European Commission Grants Conditional Approval of EZMEKLY® (mirdametinib) for the Treatment of Adult and Pediatric Patients with NF1-PN

– EZMEKLY is the first and only therapy to receive marketing authorization in the EU for both adults and children (≥2 years) with NF1-PN, a rare genetic disorder with debilitating symptoms –

STAMFORD, Conn., July 18, 2025 – SpringWorks Therapeutics, Inc., a healthcare company of Merck KGaA, Darmstadt, Germany, announced today that the European Commission (EC) granted conditional marketing authorization for EZMEKLY® (mirdametinib) for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in pediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above. EZMEKLY is the first and only therapy approved in the European Union (EU) for both adults and children with NF1-PN.

"Patients with NF1-PN often face physical and mental health challenges and impaired quality of life given the limited treatment options available for this lifelong and debilitating disease," said Ignacio Blanco, MD, PhD, Chairman of the National Reference Center for Adult Patients with Neurofibromatosis at Hospital Universitari Germans Trias i Pujol, Spain. "This approval represents an important advance, especially for adults who previously did not have an approved treatment. In clinical trials, EZMEKLY demonstrated an encouraging efficacy and safety profile in both adults and children, and importantly, is available in a tablet that dissolves easily in water for people who are unable to swallow a pill and could therefore not previously receive therapy."

"This European Commission approval is an important milestone for NF patients and caregivers, as it means more treatment options for patients with plexiform neurofibromas, including adults," said Annette Bakker, PhD, Chief Executive Officer of the Children's Tumor Foundation (CTF) and Dariusz Adamczewski, MD, Director CTF Europe. "This is the kind of progress that happens when researchers, industry and organizations like ours work together with a shared focus on delivering new treatments for patients."

NF1 is a genetic disorder that affects approximately 3 in 10,000 people in the EU, or an estimated 135,000 people.[1,2] Among patients with NF1, the lifetime risk of developing plexiform neurofibromas is approximately 30% to 50%. These tumors grow in an infiltrative pattern along the peripheral nerve sheath and can cause severe disfigurement, pain and functional impairment.[3,4] Plexiform neurofibromas can transform into malignant peripheral nerve sheath tumors, an aggressive and potentially fatal disease.[5] Surgical removal can be challenging due to the infiltrative tumor growth pattern of plexiform neurofibromas along nerves, and up to approximately 85% of plexiform neurofibromas are considered not amenable to complete resection.[6,7,8]

"Bringing innovation to patients living with rare tumors around the world is a clear reflection of our focus on addressing significant unmet needs and transforming outcomes for patients and their families," said Jan Kirsten, Global Head of Rare Tumor Business. "With the European approval of EZMEKLY, the first therapy approved for both adults and children with NF1-PN, we are taking a major step toward improving care for this underserved community and are committed to making our medicine available to eligible NF1-PN patients across Europe as quickly as possible."

The EC approval of EZMEKLY is based on results from the ongoing, multi-center, open-label, single arm Phase 2b ReNeu trial, which enrolled 114 patients with NF1-PN age 2 years or older (58 adults and 56 pediatric patients). The study met the primary endpoint of confirmed objective response rate (ORR), as assessed by blinded independent central review, demonstrating an ORR of 41% (N= 24/58) in adults and 52% in children (N=29/56). The median best percentage change in target PN volume was -41% (range: -90 to 13%) in adults and -42% (range: -91 to 48%) in children. Among those with a confirmed response, 88% percent of adults and 90% of children had a response of at least 12 months duration, and 50% and 48%, respectively, had a response of at least 24 months duration. Both adults and children also experienced early and sustained significant improvements from baseline in pain and quality of life as assessed across multiple patient-reported outcome tools.[9]

EZMEKLY demonstrated a manageable safety and tolerability profile. The most common adverse reactions reported in adults receiving EZMEKLY were dermatitis acneiform (83%), diarrhea (55%), nausea (55%), blood creatine phosphokinase increased (47%), musculoskeletal pain (41%), vomiting (37%) and fatigue (36%). The most common adverse reactions occurring in children were blood creatine phosphokinase increased (59%), diarrhea (53%), dermatitis acneiform (43%), musculoskeletal pain (41%), abdominal pain (40%), vomiting (40%), and headache (36%).[9]

EZMEKLY is available in 1 and 2 mg capsules and in a 1 mg dispersible tablet, which dissolves easily in water.

About the ReNeu Trial

ReNeu (NCT03962543) is an ongoing, multi-center, open-label, single arm, Phase 2b trial evaluating the efficacy, safety and tolerability of mirdametinib in patients ≥2 years of age with an inoperable NF1-associated PN causing significant morbidity. The study enrolled 114 patients to receive mirdametinib at a dose of 2 mg/m^2 twice daily (maximum dose of 4 mg twice daily) without regard to food. Mirdametinib was administered orally in a 3-week on, 1-week off dosing schedule as either a capsule or dispersible tablet. The primary endpoint is confirmed objective response rate (ORR) defined as the proportion of patients with a ≥20% reduction in target tumor volume on consecutive scans during the 24-cycle treatment phase, as measured by MRI and assessed by blinded independent central review. Secondary endpoints include safety and tolerability, duration of response, and changes in patient-reported outcomes from baseline to Cycle 13. The treatment phase of the trial is complete, and results were presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting. Patients who completed the treatment phase were eligible to continue receiving treatment in the optional long-term follow-up portion of the study, which is ongoing.

About NF1-PN

Neurofibromatosis type 1 (NF1) is a rare genetic disorder that arises from mutations in the NF1 gene, which encodes for neurofibromin, a key suppressor of the MAPK pathway.[10,11] NF1 is the most common form of neurofibromatosis, with an estimated global birth incidence of approximately 1 in 2,500 individuals.[3,12] In the EU, NF1 affects approximately 3 in 10,000 people, or an estimated 135,000 people.[1,2] The clinical course of NF1 is heterogeneous and manifests in a variety of symptoms across numerous organ systems, including abnormal pigmentation, skeletal deformities, tumor growth and neurological complications, such as

cognitive impairment.[13] Patients with NF1 have an 8 to 15-year mean reduction in their life expectancy compared to the general population.[1]

Patients with NF have approximately a 30% to 50% lifetime risk of developing plexiform neurofibromas, or PN, which are tumors that grow in an infiltrative pattern along the peripheral nerve sheath and that can cause severe disfigurement, pain and functional impairment; in rare cases, NF1-PN may be fatal.[3,4,5] NF1-PNs are most often diagnosed in the first two decades of life.[3] These tumors can be aggressive and are associated with clinically significant morbidities; typically, they grow more rapidly during childhood.[14,15]

Surgical removal of these tumors can be challenging due to the infiltrative tumor growth pattern along nerves and can lead to permanent nerve damage and disfigurement.[5] Up to approximately 85% of plexiform neurofibromas are considered not amenable to complete resection.[6,7,8]

About GOMEKLI®/ EZMEKLY® (mirdametinib)

GOMEKLI® (mirdametinib) is an oral, small molecule MEK inhibitor approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) not amenable to complete resection.

Mirdametinib is marketed under the brand name EZMEKLY® in the European Union and is conditionally approved by the European Commission (EC) for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in pediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above.

The FDA and the EC have granted Orphan Drug designation for mirdametinib for the treatment of NF1.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Ocular Toxicity: GOMEKLI can cause ocular toxicity including retinal vein occlusion (RVO), retinal pigment epithelium detachment (RPED), and blurred vision. In the adult pooled safety population, ocular toxicity occurred in 28% of patients treated with GOMEKLI: 21% were Grade 1, 5% were Grade 2 and 1.3% were Grade 3. RVO occurred in 2.7%, RPED occurred in 1.3%, and blurred vision occurred in 9% of adult patients. In the pediatric pooled safety population, ocular toxicity occurred in 19% of patients: 17% were Grade 1 and 1.7% were Grade 2. Conduct comprehensive ophthalmic assessments prior to initiating GOMEKLI, at regular intervals during treatment, and to evaluate any new or worsening visual changes such as blurred vision. Continue, withhold, reduce the dose, or permanently discontinue GOMEKLI as clinically indicated.

Left Ventricular Dysfunction: GOMEKLI can cause left ventricular dysfunction. GOMEKLI has not been studied in patients with a history of clinically significant cardiac disease or LVEF <55% prior to initiation of treatment. In the ReNeu study, decreased LVEF of 10 to <20% occurred in 16% of adult patients treated with GOMEKLI. Five patients (9%) required dose interruption, one patient (1.7%) required a dose reduction, and one patient required permanent discontinuation of

GOMEKLI. The median time to first onset of decreased LVEF in adult patients was 70 days. Decreased LVEF of 10 to <20% occurred in 25%, and decreased LVEF of ≥20% occurred in 1.8% of pediatric patients treated with GOMEKLI. One patient (1.8%) required dose interruption of GOMEKLI. The median time to first onset of decreased LVEF in pediatric patients was 132 days. All patients with decreased LVEF were identified during routine echocardiography, and decreased LVEF resolved in 75% of patients. Before initiating GOMEKLI, assess ejection fraction (EF) by echocardiogram. Monitor EF every 3 months during the first year and then as clinically indicated. Withhold, reduce the dose, or permanently discontinue GOMEKLI based on severity of adverse reaction.

Dermatologic Adverse Reactions: GOMEKLI can cause dermatologic adverse reactions including rash. The most frequent rashes included dermatitis acneiform, rash, eczema, maculo-papular rash and pustular rash. In the pooled adult safety population, rash occurred in 92% of patients treated with GOMEKLI and required permanent discontinuation in 11% of adult patients. In the pooled pediatric safety population, rash occurred in 72% of patients treated with GOMEKLI and resulted in permanent discontinuation of GOMEKLI in 3.4% of patients. Initiate supportive care at first signs of dermatologic adverse reactions. Withhold, reduce the dose, or permanently discontinue GOMEKLI based on severity of adverse reaction.

Embryo-Fetal Toxicity: GOMEKLI can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to the initiation of GOMEKLI. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Also advise patients to use effective contraception during treatment with GOMEKLI and for 6 weeks after the last dose (females) or 3 months after the last dose (males).

ADVERSE REACTIONS

The most common adverse reactions (>25%) in adult patients were rash (90%), diarrhea (59%), nausea (52%), musculoskeletal pain (41%), vomiting (38%), and fatigue (29%). Serious adverse reactions occurred in 17% of adult patients who received GOMEKLI. The most common Grade 3 or 4 laboratory abnormality (>2%) was increased creatine phosphokinase.
The most common adverse reactions (>25%) in pediatric patients were rash (73%), diarrhea (55%), musculoskeletal pain (41%), abdominal pain (39%), vomiting (39%), headache (34%), paronychia (32%), left ventricular dysfunction (27%), and nausea (27%). Serious adverse reactions occurred in 14% of pediatric patients who received GOMEKLI. The most common Grade 3 or 4 laboratory abnormalities (>2%) were decreased neutrophil count and increased creatine phosphokinase.

USE IN SPECIFIC POPULATIONS

Pregnancy & Lactation. Verify the pregnancy status of patients of reproductive potential prior to initiating GOMEKLI. Due to the potential for adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with GOMEKLI and for 1 week after the last dose.
You are encouraged to report negative side effects of prescription drugs to the FDA. To report suspected adverse reactions, contact SpringWorks Therapeutics at 1-888-400-SWTX (1-888-400-7989) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information for more information.

About SpringWorks Therapeutics

SpringWorks Therapeutics, a healthcare company of Merck KGaA, Darmstadt, Germany, is a commercial-stage biopharmaceutical company dedicated to improving the lives of patients with rare tumors. We developed and are commercializing the first and only FDA-approved medicine for adults with desmoid tumors and the first and only approved medicine for both adults and children with neurofibromatosis type 1 associated plexiform neurofibromas (NF1-PN). We are also advancing a portfolio of novel targeted therapy product candidates for patients with additional rare tumors and hematological cancers.

For more information, visit www.springworkstx.com and follow @SpringWorksTx on X, LinkedIn, Facebook, Instagram and YouTube.

About Merck KGaA, Darmstadt, Germany

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across life science, healthcare and electronics. More than 62,000 employees work to make a positive difference to millions of people's lives every day by creating more joyful and sustainable ways to live. From providing products and services that accelerate drug development and manufacturing as well as discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices – the company is everywhere. In 2024, Merck KGaA, Darmstadt, Germany, generated sales of € 21.2 billion in 65 countries.

The company holds the global rights to the name and trademark "Merck" internationally. The only exceptions are the United States and Canada, where the business sectors of Merck KGaA, Darmstadt, Germany, operate as MilliporeSigma in life science, EMD Serono in healthcare and EMD Electronics in electronics. Since its founding in 1668, scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. To this day, the founding family remains the majority owner of the publicly listed company.

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