News Release

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Janssen Presents Updated Results Evaluating First-in-Class GPRC5D Bispecific Antibody Talquetamab in Heavily Pretreated Patients with Multiple Myeloma

Updated results for talquetamab monotherapy and in combination with daratumumab highlighted in oral presentations at the 2022 EHA Annual Congress

June 10, 2022 (VIENNA) – The Janssen Pharmaceutical Companies of Johnson & Johnson announced updated results from the Phase 1 MonumenTAL-1 first-in-human dose-escalation study of talquetamab (NCT03399799), an investigational, off-the-shelf, T cell redirecting bispecific antibody targeting both GPRC5D, a novel multiple myeloma target, and CD3 on T cells.[1] Results from the study showed encouraging responses in heavily pretreated patients with relapsed or refractory multiple myeloma (RRMM) who received talquetamab at the recommended subcutaneous Phase 2 dose (RP2D) administered weekly (QW) or every two weeks (Q2W).[2] These data will be featured during the 2022 European Hematology Association (EHA) Annual Congress as an oral presentation on Saturday, June 11 (Abstract S182)[2] and were recently presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting (Abstract #8015).[3]

No new safety signals were identified with longer follow-up of either dose cohort.[2] The most common adverse events (AEs) at the 405 µg/kg QW dose were cytokine release syndrome (CRS;

76.7 percent; 3.3 percent Grade 3/4), neutropenia (66.7 percent; 60 percent Grade 3/4), skin-related AEs (66.7 percent; all Grade 1/2), and dysgeusia (63.3 percent; all Grade 1/2).[2]

The most common AEs at the 800 µg/kg Q2W dose were CRS (79.5 percent; all Grade 1/2), skin-related AEs (72.7 percent; 2.3 percent Grade 3/4), and dysgeusia (56.8 percent).[2] Dysgeusia (altered sense of taste) was managed with supportive care and, if needed, dose adjustments.[2] Cytopenias were mostly confined to step-up doses and cycles one and two and generally resolved within one week.[2] Infections occurred in 46.7 percent (Grade 3/4, 6.7 percent) of patients at the 405 µg/kg QW dose and 38.6 percent (Grade: 3/4, 9.1 percent) at the 800 µg/kg Q2W dose [2]

Step-up dosing was used to mitigate against severe CRS, and pre-treatment medications (including steroids) were limited to the step-up and first full doses.[2]

"Patients with multiple myeloma who are heavily pretreated need new options," said Monique Minnema, M.D., Professor, Department of Hematology, University Medical Center, Utrecht, Netherlands, and principal study investigator.[†] "The continued deep and durable responses and tolerable safety profile seen in these longer-term data suggest that at both doses, talquetamab may offer a new treatment option for relapsed or refractory patients."

The overall response rate (ORR) to talquetamab treatment was consistent across both doses.[2] With a median follow-up of 13.2 months (range 1.1-24), 70 percent (21/30) of response-evaluable patients treated with the 405 µg/kg QW dose achieved a response, 56.7 percent achieved a very good partial response (VGPR) or better, 6.7 percent achieved a complete response (CR), and 23.3 percent achieved a stringent complete response (sCR). With a median follow-up of 7.7 months (range 0.7-16), 63.6 percent (28/44) of response-evaluable patients treated with the 800 µg/kg Q2W dose achieved a response, 56.8 percent achieved a VGPR or better, 11.4 percent achieved a CR, and 9.1 percent achieved an sCR. The median duration of response (DOR) was 10.2 months (95 percent Confidence Interval (CI): 3.0–not estimable) with the 405 µg/kg QW dose and 13.0 months (95 percent CI: 5.3–not estimable) with the 800 µg/kg QW dose.[2]

Among response-evaluable patients who were triple-class refractory, a response was achieved by 65.2 percent (15/23) of patients treated with the 405 µg/kg QW dose and 67.6 percent (23/34) of patients treated with the 800 µg/kg Q2W dose.[2] In patients who were penta-drug refractory, 83.3 percent (5/6) of patients treated with the 405 µg/kg QW dose and 75 percent (9/12) of patients treated with the 800 µg/kg Q2W dose achieved a response.[2]

"With additional follow-up, these data demonstrate potential durability of talquetamab responses," said Sen Zhuang, M.D., Ph.D., Vice President, Clinical Research and Development, Janssen Research & Development, LLC. "We look forward to fully understanding the potential of this bispecific for relapsed and refractory patients through ongoing clinical development."

The primary objectives of the MonumenTAL-1 study were to identify the recommended subcutaneous Phase 2 dose (part 1) and assess the safety and tolerability of talquetamab at the recommended dose (part 2).[2] As of April 6, 2022, 130 patients with multiple myeloma who had relapsed or were refractory or intolerant to established therapies have received talquetamab in the study.[2] For part 2, 30 patients received the weekly RP2D of 405 µg/kg QW dosing schedule following step-up doses; 100 percent were triple-class exposed, 80 percent were penta-drug exposed, 76.7 percent were triple-class refractory, 20 percent were penta-drug refractory, and 30 percent had prior B-cell maturation antigen (BCMA)-directed therapy.[2] Forty-four patients received the RP2D of 800 µg/kg Q2W; 97.7 percent were triple-class exposed; 68.2 percent were penta-drug exposed, 77.3 percent were triple-class refractory, 27.3 percent were penta-drug refractory, and 27.3 percent had prior BCMA-directed therapy.[2]

Updated data from the Phase 1b TRiMM-2 Study Evaluating Talquetamab in Combination with DARZALEX *FASPRO*® (Abstract S183)

Additional data for talquetamab will be featured in an oral presentation at EHA on Saturday, June 11 (Abstract S183).[4] The Phase 1b TRiMM-2 study (NCT04108195) evaluated talquetamab in combination with DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj), the CD38-directed monoclonal antibody approved to be given subcutaneously for the treatment of patients with multiple myeloma.[4] Results from the study show heavily pretreated patients with multiple myeloma treated with the combination, including talquetamab at the recommended subcutaneous Phase 2 dose (RP2D) administered weekly (QW) or every two weeks (Q2W), achieved high rates of responses, including for patients refractory to anti-CD38 treatment.[4]

Patients received step-up doses of talquetamab followed by 400 µg/kg QW treatment (n=14) or 800 µg/kg Q2W treatment (n=44), in combination with DARZALEX *FASPRO*® at the approved dosing schedule.[4] With a median follow-up of 5.1 months, the ORR was 80.4 percent (41/51) among all response-evaluable patients.[4] Of these patients, 62.7 percent (32/51) achieved a VGPR or better, and 29.4 percent (15/51) achieved a CR or better.[4] Among patients with prior exposure

to an anti-CD38 antibody, the ORR was 77.3 percent (34/44), and the ORR was 72 percent (18/25) among patients with prior BCMA-targeted treatment.[4]

No new safety signals were identified with longer follow-up of either dose cohort, and the safety profile for the combination was comparable to each agent as a monotherapy.[4] The most common nonhematologic adverse events (AEs) at the 405 µg/kg QW dose were cytokine release syndrome (CRS; 71.4 percent; all Grade 1/2), dysgeusia (71.4 percent; N/A) and dry mouth (71.4 percent; all Grade 1/2).[4] The most common AEs at the 800 µg/kg Q2W dose were CRS (77.3 percent; all Grade 1/2), dysgeusia (59.1 percent; N/A), and anemia (43.2 percent; 18.2 percent Grade 3/4). Skin-related and nail disorders were reported in 81 percent of patients.[4] Infections were experienced by 53.4 percent of patients (17.2 percent were Grade 3 or higher), and one patient died of pneumonia.[4]

The primary objectives of the TRiMM-2 study were to identify the recommended Phase 2 dose (RP2D) for each component of the treatment combination (Part 1); characterize the safety of the treatment combination at the RP2D (Part 2); and assess antitumor activity, pharmacokinetics and pharmacodynamics for the combination treatment (Part 3).[4] Patients in the study (n=58) had received a minimum three prior lines of therapy or were double refractory to a proteasome inhibitor (PI) and an immunomodulatory agent; patients who had been exposed or refractory to an anti-CD38 therapy more than 90 days prior to the start of the trial were also included, as well as those refractory to anti-CD38 therapy.[4]

About Talquetamab

Talquetamab is a first-in-class, investigational T-cell redirecting bispecific antibody targeting both GPRC5D, a novel multiple myeloma target that does not shed over time, and CD3, the T-cell receptor.[1] CD3 is involved in activating T-cells, and GPRC5D is highly expressed on multiple myeloma cells.[5,6] Results from preclinical studies in mouse models demonstrate that talquetamab induces T-cell-mediated killing of GPRC5D-expressing multiple myeloma cells through the recruitment and activation of CD3-positive T-cells and inhibits tumor formation and growth.[7]

About DARZALEX *FASPRO*®

In August 2012, Janssen Biotech, Inc. and Genmab A/S entered into a worldwide agreement, which granted Janssen an exclusive license to develop, manufacture and commercialize daratumumab. DARZALEX *FASPRO*® is the only CD38-directed antibody approved to be given subcutaneously to treat patients with multiple myeloma and now light chain (AL) amyloidosis. DARZALEX *FASPRO*® is

co-formulated with recombinant human hyaluronidase PH20 (rHuPH20), Halozyme's ENHANZE® drug delivery technology.

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- As monotherapy in patients 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

DARZALEX *FASPRO*® in combination with bortezomib, cyclophosphamide, and dexamethasone is indicated for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Limitations of Use

DARZALEX *FASPRO*® is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials.

Full prescribing information for DARZALEX *FASPRO*® is available here.

DARZALEX *FASPRO*® IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DARZALEX *FASPRO*® is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase, or any of the components of the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX *FASPRO*®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX *FASPRO*®.

Systemic Reactions

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX *FASPRO*® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX *FASPRO*® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX *FASPRO*®. Consider administering corticosteroids and other medications after the administration of DARZALEX *FASPRO*® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX *FASPRO*® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX *FASPRO*®*.*

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX *FASPRO*®. Monitor for local reactions and consider symptomatic management.

Cardiac Toxicity in Patients With AL Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with AL amyloidosis who received DARZALEX *FASPRO*® in combination with bortezomib, cyclophosphamide, and dexamethasone. Serious cardiac disorders occurred in 16% of patients, and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied. Monitor patients with cardiac involvement of AL amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia

Daratumumab may increase neutropenia induced by background therapy*.* Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX *FASPRO*® until recovery of neutrophils. In lower body weight patients receiving DARZALEX *FASPRO*®, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX *FASPRO*® until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX *FASPRO*® can cause fetal harm when administered to a pregnant woman. DARZALEX *FASPRO*® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX *FASPRO*® and for 3 months after the last dose.
The combination of DARZALEX *FASPRO*® with lenalidomide, thalidomide, or pomalidomide is contraindicated in pregnant women because lenalidomide, thalidomide, and pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide, or pomalidomide prescribing information on use during pregnancy.

Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.
Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX *FASPRO*®. Type and screen patients prior to starting DARZALEX *FASPRO*®.

Interference With Determination of Complete Response

Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some DARZALEX *FASPRO*®-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX *FASPRO*® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema.

The most common adverse reactions (≥20%) in patients with AL amyloidosis are upper respiratory tract infection, diarrhea, peripheral edema, constipation, fatigue, peripheral sensory neuropathy, nausea, insomnia, dyspnea, and cough.
The most common hematology laboratory abnormalities (≥40%) with DARZALEX *FASPRO*® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Please see full Prescribing Information for DARZALEX *FASPRO*®.

About Multiple Myeloma

Multiple myeloma is an incurable blood cancer that affects some white blood cells called plasma cells, which are found in the bone marrow.[8] When damaged, these plasma cells rapidly spread and replace normal cells in the bone marrow with tumors. In 2020, an estimated 176,000 people worldwide were diagnosed with multiple myeloma.[9] In 2022, it is estimated that more than 34,000 people will be diagnosed with multiple myeloma, and more than 12,000 people will die from the disease in the U.S.[10] While some people diagnosed with multiple myeloma initially have no symptoms, most patients are diagnosed due to symptoms that can include bone fracture or pain, low red blood cell counts, tiredness, high calcium levels, kidney problems or infections.[11]

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, & Retina; Immunology; Infectious Diseases & Vaccines; Neuroscience; Oncology; and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at @JanssenGlobal. Janssen Research & Development, LLC is part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

†Dr. Minnema has served as a consultant to Janssen; she has not been paid for any media work.

**Kyprolis is a registered trademark of Amgen Inc.*

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Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding product development and the potential benefits and treatment impact of teclistamab and *DARZALEX FASPRO®. 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 materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC or any of the other 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 behavior 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 January 2, 2022, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in Johnson & Johnson's subsequent Quarterly Reports on Form 10-Q and other 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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