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CHMP Grants Positive Opinion for DARZALEX®▼(daratumumab) Subcutaneous Formulation for the Treatment of Patients with Multiple Myeloma

- *New subcutaneous formulation reduces the time taken for patients to receive daratumumab treatment from hours to approximately three to five minutes, with similar efficacy and fewer infusion-related reactions compared to intravenous administration*[1,2]
- *If approved, daratumumab subcutaneous formulation will be the first monoclonal antibody approved in Europe for subcutaneous administration for patients with multiple myeloma*
- *Positive Opinion is based on data from the Phase 3 COLUMBA (MMY3012) and Phase 2 PLEIADES (MMY2040) studies*

BEERSE, BELGIUM, 30 April 2020 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a Positive Opinion recommending approval for DARZALEX®▼ (daratumumab) subcutaneous (SC) formulation for the treatment of adult patients with multiple myeloma in frontline and relapsed/refractory settings. The novel SC formulation of daratumumab is co-formulated with recombinant human hyaluronidase PH20 (rHuPH20) [Halozyme's *ENHANZE*® drug delivery technology] and reduces treatment time from hours to approximately three to five minutes, with similar efficacy, and fewer infusion-related reactions compared to intravenous (IV) administration.[1,2] The CHMP's Positive Opinion for daratumumab SC formulation applies to all current daratumumab indications including newly diagnosed and transplant-ineligible patients, as well as relapsed or refractory patients.

"Despite therapeutic advances in the treatment of multiple myeloma, the time taken for administration of most intravenous treatments is relatively long and there have been few significant improvements over the years," said Maria-Victoria Mateos, M.D., Ph.D., COLUMBA primary investigator and Director of the Myeloma Unit at University Hospital of Salamanca-IBSAL, Salamanca, Spain. "The daratumumab subcutaneous formulation has the potential to transform the treatment experience for patients and physicians as it reduces time in the chair from hours to minutes, and, because it is administered as a fixed dose from the first treatment, it reduces preparation time and chances of error by eliminating the need for dose calculations."

The Positive Opinion is supported by data from the Phase 3 COLUMBA (MMY3012) and Phase 2 PLEIADES (MMY2040) studies presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting and 62nd American Society of Hematology (ASH) Annual Meeting, respectively.[1,2] The COLUMBA presentation included a non-inferiority comparison of daratumumab SC formulation to daratumumab IV formulation for co-primary endpoints of overall response rate and maximum C_{trough} concentration.[1] Furthermore, in a subsequent paper published in *The Lancet Haematology*, patient-reported treatment satisfaction scores with daratumumab SC versus daratumumab IV were reported using the modified-Cancer Therapy Satisfaction Questionnaire.[3] The PLEIADES study evaluated the daratumumab SC formulation in different combination regimens in patients with newly diagnosed multiple myeloma or with relapsed/refractory disease.[2]

"The subcutaneous formulation of daratumumab showed similar efficacy and fewer infusion-related reactions compared to intravenous daratumumab, and, overall, patients expressed satisfaction with subcutaneous therapy. If approved, we are hopeful this new formulation could offer improved quality of life for patients with multiple myeloma," said Patrick Laroche, M.D., Haematology Therapy Area Lead, Europe, Middle East and Africa (EMEA), Janssen-Cilag. "Janssen is proud to have developed a new formulation to meet the needs of our patients and continue to make a meaningful difference to the lives of those living with multiple myeloma."

"Since its first European approval in 2016, intravenous daratumumab has been used in the treatment of more than 100,000 patients worldwide and, if approved, both new and existing patients with multiple myeloma will be able to start or switch to the subcutaneous formulation as part of their multiple myeloma daratumumab-based treatment regimens," adds Craig Tendler, M.D., Vice President, Clinical Development and Global Medical Affairs, Oncology at Janssen Research & Development, LLC. "Today's Positive Opinion represents

Janssen's commitment to continuing to improve the treatment experience for patients living with multiple myeloma."

#ENDS#

In Europe, daratumumab is indicated:[4]

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant
- 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
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy

About the COLUMBA Study (MMY3012)[3,5]

The randomised, open-label, multicentre Phase 3 study included 522 patients with multiple myeloma who had received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or whose disease was refractory to both a PI and an IMiD. In the arm that received the subcutaneously (SC) administered formulation of daratumumab (n=263), patients (median age of 65) received a fixed dose of daratumumab 1,800 milligrams (mg) co-formulated with recombinant human hyaluronidase PH20 (rHuPH20) 2,000 Units per millilitre (U/mL), SC weekly for cycles 1 – 2, every two weeks for cycles 3 – 6, and every four weeks for cycle 7 and thereafter. In the daratumumab IV arm (n=259), patients (median age of 67) received daratumumab for intravenous infusion 16 milligrams per kilogram (mg/kg) weekly for cycles 1 – 2, every two weeks for cycles 3 – 6, and every four weeks for cycle 7 and thereafter. Each cycle was 28 days. Patients in both treatment arms continued until disease progression or unacceptable toxicity. Co-primary endpoints were overall response rate (ORR) (non-inferiority = 60 percent retention of the lower bound [20·8%] of the 95% CI of the SIRIUS trial, with relative risk [RR] analysed by Farrington-Manning test) and pre-dose cycle 3, day 1 (C3D1) daratumumab C_{trough} (non-inferiority = lower bound of 90 percent confidence interval (CI) for the ratio of the geometric means [GM] ≥80%).

About the PLEIADES Study (MMY2040)[6]

The non-randomised, open-label, parallel assignment study Phase 2 PLEIADES trial included 240 adults either newly diagnosed or with relapsed or refractory multiple myeloma. Patients with newly diagnosed multiple myeloma were treated with 1,800 mg of the subcutaneous formulation in combination with either bortezomib, lenalidomide and dexamethasone (D-VRd) or bortezomib, melphalan and prednisone (D-VMP). Patients with relapsed or refractory disease were treated with 1,800 mg of the subcutaneous formulation plus lenalidomide and dexamethasone (D-Rd). The primary endpoint for the D-VMP and D-Rd cohorts was overall response rate. The primary endpoint for the D-VRd cohort was very good partial response or better rate. An additional cohort of patients with relapsed and refractory multiple myeloma treated with daratumumab plus carfilzomib and dexamethasone was subsequently added to the study.

About daratumumab

Daratumumab is a first-in-class[7] biologic targeting CD38, a surface protein that is highly expressed across multiple myeloma cells, regardless of disease stage.[8] Daratumumab is believed to induce tumour cell death through multiple immune-mediated mechanisms of action, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), as well as through apoptosis, in which a series of molecular steps in a cell lead to its death.[4] A subset of myeloid derived suppressor cells (CD38+ MDSCs), CD38+ regulatory T cells (Tregs) and CD38+ B cells (Bregs) were decreased by daratumumab.[4] Since launch, it is estimated that 100,000 patients have been treated with daratumumab worldwide.[9] Daratumumab is being evaluated in a comprehensive clinical development programme across a range of treatment settings in multiple myeloma, such as in frontline and relapsed settings.[10,11,12,13,14,15,16,17] Additional studies are ongoing or planned to assess its potential in other malignant and pre-malignant haematologic diseases in which CD38 is expressed, such as smouldering myeloma.[18,19] For more information, please see https://www.clinicaltrials.gov/.

For further information on daratumumab, please see the Summary of Product Characteristics at https://www.ema.europa.eu/en/medicines/human/EPAR/darzalex.
In August 2012, Janssen Biotech, Inc. and Genmab A/S entered a worldwide agreement, which granted Janssen an exclusive licence to develop, manufacture and commercialise daratumumab.[20]

About Multiple Myeloma

Multiple myeloma (MM) is an incurable blood cancer that starts in the bone marrow and is characterised by an excessive proliferation of plasma cells.[21] In Europe, more than 48,200

people were diagnosed with MM in 2018, and more than 30,800 patients died.[22] Almost 60 percent of patients with MM do not survive more than five years after diagnosis.[23]

Although treatment may result in remission, unfortunately, patients will most likely relapse as there is currently no cure.[24] Refractory MM is when a patient's disease progresses within 60 days of their last therapy.[25,26] Relapsed cancer is when the disease has returned after a period of initial, partial or complete remission.[27] While some patients with MM have no symptoms at all, most patients are diagnosed due to symptoms that can include bone problems, low blood counts, calcium elevation, kidney problems or infections.[28] Patients who relapse after treatment with standard therapies, including proteasome inhibitors and immunomodulatory agents, have poor prognoses and few treatment options available.[29]

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

Learn more at www.janssen.com/emea. Follow us at www.twitter.com/janssenEMEA for our latest news. Janssen-Cilag, Janssen Research & Development, LLC and Janssen Biotech, Inc. are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding the benefits of daratumumab for the treatment of patients with multiple myeloma. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialise, actual results could vary materially from the expectations and projections of Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behaviour and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 29, 2019, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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ENHANZE® is a registered trademark of Halozyme.

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