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Merck KGaA, Darmstadt, Germany, Announces JAMA Publication of Phase II Results of Sprifermin for Osteoarthritis Structure Modification

- **Multi-year analysis indicates investigational sprifermin increased cartilage thickness in patients with knee osteoarthritis (OA), compared with placebo in the Phase II FORWARD trial**
- **Dose-dependent structural changes indicate potential of sprifermin to have a structure-modifying effect in OA**
- **Post-hoc, exploratory analysis of the FORWARD trial, to be featured as an oral presentation at the American College of Rheumatology (ACR) Annual Meeting, supports further investigation of sprifermin as a potential disease-modifying OA treatment in a targeted at-risk patient population**
- **There are currently no approved OA therapies for preventing or slowing disease progression**

Darmstadt, Germany, October 8, 2019 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced that results from FORWARD, a five-year, multicenter Phase II study of sprifermin, a recombinant human fibroblast growth factor-18, in patients with symptomatic radiographic knee osteoarthritis (OA) were published online in the *Journal of the American Medical Association* (JAMA). Published results, based on the two-year primary outcome and the three-year follow-up analysis from the trial, show statistically significant, dose-dependent increases in total femorotibial joint cartilage thickness compared to both baseline and placebo comparator.

"The publication of these clinical data assessing therapeutic intervention for osteoarthritis in the *Journal of the American Medical Association* and at the upcoming American College of Rheumatology Annual Meeting are noteworthy," said Luciano Rossetti, Global Head of Research & Development at the Biopharma

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business of Merck KGaA, Darmstadt, Germany. "This represents an area of significant medical need as osteoarthritis is a degenerative condition with no approved treatment options that directly target structural disease progression."

In this study of 549 patients, the primary endpoint, defined as the change in total femorotibial joint cartilage thickness from baseline at two years with sprifermin compared to placebo as measured by quantitative magnetic resonance imaging (MRI), was met. At the two-year treatment point, a mean increase in cartilage thickness was observed in the two sprifermin groups receiving the highest doses compared with the placebo group. For the groups receiving 100µg sprifermin, administered as an intra-articular injection every six months or every 12 months, the total difference in cartilage thickness was statistically significant at +0.05 mm (95% CI: 0.03-0.07) and at +0.04 mm (95% CI 0.03-0.07) respectively, compared to placebo. Two-year changes in cartilage thickness with sprifermin at a dose of 30µg every six months or every 12 months showed no significant differences versus placebo. In the three-year follow-up analysis, the statistically significant difference (+0.05 mm) in cartilage thickness, observed between sprifermin and placebo for patients who received 100µg of sprifermin every six months, was maintained.

Secondary endpoints evaluated in the trial included changes in cartilage thickness as measured by MRI in the medial and lateral compartments, as well as changes in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) core over two years. Total WOMAC scores decreased (indicating reduced symptoms) by approximately 50% compared to baseline in all treatment groups, including placebo. Statistically significant treatment effects of increased cartilage thickness were observed in the medial and lateral femorotibial compartments, including the central medial and central lateral regions, in the highest sprifermin dose group. Consistent increases in cartilage volume were observed over two years.

Adverse events were reported in more than 90% of participants across all treatment groups but were mostly mild or moderately severe and considered unrelated to treatment by the site investigators. The most frequent treatment emergent adverse events were musculoskeletal and connective tissue disorders (arthralgia, back pain), infections and infestations (upper respiratory infection, nasopharyngitis), vascular disorders (hypertension), and nervous system disorders (headache).

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Additionally, a post-hoc, exploratory analysis from the Phase II FORWARD trial that will be featured as an oral presentation at the upcoming 2019 American College of Rheumatology (ACR) Annual Meeting on Tuesday, November 12, 2019 evaluated cartilage thickness changes and symptomatic outcomes in a subgroup of OA patients with both greater pain and thinner cartilage, as measured by joint space width, at baseline who are at higher risk of further structural and symptomatic progression. In this 'at risk' subgroup, WOMAC score improvements increased over the three-year period and were significant at Year 3 (18 months after last injection) in favor of sprifermin compared to placebo (mean difference in WOMAC pain score for sprifermin 100µg every six months versus placebo: -8.75 [95% CI -22.42, 4.92]). These results support further investigation of sprifermin as a potential OA treatment for higher risk patient populations.

Merck KGaA, Darmstadt, Germany, is evaluating external partnership opportunities for its OA portfolio, including sprifermin, with the goal of finding the right partner to advance the development of structurally modifying treatments to change the course of OA. By pursuing alternative paths to internally driven development, Merck KGaA, Darmstadt, Germany, plans to further focus its efforts in inflammatory neurology and immunology (N&I) diseases with potentially overlapping inflammatory mechanisms like multiple sclerosis (MS) and systemic lupus erythematosus (SLE).

There are approximately 237 million people worldwide living with symptomatic and activity-limiting OA[1], the third most rapidly rising condition associated with disability globally.[2] OA most commonly affects the knee joints.[3] Symptomatic knee OA is associated with physical disability, reduced quality of life, and increased mortality in older adults.[3,4] Currently, OA therapies primarily target symptoms and there are no approved structure-modifying OA treatments for preventing or slowing disease progression.

About Sprifermin
Sprifermin is in clinical development to investigate its potential as a treatment for OA in the knee. It is a truncated recombinant human FGF-18 protein thought to induce chondrocyte proliferation and increased extra-cellular matrix (ECM) production, with the potential of promoting cartilage growth and repair. Sprifermin is currently in Phase II studies.

About FORWARD trial
FORWARD (FGF-18 Osteoarthritis Randomized Trial with Administration of Repeated Doses) was a five-year, multicentre, dose-finding, randomized Phase II study of sprifermin administered intra-articularly

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in patients with knee osteoarthritis (OA) conducted across 10 sites. Eligible participants were aged 40–85 years with symptomatic radiographic knee osteoarthritis and Kellgren-Lawrence grade 2 or 3. Enrolment began July 2013 and ended May 2014; last participant visit for the data reported here was May 2017. The primary outcome at two years and a follow-up analysis at three years are reported.

About Osteoarthritis
There are approximately 237 million people worldwide living with symptomatic and activity-limiting OA[1], the third most rapidly rising condition associated with disability globally. By the end stage of the disease, total knee replacement is often necessary. OA is likely to be the number one cause of total hip and knee replacement in the US. Currently there are no approved drugs for preventing or slowing disease progression.

References

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Merck KGaA, Darmstadt, Germany in Neurology and Immunology
Merck KGaA, Darmstadt, Germany has a long-standing legacy in neurology and immunology, with significant R&D and commercial experience in multiple sclerosis (MS). The company`s current MS portfolio includes two products for the treatment of relapsing MS, with a robust pipeline focusing on discovering new therapies that have the potential to modulate key pathogenic mechanisms in MS. Merck KGaA, Darmstadt, Germany aims to improve the lives of those living with MS, by addressing areas of unmet medical needs.

The company`s robust immunology pipeline focuses on discovering new therapies that have the potential to modulate key pathogenic mechanisms in chronic diseases such as MS, systemic lupus erythematosus (SLE) and forms of arthritis, including rheumatoid arthritis (RA) and osteoarthritis (OA).

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About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany is a leading science and technology company in healthcare, life science and performance materials. Around 56,000 employees work to further develop technologies that improve and enhance life – from biopharmaceutical therapies to treat cancer or multiple sclerosis, cutting-edge systems for scientific research and production, to liquid crystals for smartphones and LCD televisions. In 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 billion in 66 countries.

Scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. This is how Merck KGaA, Darmstadt, Germany has thrived since its founding in 1668. The founding family remains the majority owner of the publicly listed company. Merck KGaA, Darmstadt, Germany holds the global rights to the Merck name and brand. The only exceptions are the United States and Canada, where the business sectors of Merck KGaA, Darmstadt, Germany operate as EMD Serono in healthcare, MilliporeSigma in life science, and EMD Performance Materials.