# CHMP Issues Positive Opinion Recommending DARZALEX® (daratumumab) for Relapsed or Refractory Multiple Myeloma

## Company Announcement

- **CHMP issued positive opinion for DARZALEX for relapsed or refractory multiple myeloma**
- **Final decision from European Commission expected in the coming months**
- **Opinion based on data from two Phase III studies, CASTOR and POLLUX**

**Copenhagen, Denmark; February 24, 2017 – Genmab A/S (Nasdaq Copenhagen: GEN) announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion recommending broadening the existing marketing authorization for DARZALEX® (daratumumab) in the European Union.** The recommendation is for the use of DARZALEX® (daratumumab) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. The variation to the Marketing Authorization for this indication was submitted to the EMA in August 2016. In August 2012, Genmab granted Janssen Biotech, Inc. an exclusive worldwide license to develop, manufacture and commercialize daratumumab.

The positive opinion of the CHMP was based on data from two Phase III studies: the CASTOR study of daratumumab in combination with bortezomib and dexamethasone versus bortezomib and dexamethasone alone in patients with relapsed or refractory multiple myeloma, and the POLLUX study of daratumumab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with relapsed or refractory multiple myeloma. The submission also included supporting data from two early stage studies: the Phase I MMY1001 study (daratumumab in combination with pomalidomide and dexamethasone) and the Phase I/II GEN503 study (daratumumab in combination with lenalidomide and dexamethasone).

“We are very pleased to receive this positive opinion from the CHMP which brings the potential for patients in Europe with relapsed or refractory multiple myeloma to have access to treatment with DARZALEX a key step closer. We very much look forward to a final decision from the European Commission on the application to expand the product label,” said Jan van de Winkel, Ph.D., Chief Executive Officer of Genmab.

A CHMP opinion is one of the final steps in the regulatory process of the European Medicines Agency. A final decision by the European Commission is anticipated within two months.

**About the CASTOR study**
The Phase III CASTOR study included 498 patients who had relapsed or refractory multiple myeloma. Patients were randomized to receive either daratumumab combined with subcutaneous bortezomib (a type of chemotherapy, called a proteasome inhibitor) and dexamethasone (a corticosteroid), or bortezomib and dexamethasone alone. The study met the primary endpoint of improving progression free survival (PFS); Hazard Ratio (HR) = 0.39, 95% CI 0.28-0.53, p<0.0001. Patients who received treatment with daratumumab in combination with bortezomib and dexamethasone had a 61% reduction in risk of their disease progressing, compared to those who did not receive daratumumab. The median PFS for patients treated with daratumumab has not been reached, compared to median PFS of 7.2 months for patients who did not receive daratumumab. Daratumumab also significantly increased the overall response rate (ORR) (83% vs. 63%, p<0.0001), including doubling rates of complete response (CR) or better (19% vs. 9%) and rates of very good partial response (VGPR) or better (59% vs. 29%). The proportion of patients that achieved minimal residual disease (MRD) negative status at the $10^{-4}$ threshold (one tumor cell in 10,000 white cells) was 13.5% vs 2.8%, p<0.000006 for patients treated with daratumumab versus patients who did not receive daratumumab. The most common grade 3 or 4 adverse events in patients treated with daratumumab in combination with bortezomib and

dexamethasone compared to those who only received bortezomib and dexamethasone were thrombocytopenia (45% vs 33%), anemia (14% vs 16%) and neutropenia (13% vs 4%). Daratumumab-associated infusion-related reactions were reported in 45% of patients, were mostly grade 1/2, and occurred predominantly during the first infusion. This is consistent with the reported safety profile of daratumumab monotherapy and combination therapy of bortezomib and dexamethasone.

**About the POLLUX study**

The Phase III POLLUX study enrolled 569 patients who had relapsed or refractory multiple myeloma. Patients were randomized to receive either daratumumab combined with lenalidomide (an immunomodulatory drug) and dexamethasone, or lenalidomide and dexamethasone alone. The study met the primary endpoint of improving progression-free survival (PFS) (Hazard Ratio (HR) = 0.37; 95% CI 0.27-0.52; p<0.0001) for patients treated with daratumumab versus patients who did not receive daratumumab. Patients who received treatment with daratumumab in combination with lenalidomide and dexamethasone had a 63% reduction in risk of their disease progressing, compared to those who did not receive daratumumab. The median PFS for patients treated with daratumumab in combination with lenalidomide and dexamethasone has not been reached, compared to an estimated median PFS of 18.4 months for patients who received lenalidomide and dexamethasone alone. Additionally, daratumumab significantly increased ORR (93% vs. 76%, p<0.0001), including doubling rates of CR or better (43% vs. 19%), as well as rates of VGPR or better (76% vs. 44%). The proportion of patients that achieved minimal residual disease (MRD) negative status at the $10^{-4}$ threshold was 29% vs 7.8%, p<0.000001 for patients treated with daratumumab versus patients who did not receive daratumumab. The most common grade 3 or 4 adverse events in patients treated with daratumumab in combination with lenalidomide and dexamethasone versus those who received only lenalidomide and dexamethasone were neutropenia (52% vs 37%), thrombocytopenia (13% vs 14%), and anemia (12% vs 20%). Daratumumab-associated infusion-related reactions occurred in 48% of patients, were mostly grade 1/2, and occurred predominantly during the first infusion. Overall, the reported safety profile was consistent with known toxicities of daratumumab monotherapy and combination therapy of lenalidomide and dexamethasone.

Data from both the CASTOR study and the POLLUX study were published in *The New England Journal of Medicine* in August 2016, and October 2016, respectively.

**About multiple myeloma**

Multiple myeloma is an incurable blood cancer that starts in the bone marrow and is characterized by an excess proliferation of plasma cells.[1] Multiple myeloma is the third most common blood cancer in the U.S., after leukemia and lymphoma.[2] Approximately 30,330 new patients were expected to be diagnosed with multiple myeloma and approximately 12,650 people were expected to die from the disease in the U.S. in 2016.[3] Globally, it was estimated that 124,225 people would be diagnosed and 87,084 would die from the disease in 2015.[4] While some patients with multiple myeloma have no symptoms at all, most patients are diagnosed due to symptoms which can include bone problems, low blood counts, calcium elevation, kidney problems or infections.[5] Patients who relapse after treatment with standard therapies, including proteasome inhibitors or immunomodulatory agents, have poor prognoses and few treatment options.[6]

**About DARZALEX® (daratumumab)**

DARZALEX® (daratumumab) injection for intravenous infusion is indicated in the United States in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy and as a monotherapy for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent.[6] DARZALEX is the first monoclonal antibody (mAb) to receive U.S. Food and Drug Administration (FDA) approval to treat multiple myeloma. DARZALEX is indicated in

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Europe for use as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. For more information, visit www.DARZALEX.com.

Daratumumab is a human IgG1k monoclonal antibody (mAb) that binds with high affinity to the CD38 molecule, which is highly expressed on the surface of multiple myeloma cells. Daratumumab triggers a person's own immune system to attack the cancer cells, resulting in rapid tumor cell death through multiple immune-mediated mechanisms of action and through immunomodulatory effects, in addition to direct tumor cell death, via apoptosis (programmed cell death).[6,7,8,9,10]

Daratumumab is being developed by Janssen Biotech, Inc. under an exclusive worldwide license to develop, manufacture and commercialize daratumumab from Genmab. Five Phase III clinical studies with daratumumab in relapsed and frontline multiple myeloma settings are currently ongoing, and additional studies are ongoing or planned to assess its potential in other malignant and pre-malignant diseases on which CD38 is expressed, such as smoldering myeloma, non-Hodgkin's lymphoma, NKT-cell lymphoma, amyloidosis, myelodysplastic syndromes and solid tumors. Daratumumab has received two Breakthrough Therapy Designations from the U.S. FDA, for multiple myeloma, as both a monotherapy and in combination with other therapies.

**About Genmab**
Genmab is a publicly traded, international biotechnology company specializing in the creation and development of differentiated antibody therapeutics for the treatment of cancer. Founded in 1999, the company has two approved antibodies, DARZALEX® (daratumumab) for the treatment of certain multiple myeloma indications, and Arzerra® (ofatumumab) for the treatment of certain chronic lymphocytic leukemia indications. Daratumumab is in clinical development for additional multiple myeloma indications, other blood cancers, and solid tumors. A subcutaneous formulation of ofatumumab is in development for relapsing multiple sclerosis. Genmab also has a broad clinical and pre-clinical product pipeline. Genmab's technology base consists of validated and proprietary next generation antibody technologies - the DuoBody® platform for generation of bispecific antibodies, and the HexaBody® platform which creates effector function enhanced antibodies. The company intends to leverage these technologies to create opportunities for full or co-ownership of future products. Genmab has alliances with top tier pharmaceutical and biotechnology companies. For more information visit www.genmab.com.

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