TEPKINLY® (epcoritamab) Receives Second European Commission Approval for the Treatment of Adults with Relapsed/Refractory Follicular Lymphoma

Company Announcement

- **TEPKINLY is the first and only subcutaneous bispecific antibody approved as a monotherapy in the European Union to treat both relapsed or refractory (R/R) follicular lymphoma (FL) and R/R diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy**

COPENHAGEN, Denmark; August 19, 2024 – Genmab A/S (Nasdaq: GMAB) today announced that the European Commission (EC) has granted conditional marketing authorization for TEPKINLY® (epcoritamab) as a monotherapy for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) after two or more lines of systemic therapy. TEPKINLY is the first and only subcutaneous T-cell engaging bispecific antibody approved for the treatment of this patient population in the European Union (EU), as well as the European Economic Area (EEA) countries (Iceland, Liechtenstein, Norway) and Northern Ireland.

“Follicular lymphoma can be challenging to treat and today’s approval of TEPKINLY for the treatment of relapsed/refractory follicular lymphoma after two or more lines of systemic therapy marks an important milestone for patients in the European Union who are in need of more options offering a balance of meaningful efficacy and favorable safety,” said Jan van de Winkel, Ph.D., President and Chief Executive Officer of Genmab. “Alongside our partner AbbVie, we are committed to exploring the continued development of epcoritamab as a potential core therapy across B-cell malignancies.”

FL is typically a slow-growing form of Hodgkin’s lymphoma (NHL) that arises from B-cell lymphocytes. FL is the second most common form of NHL overall, accounting for 20-30 percent of all NHL cases, and represents 10-20 percent of all lymphomas in the western world.[i] FL is considered incurable, and there is no standard of care treatment for third-line or later FL.[i,ii] Patients who achieve remission also often experience relapse.[iii,iv,v]

The conditional marketing authorization is supported by data from the Phase 1/2 EPCORE® NHL-1 clinical trial: an open-label, multi-cohort, multicenter, single-arm trial that evaluated TEPKINLY as monotherapy in patients with R/R FL after two or more lines of prior systemic therapy. Patients included in the study were refractory to both anti-CD20 monoclonal antibody therapy and an alkylating agent (70% having double refractory disease), patients who were refractory to last prior treatment (82%), and patients whose disease progressed within two years of initiating first systemic therapy (52%). The results published in the *Lancet Haematology* showed that patients treated with TEPKINLY (n=128) had an overall response rate (ORR) of 83% and a complete response (CR) rate of 63%. At a median follow-up of 16.2 months, the median duration of response was 21.4 months (13.7, NR). Duration of complete response (DOCR) was not reached.

The study included a planned separate optimization cohort, which evaluated 86 patients with the recommended 3-step-up doses for cytokine release syndrome (CRS) mitigation. Hospitalization was not mandatory in the cycle 1 optimization cohort. With the optimized regimen, 40% of patients experienced Grade 1 CRS and 9% experienced Grade 2 (no Grade 3 or higher CRS were reported). No immune effector cell-associated neurotoxicity syndrome (ICANS) cases were reported in this cohort.

The safety profile of epcoritamab in the pivotal cohort was similar to reports of epcoritamab monotherapy in the pivotal EPCORE NHL-1 diffuse large B-cell lymphoma (DLBCL) cohort. In the pooled safety population (n=382), the most common adverse reactions (≥ 20%) with TEPKINLY were CRS, injection

site reactions, fatigue, viral infection, neutropenia, musculoskeletal pain, pyrexia, and diarrhea. The most frequent serious adverse reaction (≥ 10%) was cytokine release syndrome (34%). Fourteen patients (3.7%) experienced a fatal adverse reaction (pneumonia in 9 (2.4%) patients, viral infection in 4 (1.0%) patients, and ICANS in 1 (0.3%) patient.

“The approval of epcoritamab by the European Commission is a promising update for the lymphoma community,” said Kate Rogers, CEO of the Follicular Lymphoma Foundation. “Given that relapsed or refractory follicular lymphoma can be a very challenging form of cancer to treat, especially in later lines of therapy, it is critical that patients and physicians have additional options when it comes to treating this type of cancer.”

About the EPCORE® NHL-1 Trial
EPCORE® NHL-1 is an open-label, multi-center safety and preliminary efficacy trial of epcoritamab that consists of three parts: a dose escalation part; an expansion part; and an optimization part. The trial was designed to evaluate subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin’s lymphoma (B-NHL), including FL. In the expansion part, additional patients were enrolled to further explore the safety and efficacy of epcoritamab in three cohorts of patients with different types of relapsed/refractory B-NHLs who have limited therapeutic options. The expansion part generated pivotal data from patients with FL and DLBCL. The optimization part evaluated additional CRS mitigation strategies during cycle 1. The primary endpoint of the expansion part was overall response rate (ORR) as assessed by an Independent Review Committee (IRC). Secondary efficacy endpoints included duration of response, complete response rate, duration of complete response, progression-free survival, and time to response as determined by the Lugano criteria. Overall survival, time to next therapy, and rate of minimal residual disease negativity were also evaluated as secondary efficacy endpoints. The primary endpoint of the optimization part was the rate of ≥ Grade 2 CRS events and all grade CRS events from first dose of epcoritamab through 7 days following administration of the second full dose of epcoritamab.

About Epcoritamab
Epcoritamab is an IgG1-bispecific antibody created using Genmab's proprietary DuoBody® technology and administered subcutaneously. Genmab's DuoBody-CD3 technology is designed to direct cytotoxic T cells selectively to elicit an immune response toward target cell types. Epcoritamab is designed to simultaneously bind to CD3 on T cells and CD20 on B cells and induces T-cell-mediated killing of CD20+ cells.[vi]

Epcoritamab (approved under the brand name EPKINLY in the U.S. and Japan, and TEPKINLY in the EU) has received regulatory approval in certain lymphoma indications in several territories. Epcoritamab is being co-developed by Genmab and AbbVie as part of the companies' oncology collaboration. The companies will share commercial responsibilities in the U.S. and Japan, with AbbVie responsible for further global commercialization. Both companies will pursue additional international regulatory approvals for the investigational R/R FL indication and additional approvals for the R/R DLBCL indication.

Genmab and AbbVie continue to evaluate the use of epcoritamab as a monotherapy, and in combination, across lines of therapy in a range of hematologic malignancies. This includes four ongoing Phase 3, open-label, randomized trials including a trial evaluating epcoritamab as a monotherapy in patients with R/R DLBCL compared to investigators choice chemotherapy (NCT04628494), a trial evaluating epcoritamab in combination with R-CHOP in adult participants with newly diagnosed DLBCL (NCT05578976), a trial evaluating epcoritamab in combination with rituximab and lenalidomide (R2) in patients with R/R FL (NCT05409066), and a trial evaluating epcoritamab in combination with rituximab and lenalidomide (R2) compared to chemoimmunotherapy in patients with previously untreated FL

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(NCT06191744). The safety and efficacy of epcoritamab has not been established for these investigational uses. Please visit www.clinicaltrials.gov for more information.

EU Indications and Important Safety Information about Tepkinly® ▼ (epcoritamab)

Indications
Tepkinly (epcoritamab) as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Important Safety Information

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use
Cytokine release syndrome (CRS)
CRS, which may be life-threatening or fatal, occurred in patients receiving Tepkinly. The most common signs and symptoms of CRS include pyrexia, hypotension and hypoxia. Other signs and symptoms of CRS in more than two patients include chills, tachycardia, headache and dyspnoea.

Most CRS events occurred in Cycle 1 and were associated with the first full dose of Tepkinly. Administer prophylactic corticosteroids to mitigate the risk of CRS. Patients should be monitored for signs and symptoms of CRS following Tepkinly administration. At the first signs or symptoms of CRS, institute treatment of supportive care with tocilizumab and/or corticosteroids as appropriate. Patients should be counselled on the signs and symptoms associated with CRS and patients should be instructed to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Management of CRS may require either temporary delay or discontinuation of Tepkinly based on the severity of CRS. Patients with DLBCL should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of CRS.

Immune effector cell-associated neurotoxicity syndrome (ICANS)
ICANS, including a fatal event, have occurred in patients receiving Tepkinly. ICANS may manifest as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema. The majority of cases of ICANS occurred within Cycle 1 of Tepkinly treatment, however some occurred with delayed onset. Patients should be monitored for signs and symptoms of ICANS following Tepkinly administration. At the first signs or symptoms of ICANS treatment with corticosteroids and non-sedating-anti-seizure medicinal products should be instituted as appropriate. Patients should be counselled on the signs and symptoms of ICANS and that the onset of events may be delayed. Patients should be instructed to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Tepkinly should be delayed or discontinued as recommended. Patients with DLBCL should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of ICANS .

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Serious infections
Treatment with Tepkinly may lead to an increased risk of infections. Serious or fatal infections were observed in patients treated with Tepkinly in clinical studies. Administration of Tepkinly should be avoided in patients with clinically significant active systemic infections. As appropriate, prophylactic antimicrobials should be administered prior to and during treatment with Tepkinly. Patients should be monitored for signs and symptoms of infection, before and after Tepkinly administration, and treated appropriately. In the event of febrile neutropenia, patients should be evaluated for infection and managed with antibiotics, fluids and other supportive care, according to local guidelines.

Tumour Lysis Syndrome (TLS)
TLS has been reported in patients receiving Tepkinly. Patients at an increased risk for TLS are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent. Patients should be monitored for signs or symptoms of TLS, especially patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function. Patients should be monitored for blood chemistries and abnormalities should be managed promptly.

Tumour flare
Tumour flare has been reported in patients treated with Tepkinly. Manifestations could include localized pain and swelling. Consistent with the mechanism of action of Tepkinly, tumour flare is likely due to the influx of T-cells into tumour sites following Tepkinly administration. There are no specific risk factors for tumour flare that have been identified; however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumour flare in patients with bulky tumours located in close proximity to airways and/or a vital organ. Patients treated with Tepkinly should be monitored and evaluated for tumour flare at critical anatomical sites.

CD20-negative disease
There are limited data available on patients with CD20-negative DLBCL and patients with CD20-negative FL treated with Tepkinly, and it is possible that patients with CD20-negative DLBCL and CD20-negative FL may have less benefit compared to patients with CD20-positive DLBCL and patients with CD20-postitive FL, respectively. The potential risks and benefits associated with treatment of patients with CD20-negative DLBCL and FL with Tepkinly should be considered.

Immunisation
Live and/or live-attenuated vaccines should not be given during Tepkinly therapy. Studies have not been conducted in patients who received live vaccines.

Fertility, pregnancy and lactation
Tepkinly is not recommended during pregnancy and in women of childbearing potential not using contraception.

Effects on ability to drive and use machines
Tepkinly has minor influence on the ability to drive and use machines. Due to the potential for ICANS, patients should be advised to exercise caution while (or avoid if symptomatic) driving, cycling or using heavy or potentially dangerous machines.

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Undesirable effects

Summary of the safety profile

The safety of Tepkinly was evaluated in 382 patients with relapsed or refractory large B-cell lymphoma (N=167), FL (N=129) and FL (3-step step-up dose schedule N=86) after two or more lines of systemic therapy and included all the patients who enrolled to the 48 mg dose and received at least one dose of TEPKINLY. The most common adverse reactions (≥ 20%) were CRS, injection site reactions, fatigue, viral infection, neutropenia, musculoskeletal pain, pyrexia, and diarrhoea.

Serious adverse reactions occurred in 50% of patients. The most frequent serious adverse reaction (≥ 10%) was cytokine release syndrome (34%). Fourteen patients (3.7%) experienced a fatal adverse reaction (pneumonia in 9 (2.4%) patients, viral infection in 4 (1.0%) patients, and ICANS in 1 (0.3%) patient). Adverse reactions that led to discontinuation occurred in 6.8% of patients. Discontinuation of Tepkinly due to pneumonia occurred in 14 (3.7%) patients, viral infection in 8 (2.1%) patients, fatigue in 2 (0.5%) patients, and CRS, ICANS, or diarrhoea, in 1 (0.3%) patient each.

Dose delays due to adverse reactions occurred in 42% of patients. Adverse reactions leading to dose delays (≥ 3%) were viral infections (17%), CRS (11%), neutropenia (5.2%), pneumonia (4.7%), upper respiratory tract infection (4.2%), and pyrexia (3.7%).

This is not a complete summary of all safety information.

See Tepkinly® full Summary of Product Characteristics (SmPC) at www.ema.europa.eu

Globally, prescribing information varies; refer to the individual country product label for complete information.

About Genmab

Genmab is an international biotechnology company with a core purpose of guiding its unstoppable team to strive toward improving the lives of patients with innovative and differentiated antibody therapeutics. For 25 years, its passionate, innovative and collaborative team has invented next-generation antibody technology platforms and leveraged translational, quantitative and data sciences, resulting in a proprietary pipeline including bispecific T-cell engagers, antibody-drug conjugates, next-generation immune checkpoint modulators and effector function-enhanced antibodies. By 2030, Genmab's vision is to transform the lives of people with cancer and other serious diseases with knock-your-socks-off (KYSO®) antibody medicines.

Established in 1999, Genmab is headquartered in Copenhagen, Denmark, with international presence across North America, Europe and Asia Pacific. For more information, please visit Genmab.com and follow us on LinkedIn and X.

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This Media Release contains forward looking statements. The words "believe," "expect," "anticipate," "intend" and "plan" and similar expressions identify forward looking statements. Actual results or performance may differ materially from any future results or performance expressed or implied by such statements. The important factors that could cause our actual results or performance to differ materially include, among others, risks associated with pre-clinical and clinical development of products, uncertainties related to the outcome and conduct of clinical trials including unforeseen safety issues, uncertainties related to product manufacturing, the lack of market acceptance of our products, our inability to manage growth, the competitive environment in relation to our business area and markets, our inability to attract and retain suitably qualified personnel, the unenforceability or lack of protection of our patents and proprietary rights, our relationships with affiliated entities, changes and developments in technology which may render our products or technologies obsolete, and other factors. For a further discussion of these risks, please refer to the risk management sections in Genmab's most recent financial reports, which are available on www.genmab.com and the risk factors included in Genmab's most recent Annual Report on Form 20-F and other filings with the U.S. Securities and Exchange Commission (SEC), which are available at www.sec.gov. Genmab does not undertake any obligation to update or revise forward looking statements in this Media Release nor to confirm such statements to reflect subsequent events or circumstances after the date made or in relation to actual results, unless required by law.

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[i] Lymphoma Research Foundation official website. https://lymphoma.org/aboutlymphoma/nhl/fl/. Accessed February 2024.
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[vi] Engelberts PJ, Hiemstra IH, de Jong B, et al. DuoBody-CD3xCD20 induces potent T-cell-mediated killing of malignant B cells in preclinical models and provides opportunities for subcutaneous dosing. EBioMedicine. 2020;52:102625. doi: 10.1016/j.ebiom.2019.102625.