached, and for subjects who achieved a PR (n=3) the median PFS was 14.8 months (95% CI: 5.6, NR).

The median OS was 14.9 months (95% CI: 8.4, NR). The estimated percentage of subjects who remained alive at 12 and 18 months was 61.1% and 44.4%, respectively. For subjects who achieved a CR (n=17) median OS was not reached, and for subjects who achieved a PR (n=3) the median OS was 15.6 months (95% CI: 14.8, NR).

Analysis of MRD using the ctDNA assay showed that 17 of the 30 MRD-evaluable subjects, defined as subjects with ≥1 on-treatment MRD sample, achieved MRD negativity (56.7%; 95% CI: 37.4, 74.5). Of the 17 subjects who achieved MRD negativity, a best overall response of CR was achieved for 15 subjects and PR for 2 subjects. Among these 17 subjects, the median duration of MRD negativity was 11.6 months (95% CI: 1.9, NR), and an estimated 90.0% of subjects (95% CI: 47.3, 98.5) remained MRD negative at 6 months. Among subjects with DLBCL who achieved MRD negativity, PFS was prolonged compared to subjects who had only MRD-positive status.

One (2.9%) subject was confirmed ADA positive at baseline (titer value <1) through C2D22, was ADA negative or of indeterminate ADA status through C15D1, then was intermittently confirmed ADA positive with a titer value of ≥1 at C21D1 as of data cutoff date. One subject with an indeterminate ADA status at baseline tested as confirmed ADA positive (titer value <1) at the C6D15 time point only then was ADA negative at all subsequent time points. Overall, the presence of ADA was transient and did not appear to impact efficacy or safety in these subjects.

Pharmacokinetic/Pharmacodynamic Results

Dose Escalation Part (N=9)

The PK profile of SC epcoritamab in Japanese subjects was characterized by slow absorption (typical of other biologics administered SC) with a geometric mean t_{max} of approximately 4 days. C_{max} increased approximately proportionally (ratio of ~2.5) from the 24 mg dose to the 48 mg dose. The $AUC_{0-\infty}$ and AUC_{0-last} values also increased approximately dose proportionally (ratios of ~2.7 and ~2.2, respectively) as the dose increased from 24 to 48 mg.

Epcoritamab treatment resulted in transient elevation of circulating cytokines (ie, IFN-γ, IL-6, IL-10, and TNF-α), mostly occurring after the first full dose of epcoritamab (24 mg or 48 mg) at C1D15, with minimal elevations at subsequent doses.

Monotherapy Expansion Part – DLBCL Cohort (N =36)

At the 48 mg full dose of epcoritamab, plasma concentrations for the DLBCL expansion cohort were similar to those for subjects in the Dose Escalation Part.

Peak concentrations of IFN-γ, IL-6, IL-10, and TNF-α occurred after administration of the first full dose of epcoritamab (48 mg) at C1D15.

Safety Results

Dose Escalation Part (N=9)

No DLTs were observed during the DLT evaluation period, and no MTD was identified.

As of the data cutoff date, all 9 subjects in the Dose Escalation Part (in either the 24 mg or 48 mg cohorts) had experienced ≥1 treatment-emergent adverse event (TEAE). The most frequently reported TEAEs were CRS (8 [88.9%] subjects), injection site erythema (5 [55.6%] subjects), platelet count decreased (4 [44.4%] subjects), nausea (4 [44.4%] subjects), anemia (4 [44.4%] subjects), injection site reaction (3 [33.3%] subjects), neutrophil count decreased (3 [33.3%] subjects), and white blood cell count decreased (3 [33.3%] subjects).

Grade 3 or 4 TEAEs were reported for 7 (77.8%) subjects. The most common (in ≥30% of subjects) were neutrophil count decreased (33.3%; 3 subjects) and white blood cell count decreased (33.3%; 3 subjects).

Serious TEAEs were reported in 2 (22.2%) subjects: CRS (considered related to epcoritamab by the investigator) and depressed level of consciousness (considered not related to epcoritamab by the investigator) in 1 subject; and COVID-19 pneumonia (considered not related to epcoritamab by the investigator) in the other subject.

There were no fatal (grade 5) TEAEs. Five (55.6%) subjects died, all with the primary cause of death as disease progression.

There were no subjects with TEAEs that led to treatment discontinuation. Two (22.2%) subjects had TEAEs that led to dose delay. The first subject had a 1-day delay of C1D8 dosing due to neutrophil count decreased. The second subject had a delay following C22D1 dosing due to concomitant events of COVID-19 pneumonia and post-COVID-19 syndrome, followed by a second dose delay due to pyrexia that occurred in concomitance with post-COVID-19 syndrome.

CRS, which was designated as an AESI, was reported in 8 (88.9%) subjects. CRS was a maximum grade 1 in 5 (55.6%) subjects, a maximum grade 2 in 2 (22.2%) subjects, and a maximum grade 3 in 1 (11.1%) subject. No grade 4 or 5 CRS events occurred. No CRS events led to treatment discontinuation or dose delay. The most common CRS symptom was fever (100% of subjects with CRS). The median time from first dose of epcoritamab to first CRS onset was 13.5 days (range: 2, 16). As of the data cutoff date, all subjects had CRS resolved, with a median time to CRS resolution of 7.0 days (range: 2, 21).

No subjects experienced an event of ICANS.

CTLS, which was designated as an AESI, was reported in 1 (11.1%) subject. This subject had a grade 2 event of CTLS (after the priming dose) lasting 2 days, a grade 3 event (after the intermediate dose) lasting 3 days, and a grade 2 event (after the first full dose of 48 mg) lasting 2 days; all events resolved with treatment.

Neurological events (broad definition) were reported for 4 (44.4%) subjects, and these were considered related to epcoritamab for 3 (33.3%) subjects. All events were reported in 1 (11.1%) subject each with a maximum severity of grade 1 or 2 (events of dysgeusia, headache, restless legs syndrome, and agitation) except 1 subject with grade 3 depressed level of consciousness (which was also serious and considered not related to epcoritamab by the investigator). Cytopenia events (broad term) were reported for 7 (77.8%) subjects, including 2 (22.2%) subjects with grade 1 events, 2 (22.2%) subjects with grade 3 events, and 3 (33.3%) subjects with grade 4 events. In the system organ class (SOC) of Infections and Infestations, TEAEs were reported for 2 (22.2%) subjects and none were considered related to epcoritamab by the investigator. One (11.1%) subject had TEAEs of COVID-19

pneumonia (maximum grade 3, serious) and post-acute COVID-19 syndrome (maximum grade 2, not serious). Injection site reaction events were reported for 7 (77.8%) subjects. Pyrexia (not attributed to CRS) was reported for 2 (22.2%) subjects. No subjects had tumor flare or hemophagocytic lymphohistiocytosis (HLH) events reported.

Monotherapy Expansion Part – DLBCL Cohort (N=36)

As of the data cutoff date, all 36 subjects in the DLBCL expansion cohort experienced ≥1 TEAE. The most frequently reported TEAEs (in ≥20% of subjects) were CRS (30 [83.3% subjects), injection site reaction (21 [58.3%] subjects), neutrophil count decreased (13 [36.1%] subjects), hypokalemia (10 [27.8%] subjects), lymphocyte count decreased (9 [25.0%] subjects), decreased appetite (9 [25.0%] subjects), platelet count decreased (8 [22.2%] subjects), and rash (8 [22.2%] subjects).

Grade 3 or 4 TEAEs were reported for 30 (83.3%) subjects. The most common (in ≥10% of subjects) were neutrophil count decreased (13 [36.1%] subjects), lymphocyte count decreased (9 [25.0%] subjects), hypokalemia (6 [16.7%] subjects), platelet count decreased (5 [13.9%] subjects), and white blood cell count decreased (5 [13.9%] subjects).

Serious TEAEs were reported in 17 (47.2%) subjects. CRS was the most frequently reported serious TEAE (7 [19.4%] subjects), followed by COVID-19, COVID-19 pneumonia, pneumonia, and UTI (2 [5.6%] subjects each). CRS was also the most frequently reported treatment-related serious TEAE (7 [19.4%] subjects). All other serious TEAEs and treatment-related serious TEAEs were reported for 1 (2.8%) subject each.

There were no fatal (grade 5) TEAEs. Twenty-two (61.1%) subjects died during the trial, 19 (52.8%) subjects with the primary cause of death as disease progression and 3 (8.3%) subjects with the primary cause of death as cancer of head of pancreas, sudden death not related to study drug or AE, and "other," respectively.

TEAEs leading to treatment discontinuation were reported in 5 (13.9%) subjects: muscular weakness (considered related to epcoritamab by the investigator); and chronic myelomonocytic leukemia, pancreatic carcinoma, COVID-19, and ECG QT prolonged (all considered not related to epcoritamab by the investigator). TEAEs leading to dose delay were reported in 17 (47.2%) subjects; the most common events were neutrophil count decreased (5 [13.9%] subjects), CRS (3 [8.3%] subjects), UTI (3 [8.3%] subjects), COVID-19 pneumonia (2 [5.6%] subjects), and pneumonia (2 [5.6%] subjects).

CRS, which was designated as an AESI, was reported in 30 (83.3%) subjects. CRS was a maximum grade 1 in 18 (50.0%) subjects, a maximum grade 2 in 9 (25.0%) subjects, and a maximum grade 3 in 3 (8.3%) subjects. No grade 4 or 5 CRS events occurred. No CRS events led to treatment discontinuation, and 3 (8.3%) subjects had CRS that led to dose delay. The most common CRS symptom was fever (100% of subjects with CRS). The median time from first dose of epcoritamab to first CRS onset was 15.5 days (range: 2, 28), which corresponds to the time of first full dose of epcoritamab. As of the data cutoff date, all subjects had CRS resolved, with median time to CRS resolution of 4.5 days (range: 1, 14).

ICANS, which was designated as an AESI, was reported in 1 (2.8%) subject. The event was serious, considered related to epcoritamab by the investigator, and a maximum grade 1 in severity. The time to ICANS onset was 5 days, and the event resolved with treatment in 3 days.

No subjects in the DLBCL expansion cohort had CTLS.

Neurological events (broad definition) were reported for 11 (30.6%) subjects, and these were considered related to epcoritamab for 2 (5.6%) subjects. The most common neurological event (≥5% of subjects) was headache (3 [8.3%] subjects). Cytopenia events (broad term) were reported for 25 (69.4%) subjects, including 2 (5.6%) subjects with grade 2 events, 7 (19.4%) subjects with grade 3 events, and 16 (44.4%) subjects with grade 4 events. In the SOC of Infections and Infestations, TEAEs were reported for 18 (50.0%) subjects and were considered related to epcoritamab by the investigator for 10 (27.8%) subjects. The most common infection events (≥5% of subjects) were UTI (5 [13.9%] subjects); COVID-19 and pneumonia (3 [8.3%] subjects each); and bronchitis, COVID-19 pneumonia, herpes simplex, and sepsis (2 [5.6%] subjects each). COVID-19 relevant TEAEs were reported for 4 (11.1%) subjects all considered not related to epcoritamab by the investigator. Injection site reaction events were reported for 25 (69.4%) subjects. Pyrexia (not attributed to CRS) was reported for 3 (8.3%) subjects. One (2.8%) subject had tumor flare reported, and no subjects had HLH events reported.

Trial Limitations

No notable trial limitations were identified by the sponsor.

Conclusions

- Following analysis of the overall safety, efficacy, and PK data from the Dose Escalation Part of the trial, as well as PK modeling, the RP2D regimen of epcoritamab in Japanese subjects was defined as a priming dose of 0.16 mg (C1D1), an intermediate dose of 0.8 mg (C1D8), and a full dose of 48 mg epcoritamab (C1D15, C1D22, and thereafter). No DLTs were observed during the DLT evaluation period, and an MTD was not identified.
- The PK profile of epcoritamab in Japanese subjects was characterized by slow absorption and a dose-proportional increase in C_{max}, $AUC_{0-\infty}$, and AUC_{0-last} values as the dose increased from 24 mg to 48 mg.
- Clinically meaningful deep and durable responses were observed in subjects with DLBCL. Based on IRC assessment using Lugano criteria, the ORR was 55.6%, and the CR rate was 47.2%. After a median follow up of 16.6 months, the median DOR was 15.2 months.
- The safety profile of epcoritamab in Japanese subjects with DLBCL is considered manageable with appropriate monitoring and mitigation measures, including dose delays and/or supportive care, and is consistent with that expected for a bispecific CD3/CD20-directed T cell engager. AESIs included CRS, ICANS, and CTLS, which were mostly grade 1 or 2 in severity.

Date of Report: 04 Oct 2023

9.8 Changes in the Conduct of the Trial or Planned Analyses

9.8.1 Protocol Amendments

A total of 6 protocol amendments were made to the original protocol (dated 20 May 2020, protocol version 1.0). No subjects were enrolled under the original protocol. Protocol amendments are included in Appendix 16.1.1. A summary of key changes with each amendment is provided in Table 9-4.

Table 9-4 Protocol Amendments

Amendment Number	Issue Date	Key Changes
Amendment 1, version 2.0	01 Jul 2020	Based on regulatory authority feedback, the protocol was amended to clarify details around hepatitis testing, DLT criteria, the requirement for pharmacogenomic sample collection, and safety reporting. In addition, a correction to the contraception table was made. • Added a new DLT criterion: any AE considered related to epcoritamab treatment that causes a delay in dosing of >7 days. • Clarified that all subjects must consent to the collection and use of MRD samples to participate in this trial. • Clarified that there is no interaction between epcoritamab and hormonal contraception. • Allowed a window of time for collection of PK samples collected after the 24-hour time point. • To improve clarity, additional details regarding evaluation of events occurring during the DLT evaluation period were added. • Clarified that for subjects with chronic infection, testing for hepatitis B must be negative prior to treatment with epcoritamab, and would be monitored monthly throughout the trial.
Amendment 2, version 3.0	11 Mar 2021	Updates to the protocol were made to change to a commercially available saline solution as diluent, make corrections and clarifications, to allow a 6-week interruption in epcoritamab treatment, to provide details of requirements for pre-medication and CRS prophylaxis, and to align with program protocols. • Implemented mandatory bone marrow biopsy requirement for all subjects at screening. • Deleted HIV from visit assessment schedules; modified HIV exclusion criterion. • Added ECOG performance status score ≤2 to the inclusion criteria. • Added information on management for chronic infection with hepatitis B.
Amendment 3, version 4.0	02 Dec 2021	The overall rationale of this amendment was applicable to the Combination Therapy Expansion Part. The changes applicable to the Dose Escalation and Monotherapy Expansion Part included: • For the Dose Escalation Part, clarified that ORR, CR rate, DOR, and PFS determined by Lugano criteria would be assessed by the investigator rather than the IRC. • For the Monotherapy Expansion Part, added DOCR, TTCR, and TTR assessed by the IRC to the secondary

Amendment Number	Issue Date	Key Changes
		endpoints for anti-lymphoma efficacy determined by Lugano criteria and LYRIC. • For the Monotherapy Expansion Part, the following process was removed: expedited IRC review and confirmation of investigator-assessed PD according to Lugano criteria and LYRIC. This was originally included in the protocol to avoid premature discontinuation in case of pseudoprogression but was not implemented. • Removed "hospitalizations" as a secondary safety endpoint. • Added that biomarker assessments would also be performed to explore the relationship to efficacy or mechanism of action of epcoritamab.
Amendment 4, version 5.0	27 Jun 2022	Updates to the protocol were made to correct typographical errors and inconsistencies identified within the amendment, as included in Protocol Clarification Letters 2 and 3, as well as to align content with other ongoing trials in the epcoritamab program. The majority of changes with this amendment were applicable only to the Combination Therapy Expansion Part. The changes in trial conduct applicable to the Dose Escalation and Monotherapy Expansion Parts included: • Clarified that during Cycle 1 only, subjects must stay for at least 2 hours after epcoritamab administration on non-hospitalization visits. • Clarified the mechanisms by which survival status could be obtained. • Corrected the exclusion criteria for assessment of renal function by CrCl instead of eGFR. • Updated the dosages and administration section with strongly recommended guidelines for Cycle 1 treatment. • Clarified that pregnancy testing could be "via serum" or urine.
Amendment 5, version 6.0	22 Aug 2022	The overall rationale for this amendment was to update the classification of tocilizumab as an Investigational Medicinal Product in its use as treatment for CRS. • Added exploratory objectives, endpoints, and analyses to evaluate the effect of anti-cytokine therapy on CRS. • Added tocilizumab (according to local prescribing information) to the list of other trial treatments for management of CRS, including instructions for use and administration.
Amendment 6, version 7.0	25 Jan 2023	The primary reason for this amendment was to prespecify compliance with the Good Post-marketing Study Practice regulations in Japan based on epcoritamab marketing approval status in Japan. In addition, the sample size for the Monotherapy Expansion Part – FL Cohort was updated to align with the GCT3013-01 trial to facilitate extrapolation of trial results.

Abbreviations: AE = adverse event; CR = complete response; CrCl = creatinine clearance; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; DOCR = duration of complete response; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; FL = follicular lymphoma; HIV = human immunodeficiency virus; IRC = Independent Review Committee; LYRIC = LYmphoma Response to Immunomodulatory therapy Criteria; MRD = minimal

residual disease; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic(s); TTCR = time to complete response; TTR = time to response.
Note: Only the changes relevant to the Escalation and Expansion Monotherapy parts (both DLBCL and FL cohorts) are indicated.

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Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Epcoritamab or GEN3013		
Name of Active Ingredient: Epcoritamab		
Title of Study: Safety and Preliminary Efficacy of Epcoritamab (GEN3013; DuoBody®-CD3×CD20) in Japanese Subjects with Relapsed or Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL) - A Phase 1/2, Open-Label, Dose-Escalation Trial with Expansion Cohorts		
Investigator: [redacted] MD, PhD		
Study Site(s)**:** As of the cutoff date for this interim report (21 April 2023), subjects were enrolled at 12 sites in Japan.		
Publications: No articles or abstracts were published as of the cutoff date for this interim report (21 April 2023).		
Studied Period (Years): First Subject First Visit: 05 Jan 2021 (Monotherapy Expansion Part - FL Cohort) Last Subject Last Visit: Trial is ongoing	**Phase of Development:** Phase 1/2	

Objectives and Endpoints:

Primary Objective

- Evaluate anti-lymphoma efficacy as determined by Lugano criteria

Secondary Objectives

- Further evaluate anti-lymphoma efficacy as determined by Lugano criteria
- Further evaluate anti-lymphoma efficacy as determined by Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC)
- Further evaluate anti-lymphoma efficacy
- Evaluate safety and tolerability of epcoritamab
- Evaluate pharmacokinetic (PK) and immunogenicity of epcoritamab
- Further assess the preliminary antitumor activity of epcoritamab

Exploratory Objectives

- Evaluate biomarkers predictive of clinical response to epcoritamab
- Evaluate the effect of anti-cytokine therapy on cytokine release syndrome (CRS)

Primary Endpoint

- Overall response rate (ORR) as determined by Lugano criteria as assessed by Independent Review Committee (IRC)

Objectives and Endpoints (Continued):

Secondary Endpoints

- Complete response (CR) rate as determined by Lugano criteria as assessed by IRC
- Duration of response (DOR) as determined by Lugano criteria as assessed by IRC
- Progression-free survival (PFS) as determined by Lugano criteria as assessed by IRC
- Duration of complete response (DOCR) determined by Lugano criteria, as assessed by IRC
- Time to complete response (TTCR) determined by Lugano criteria, as assessed by IRC
- Time to response (TTR) determined by Lugano criteria, as assessed by IRC
- ORR as determined by LYRIC, as assessed by IRC
- CR rate as determined by LYRIC, as assessed by IRC
- DOR as determined by LYRIC, as assessed by IRC
- PFS as determined by LYRIC, as assessed by IRC
- DOCR determined by LYRIC, as assessed by IRC
- TTCR determined by LYRIC, as assessed by IRC
- TTR determined by LYRIC, as assessed by IRC
- Time to next (anti-lymphoma) therapy (TTNT)
- Overall survival (OS)
- Safety (ie, adverse events [AEs], laboratory parameters, and cytokine measures)
- PK parameters (clearance, volume of distribution, area under the concentration-time curve from time zero to the last measurable concentration [$AUC_{0\text{-last}}$] and area under the concentration-time curve from time zero extrapolated to infinity [$AUC_{0\text{-}\infty}$], maximum concentration [C_{max}], time to reach Cmax [t_{max}], predose values, and elimination half-life [$t_{1/2}$]), and incidence of anti-drug antibodies (ADAs) to epcoritamab
- Rate and duration of MRD negativity

Exploratory Endpoints

- Expression of CD3, CD20, and other molecular markers in tumor biopsies pre-treatment
- Evaluation of the overall impact (efficacy and safety) of anti-cytokine therapies on CRS

Methodology:

This was a phase 1/2, open-label, single-country, interventional trial in Japanese subjects with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL). The trial included 2 parts: a Dose Escalation Part (enrolling up to 18 evaluable subjects) and an Expansion Part comprised of a Monotherapy Part (enrolling approximately 55 subjects: 35 subjects with diffuse large B-cell lymphoma [DLBCL] and 20 subjects with follicular lymphoma [FL] Grade 1-3A planned) and a Combination Therapy Part.

This CSR describes the updated analysis of results for the FL cohort of the Monotherapy Expansion Part of the trial only.

The Monotherapy Expansion Part consisted of a screening period (up to 21 days prior to C1D1), a treatment period (C1D1 until epcoritamab discontinuation), and a safety follow-up period (60 days after the last dose of epcoritamab). Survival status was also monitored approximately every 3 months for subjects who discontinued trial treatment.

Methodology (Continued):

This report describes the primary analysis results for the FL cohort of the Monotherapy Expansion Part of the trial only. An update of the primary analysis for the Dose Escalation Part and the DLBCL cohort of the Monotherapy Expansion Part of the trial are presented in a separate report. The results for the combination therapy part (Treatment Arms 2 to 5) will be reported separately.

Number of Subjects (Planned and Analyzed):

A sample size of 20 subjects was planned for the FL expansion cohort. A total of 21 subjects received the epcoritamab regimen of 0.16 mg priming dose, 0.8 mg intermediate dose, and 48 mg full dose.

Diagnosis and Main Criteria for Inclusion:

Subjects were ≥ 20 years old, of Asian race and Japanese ethnicity, had documented evidence of CD20-positive, mature B-cell neoplasm according to World Health Organization (WHO) classification 2016 or WHO classification 2008 based on a representative pathology report, and were previously treated with ≥ 2 lines of systemic antineoplastic therapy including ≥ 1 anti-CD20 monoclonal antibody (mAb) -containing therapy. Subjects had measurable disease with involvement of ≥ 2 clearly demarcated lesions/nodes with a 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 short axis ≥ 1.0 cm, based on computed tomography (CT) or magnetic resonance imaging (MRI). Subjects were required to meet a predefined per-protocol washout period from prior antineoplastic agent(s) and have a life expectancy > 3 months on standard of care treatment. Subjects had been diagnosed with FL grade 1-3A at initial diagnosis with no evidence of clinical or histological transformation.

Subjects were excluded from participating in both parts of the trial if they had primary central nervous system (CNS) lymphoma or known CNS involvement, past or current malignancy (other than noted in the protocol), aspartate transaminase (AST) and/or alanine transaminase (ALT) > 3× the upper limit of normal (ULN), total bilirubin > 1.5× ULN, creatinine clearance (CrCl) < 45 mL/min/1.73 m^2, clinically significant cardiac disease, acute infections, chronic ongoing infectious diseases requiring treatment, diseases or treatments resulting in immunosuppression, seizure disorders requiring therapy, or a history of confirmed progressive multifocal leukoencephalopathy. Subjects were also excluded if they had prior autologous stem cell transplantation (ASCT) within 100 days before first epcoritamab administration, any prior allogeneic stem cell transplantation or solid organ transplantation, or prior therapy with an investigational bispecific antibody targeting CD3 and CD20. Subjects with a positive test result for human T-cell lymphotropic virus type 1 (HTLV-1) were also excluded.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

The epcoritamab drug product was provided as a concentrate for solution in 2 concentrations: 5 mg/mL and 60 mg/mL. Diluted doses were prepared using a diluent as applicable at the site/pharmacy.

A priming dose of 0.16 mg was administered on Cycle 1 Day 1 (C1D1), followed by an intermediate dose of 0.8 mg on C1D8, and a full dose of 48 mg on C1D15 and thereafter.

Epcoritamab was administered by SC injection.

The following lot numbers were released for use during the FL expansion part of the trial:

- Epcoritamab 5 mg/mL: B3323, B3576, B3782
- Epcoritamab 60 mg/mL: B3409, B3441, B3705, B3718, B3719, B4043

Duration of Treatment:

For each subject, the treatment period continued until disease progression unless the subject fulfilled one of the discontinuation criteria. The trial will run for a maximum of 3 years after the last subject's first dose.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Not applicable.

Criteria for Evaluation

Efficacy:

The following efficacy evaluations/endpoints were collected during the study: imaging assessments, physical exam with assessment of constitutional symptoms, Eastern Cooperative Oncology Group (ECOG) performance status, minimal residual disease (MRD) status, and other procedures as necessary.

For the imaging assessments, the same radiographic modality used at screening for disease evaluation was used throughout the trial for response evaluations. Disease evaluation by alternative radiological imaging, physical examination, or other procedures was performed at the site level throughout the trial, as indicated (using the same method of assessment used to assess disease at screening).

All efficacy assessments were conducted throughout the trial until disease progression, death or withdrawal of consent from trial participation occurred. Efficacy assessments and disease progression were determined by an IRC, according to both Lugano criteria and LYRIC. The LYRIC includes assessment of indeterminate response.

Pharmacokinetic:

Venous blood samples were collected for measurement of plasma concentrations of epcoritamab. The following PK parameters were calculated based on non-compartmental methods: clearance, volume of distribution, maximum (peak) observed plasma drug concentration (C_{max}), time to reach maximum (peak) plasma drug concentration (T_{max}), AUC ($AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$), predose trough concentrations (C_{Trough}) and elimination half-life ($t_{1/2}$).

Safety:

Safety and tolerability were evaluated based on AEs, physical examinations, clinical laboratory assessments, vital signs, electrocardiograms (ECGs), ECOG performance status, immune effector cell-associated neurotoxicity syndrome (ICANS), constitutional symptoms, survival status, PK, immunogenicity, and safety biomarker assessments.

All AEs, whether serious or nonserious, were reported from the first epcoritamab dose until 60 days after the last dose of epcoritamab, the subject withdrew consent, the subject started a new anticancer treatment, or the subject died, whichever came first. Serious treatment-emergent adverse events (TEAEs) considered related to epcoritamab or tocilizumab by the investigator were reported after the safety follow-up visit (> 60 days after last dose). treatment-related serious TEAEs, including serious adverse event of special interest (AESIs), that were still ongoing after the safety follow-up visit were followed on a regular basis, according to the investigator's clinical judgment, until the event resolved or until the investigator assessed it as chronic and all queries were resolved.

Statistical Methods

Efficacy:

The primary endpoint of ORR was defined as the proportion of subjects who achieved a best overall response (BOR) of CR or partial response (PR) in an analysis set. ORR was evaluated by the investigator and was also evaluated by the IRC. The primary analysis was conducted approximately 6 months after the last subject's first dose for the Monotherapy Expansion Part.

The primary analysis of ORR was by IRC assessment per Lugano criteria in the full analysis set (FAS) and corresponding 95% CIs were calculated.

Sensitivity analyses of ORR were performed in a similar manner as the primary analysis for IRC-assessed ORR per Lugano criteria (per protocol [PP], response evaluable set [RES], and modified response evaluable set [mRES] populations), IRC-assessed CT based ORR per Lugano criteria (FAS and RES populations), and investigator-assessed ORR per Lugano criteria (FAS, PP, RES, and mRES populations). Supplementary analyses of ORR were performed to explore the impacts of demographic and baseline disease characteristic on the treatment effect in the FAS in subgroup analyses. In addition, concordance between IRC- and investigator-assessed BOR based on Lugano criteria in the FAS was summarized using kappa statistics.

The key secondary endpoint of IRC-assessed ORR per LYRIC was analyzed in the FAS along with corresponding 95% exact CI. An additional response category per LYRIC included IR. Sensitivity analyses for IRC-assessed ORR per LYRIC were also conducted for the RES population. Similar analyses were also performed for investigator assessed ORR per LYRIC in the FAS.

Other key secondary efficacy endpoints included DOR, CR rate, DOCR, PFS, TTR, TTCR, OS, TTNT, and rate of MRD-negativity.

Pharmacokinetic:

Descriptive statistics of PK concentrations at different time points were summarized and plotted when deemed appropriate.

Pharmacodynamics:

Pharmacodynamic markers in blood samples linked to the mechanism of action of epcoritamab were assessed.

Immunogenicity:

Results from ADA analyses and titers for ADA positive samples were summarized for the immunogenicity analysis set (IAS).

Biomarkers:

Biomarker assessments that are intended to evaluate potential pharmacodynamic markers and to identify markers predictive of response or resistance to epcoritamab were exploratory in nature.

Safety:

AEs were summarized for on-treatment AEs (ie, TEAEs), treatment-related TEAEs, serious adverse events (SAEs), AEs leading to dose delays, AEs leading to treatment discontinuation, treatment-related SAEs, and AESIs.

AESIs were defined as events identified by the sponsor to be of scientific and medical concern specific to epcoritamab. AESIs included CRS, ICANS, and clinical tumor lysis syndrome (CTLS), all of which may be considered on-target toxicities.

For analysis and reporting purposes, partial/missing AE onset/end date/time were imputed.

Statistical Methods (Continued):

Other safety endpoints that were analyzed included death, selective laboratory parameters, vital signs, ECGs, and ECOG performance status. Constitutional symptoms were provided in subject listings only.

Data for tocilizumab-related effects (time from treatment to resolution of CRS and CRS signs and symptoms, post-treatment AEs, laboratory data) were also summarized.

Summary/Conclusions

Efficacy Results:

The results presented below are mainly based on IRC assessment determined by Lugano criteria, unless specified otherwise:

- Response rates in subjects treated with epcoritamab in the FL cohort were high. ORR (CR+PR) was 95.2% (95% CI: 76.2%, 99.9%), and the CR rate was 76.2% (95% CI: 52.8%, 91.8%).
- In pre-specified subgroups, including subpopulations that are traditionally challenging to treat such as elderly subjects, heavily pre-treated subjects, subjects with advanced disease, and subjects considered double refractory to anti-CD20 and alkylating agent and/or with disease progression within 24 months (POD24) disease, ORRs and CR rates were generally consistent with the overall population.
- Responses were durable in subjects with FL treated with epcoritamab. After a median DOR follow-up of 15.3 months (95% CI: 9.7, 20.6), the median DOR was 23.1 months (95% CI: 4.4, NR). The estimated percentage of subjects remaining in response at 12 and 18 months was 68.4% and 60.8%, respectively.
- After a median follow-up of 15.3 months (95% CI: 13.8, 20.8), the median DOCR was 23.1 months (95% CI: 15.0, NR).
- Responses were generally achieved early with epcoritamab treatment. The median TTR was 1.4 months (range: 1.2, 2.6) for all responders, and the median TTCR was 1.4 months (range: 1.2, 2.8) for complete responders representing early responses.
- Longer term outcomes (PFS, OS) observed were clinically meaningful:
  - After a median follow-up of 16.7 months (95% CI: 10.9, 21.9), the median PFS was 24.3 months (95% CI: 5.7, NR). The estimated percentage of subjects remaining in response at 21 and 24 months was 61.4%.
  - After a median follow-up of 21.2 months (95% CI: 18.0, 24.0), the median OS was not reached (95% CI: 24.3, NR). The estimated percentage of subjects alive at 21 and 24 months was 100% for each.
- The overall MRD negativity rate per PMBC assay with a cutoff of 10^{-6} among subjects who were MRD-evaluable was 88.9% (95% CI: 65.3%, 98.6%). Although data are limited, subjects who achieved MRD negativity had improved PFS compared to subjects who had an MRD positive status.

Safety Results:

- As of the data cutoff date of 21 April 2023, all 21 subjects in the FL expansion cohort experienced ≥ 1 TEAE. The most frequently reported TEAEs by preferred term (PT) (in ≥ 25% of subjects) were CRS, injection site reaction, neutrophil count decreased, rash, ALT increased, and AST increased.
- Grade 3 or 4 TEAEs were reported for 15 (71.4%) subjects. The most frequently reported (in ≥ 10% of subjects) Grade 3 or 4 TEAEs by PT were neutrophil count decreased, ALT increased, and lymphocyte count decreased.
- Serious TEAEs were reported in 12 (57.1%) subjects. CRS was the most frequently reported serious TEAE and treatment-related serious TEAE. All other serious TEAEs were reported for ≤ 2 subjects.
- There were no fatal (Grade 5) TEAEs in the FL cohort. Overall, 1 (4.8%) subject with FL died during the trial, which occurred during the survival follow-up period (> 60 days post last dose)
- TEAEs leading to dose delay were reported in 10 (47.6%) subjects; the most frequently reported event that led to dose delay was CRS.
- TEAEs leading to treatment discontinuation were reported in 4 (19.0%) subjects; progressive multifocal leukoencephalopathy was the only event that led to treatment discontinuation in more than 1 subject.
- CRS, which was designated as an AESI, was reported in 19 (90.5%) subjects. The majority of subjects experienced Grade 1 CRS (14 [66.7%]), followed by Grade 2 events (4 [19.0%] subjects). One (4.8%) subject experienced Grade 3 CRS and no subjects had Grade 4 or higher CRS. The median time to first CRS onset was 15.0 days (range: 1, 20), which corresponds to the time of first full dose of epcoritamab. As of the data cutoff date of 21 April 2023, all CRS events achieved resolution with median time to resolution of 4.0 days (range: 1, 9).
- No subjects in the FL cohort had an AESI of ICANS or CTLS.
- Other AEs of interest examined in this trial included neurological events, cytopenia events, infection events, injection site reactions, pyrexia, tumor flare, and HLH:
  - Neurological events (broad definition) occurred in 6 (28.6%) subjects, and these were related to treatment for 4 (19.0%) subjects. Overall, the most frequently reported neurological event (≥ 5% subjects) was post herpetic neuralgia (2 [9.5%] subjects).
  - Overall, 10 (47.6%) subjects had at least 1 cytopenia event (broad definition); 8 (38.1%) subjects experienced neutropenia (grouped), 1 (4.8%) subject experienced febrile neutropenia, and 3 (14.3%) subjects experienced lymphopenia (grouped). No events of thrombocytopenia or anemia were reported.
  - In the system organ class (SOC) Infections and infestations, TEAEs were reported for 12 (57.1%) subjects; most common infection event by PT was coronavirus disease - 2019 (COVID-19) (3 [14.3%] subjects). Treatment-related infection TEAEs were reported in 6 (28.6%) subjects, with the most common being herpes zoster and progressive multifocal leukoencephalopathy (2 [9.5%] subjects each).

Summary/Conclusions (Continued)

Safety Results (Continued):

- Serious TEAEs in the SOC Infections and infestations were reported for 8 (38.1%) subjects; the most frequently reported serious infections by PT were herpes zoster and progressive multifocal leukoencephalopathy (2 [9.5%] subjects each). Treatment-related serious TEAEs were reported for 5 (23.8%) subjects and included herpes zoster and progressive multifocal leukoencephalopathy (2 [9.5%] subjects each), and COVID-19 pneumonia and pneumonia (1 [4.8%] subject each).
- A total of 15 (71.4%) subjects had at least 1 TEAE that was identified as an injection site reaction. All events were considered related to epcoritamab by the investigator and all injection site reaction events were a maximum severity of Grade 1.
- Five (23.8%) subjects had at least one pyrexia event (not attributed to CRS).
- No events of tumor flare or HLH were reported during the trial.

- Hematology and coagulation laboratory measurements were mostly Grade 1 to Grade 2; Grade 3 or 4 events were observed for decreased absolute lymphocytes count and decreased absolute neutrophils count. No subjects had elevated liver enzymes that met laboratory criteria of Hy's Law. During the on-treatment period overall, worst QT interval corrected for heart rate (Fridericia's correction) (QTcF) intervals were recorded as > 450 to 480 msec for 2 (9.5%) subjects. No clinically significant ECG abnormalities were observed.
- Overall, epcoritamab had a manageable and tolerable safety profile in Japanese subjects with FL.

Conclusions:

In the Japanese FL cohort of the study, the 21 subjects were of advanced age (median age: 65.0 years) with the majority having advanced staged lymphoma (Ann-Arbor Stages III IV in 81.0% of subjects), a FL International Prognostic Index (FLIPI) score ≥ 3 (52.4% of subjects), and being double refractory to an anti-CD20 and alkylating agent (57.1% of subjects). Additionally, 57.1% of subjects with R/R FL had disease progression within 24 months (POD24) from any first line therapy, and were heavily pre-treated (median of 4.0 [range: 2, 10] prior lines of systemic anti lymphoma therapy). These subjects represent a population that is clinically very challenging to treat, with historically poor responses and survival outcomes.

Based on IRC assessment determined by Lugano criteria, the ORR in FL subjects was 95.2%, and the CR rate was 76.2%. After a median follow-up of 15.3 months (95% CI: 9.7, 20.6), the median DOR in all responders was 23.1 months (95% CI: 4.4, NR). Efficacy was consistent across the pre-specified subgroups, including elderly, heavily pre-treated and highly refractory (e.g., subjects with double refractory or POD24 disease).

The safety profile of epcoritamab is considered manageable with appropriate prophylaxis, monitoring, and mitigation measures, including supportive care and/or dose delays, and is consistent with on-target toxicities of a bispecific CD3/CD20-directed T-cell engager. The AESIs included CRS, ICANS and CTLS. CRS was mostly Grade 1 or Grade 2 in severity, and no ICANS or CTLS were reported in the study.

Clinically meaningful, deep, and durable responses were observed in Japanese subjects with R/R FL, and the safety profile of epcoritamab in this population is considered manageable with appropriate monitoring, mitigation measures, and supportive care.

Date of Report: 10 Oct 2023

Changes in the Conduct of the Study or Planned Analyses

Protocol Changes

The original protocol (Version 1.0, 20 May 2020) had 6 versions/amendments. No subjects were enrolled under the original protocol.

The original protocol and protocol versions/amendments not incorporated into a previous version/amendment are provided in Appendix 16.1.1. A summary of key changes with each amendment is provided below.

Amendment Number	Issue Date	Key Changes
Amendment 1, version 2.0	01 Jul 2020	Based on regulatory authority feedback, the protocol was amended to clarify details around hepatitis testing, DLT criteria, the requirement for pharmacogenomic sample collection, and safety reporting. In addition, a correction to the contraception table was made. • Added a new DLT criterion: any AE considered related to epcoritamab treatment that causes a delay in dosing of > 7 days. • Clarified that all subjects must consent to the collection and use of MRD samples to participate in this trial. • Clarified that there is no interaction between epcoritamab and hormonal contraception. • Allowed a window of time for collection of PK samples collected after the 24-hour time point. • To improve clarity, additional details regarding evaluation of events occurring during the DLT evaluation period were added. • Clarified that for subjects with chronic infection, testing for hepatitis B must be negative prior to treatment with epcoritamab, and would be monitored monthly throughout the trial.
Amendment 2, version 3.0	11 Mar 2021	Updates to the protocol were made to change to a commercially available saline solution as diluent, make corrections and clarifications, to allow a 6-week interruption in epcoritamab treatment, to provide details of requirements for pre-medication and CRS prophylaxis, and to align with program protocols. • Implemented mandatory bone marrow biopsy requirement for all subjects at screening. • Deleted HIV from visit assessment schedules; modified HIV exclusion criterion. • Added ECOG performance status score ≤ 2 to the inclusion criteria. • Added information on management for chronic infection with hepatitis B.
Amendment 3, version 4.0	02 Dec 2021	The overall rationale of this amendment was applicable to the Combination Therapy Expansion Part. The changes applicable to the Monotherapy Expansion Part included: • Added DOCR, TTCR, and TTR assessed by the IRC to the secondary endpoints for anti-lymphoma efficacy determined by Lugano criteria and LYRIC. • The following process was removed: expedited IRC review and confirmation of investigator-assessed PD according to Lugano criteria and LYRIC. This was originally included in the protocol to avoid premature discontinuation in case of pseudoprogression but was not implemented. • Removed "hospitalizations" as a secondary safety endpoint. • Added that biomarker assessments would also be performed to explore the relationship to efficacy or mechanism of action of epcoritamab.

Amendment Number	Issue Date	Key Changes
Amendment 4, version 5.0	27 Jun 2022	Updates to the protocol were made to correct typographical errors and inconsistencies identified within the amendment, as included in Protocol Clarification Letters 2 and 3, as well as to align content with other ongoing trials in the epcoritamab program. The majority of changes with this amendment were applicable only to the Combination Therapy Expansion Part. The changes in study conduct applicable to the Monotherapy Expansion Parts included: • Clarified that during Cycle 1 only, subjects must stay for at least 2 hours after epcoritamab administration on non-hospitalization visits. • Clarified the mechanisms by which survival status could be obtained. • Corrected the exclusion criteria for assessment of renal function by CrCl instead of eGFR. • Updated the dose and administration section with strongly recommended guidelines for Cycle 1 treatment. • Clarified that pregnancy testing could be "via serum" or urine.
Amendment 5, version 6.0	22 Aug 2022	The overall rationale for this amendment was to update the classification of tocilizumab as an Investigational Medicinal Product in its use as treatment for CRS. • Added exploratory objectives, endpoints, and analyses to evaluate the effect of anti-cytokine therapy on CRS. • Added tocilizumab (according to local prescribing information) to the list of other trial treatments for management of CRS, including instructions for use and administration.
Amendment 6, version 7.0	25 Jan 2023	The primary reason for this amendment was to prespecify compliance with the Good Post-marketing Study Practice regulations in Japan based on epcoritamab marketing approval status in Japan. In addition, the sample size for the Monotherapy Expansion Part – FL Cohort was updated to align with the GCT3013-01 trial to facilitate extrapolation of study results.

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