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News Release

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Merck KGaA, Darmstadt, Germany, Announces Positive Outcome of IIIb Study for Kuvan

- **Primary endpoint met in SPARK study: significant increase in phenylalanine tolerance demonstrated after 26 weeks of the study in children less than 4 years of age with phenylketonuria and responsive to Kuvan treated with Kuvan plus a phenylalanine-restricted diet, versus diet alone**
- **SPARK study was conducted as a post-authorization measure and results will be submitted to EMA this year**

Darmstadt, Germany, April 24 – Merck KGaA, Darmstadt, Germany, a leading company for innovative and top-quality high-tech products in the pharmaceutical and chemical sectors, announced today that the Phase IIIb SPARK* study has met its primary endpoint. The results of the first 26 weeks of this study demonstrated that the addition of Kuvan® (sapropterin dihydrochloride) to a phenylalanine-restricted diet in children less than 4 years of age who have phenylketonuria (PKU) and have been previously shown to be responsive to Kuvan significantly increased tolerance to phenylalanine compared with a phenylalanine-restricted diet alone. The safety profile of Kuvan in this population was consistent with the safety profile for Kuvan described in the European Summary of Product Characteristics. The 26-week results will be submitted for presentation at upcoming international scientific meetings and for publication in a peer-reviewed journal. SPARK was requested by the European Medicines Agency (EMA) as a post-authorization measure and demonstrates the company's commitment to addressing areas of high unmet medical need. The positive

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outcome of the study will enable the submission of a regulatory application for a label extension later this year.

Dr John Orloff, Global Head of Clinical Development at the company's biopharmaceutical division, underlined the company's commitment to better management of PKU for all those affected by it: "PKU is a serious rare disease that has a significant impact on patients and their families. We are delighted by the positive outcome of this study, and remain dedicated to further improving our understanding of PKU in infants and young children."

PKU is an inborn metabolic disorder that causes the toxic accumulation of phenylalanine, an essential amino acid found in all protein-containing foods, in the brain and blood.[1,2] Untreated, PKU can lead to intellectual disability, seizures and other serious medical problems.[1,2] In many countries, implementation of national newborn screening programs has allowed identification of children with PKU at birth, enabling the management of the disease to begin as early as possible in order to avoid potentially severe neurological damage.[3]

"This is the first time a controlled study such as this has been conducted in children below 4 years of age with PKU" said Professor Ania Muntau, Klinikum University Munich, Germany, and lead investigator for SPARK. "These study findings with Kuvan in addition to phenylalanine-restricted diet could lead to a new disease management approach to control blood phenylalanine levels right from birth."

SPARK is a Phase IIIb, multicenter, open-label, randomized, controlled study designed to assess the efficacy, safety, and population pharmacokinetics of Kuvan in patients younger than 4 years old with PKU and who have been previously shown to be responsive to Kuvan in a response test. The study was conducted under a Pediatric Investigational Plan. Patients were randomized to Kuvan (10 mg/kg/day) plus a phenylalanine-restricted diet, or to a phenylalanine-restricted diet alone, for 26 weeks, and the primary endpoint of the study was to compare phenylalanine tolerance achieved in both arms after 26 weeks of treatment. Secondary study endpoints included change in levels of blood phenylalanine during the study period, change in dietary phenylalanine tolerance over time (from

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baseline to 26 weeks) in both groups, as well as assessment of neurodevelopmental function, growth parameters and safety. The long-term efficacy and safety of Kuvan will be assessed in the study's 3-year extension period, in which all patients will be offered to receive Kuvan in addition to the phenylalanine-restricted diet.

European marketing authorization was granted for Kuvan in 2008. Kuvan was the first, and remains the only, medication in combination with dietary modifications in Europe designed to reduce the concentration of phenylalanine in the blood and in the brain in those patients who are responsive to Kuvan to prevent the debilitating effects of PKU.[4] Kuvan is indicated in patients of all ages with tetrahydrobiopterin (BH4) deficiency, and in those aged 4 years and above with PKU (due phenylalanine hydroxylase enzyme deficiency) who are responsive to Kuvan. Currently, there is no licensed medication in Europe for the treatment of PKU in the 0–4 years age group. Kuvan is marketed by the biopharmaceutical division of Merck KGaA, Darmstadt, Germany, outside the USA, Canada and Japan, by BioMarin in the USA and Canada, and under the name Biopten® by Asubio Pharma in Japan. In the USA and Europe, Kuvan received orphan drug designation.

*SPARK: **S**afety **P**ediatric Effic**A**cy Pha**R**macokinetic with **K**uvan (sapropterin dihydrochloride)

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About phenylketonuria (PKU)

PKU is an autosomal recessive genetic disorder caused by a defect or a deficiency of the enzyme phenylalanine hydroxylase (PAH). PAH is required for the metabolism of phenylalanine (Phe), an essential amino acid found in all protein-containing foods. It affects approximately 1/10,000 newborns in Europe and 1/15,000 in the US. If PKU patients are not treated with a Phe-restricted diet, Phe will accumulate in the blood and brain to abnormally high levels, thereby resulting in a variety of complications including clinically significant mental retardation and brain damage, mental illness, seizures and tremors, and cognitive problems. Universal systematic newborn screening programs were developed in the 1960s and early 1970s to enable diagnosis of all patients with PKU patients at birth.

About tetrahydrobiopterin (BH4) deficiency

BH4 deficiency is a very rare inborn error of metabolism, and is estimated to account for 1–2 % of cases of hyperphenylalaninemia (HPA). BH4 deficiency is an autosomal recessive genetic condition and can result from deficiencies of any of the five different enzymes involved in BH4 synthesis and regeneration. BH4 is a necessary co-factor for PAH. Therefore, BH4 deficiency impairs PAH activity leading to a biochemical situation similar to PKU, with HPA resulting from deficient conversion of Phe to tyrosine. In addition, since BH4 is also a necessary co-factor for both tyrosine hydroxylase and tryptophan hydroxylase, BH4 deficiency causes deficiencies in the downstream neurotransmitter products of these amino acids including catecholamines and

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serotonin. Dietary limitation of whole protein or Phe intake is often not necessary with BH4 treatment. However, since BH4 does not cross the blood brain barrier, concomitant therapy with neurotransmitter precursors, i.e. levodopa and 5-hydroxytryptophan, may be necessary to boost central nervous system substrate levels for catecholamine and serotonin synthesis, respectively.

About Kuvan

Kuvan® (sapropterin dihydrochloride) is an oral therapy and the first treatment indicated in Europe in conjuction with a Phe-restricted diet, for the treatment of hyperphenylalaninemia (HPA) due to phenylketonuria (PKU) in patients from the age of 4 who have shown to be responsive to Kuvan, or due to tetrahydrobiopterin (BH4) deficiency. Kuvan was developed jointly by BioMarin Pharmaceutical Inc. and Merck KGaA, Darmstadt, Germany, biopharmaceutical division. In the US, Kuvan is marketed by BioMarin and is indicated for the treatment of HPA due to PKU without age restriction. The current label states that safety and efficacy of Kuvan in pediatric patients less than 4 years of age have not been established in clinical studies. Kuvan is to be used in conjunction with a Phe-restricted diet.

Kuvan is the synthetic form of 6R-BH4, a naturally occurring co-factor that works in conjunction with the enzyme phenylalanine hydroxylase (PAH) to metabolize phenylalanine (Phe) into tyrosine. Clinical data show that Kuvan produces significant reductions in blood Phe concentration in a large subset of patients.

Most common side effects reported with the use of Kuvan include headache, runny nose, diarrhea, vomiting, sore throat, cough, abdominal pain, stuffy nose and low levels of phenylalanine in the blood.

Kuvan is approved in 49 countries worldwide, including member states of the European Union and the USA. Under the terms of the agreement with BioMarin, Merck KGaA, Darmstadt, Germany, biopharmaceutical division has exclusive rights to market Kuvan in all territories outside the USA, Canada and Japan.

About Merck KGaA, Darmstadt, Germany

Merck KGaA of Darmstadt, Germany, is a leading company for innovative and top-quality high-tech products in the pharmaceutical and chemical sectors. Its subsidiaries in Canada and the United States operate under the umbrella brand EMD. Around 38,000 employees work in 66 countries to improve the quality of life for patients, to further the success of customers and to help meet global challenges. The company generated total revenues of € 11.1 billion in 2013 with its four divisions: Biopharmaceuticals, Consumer Health, Performance Materials and Life Science Tools. Merck KGaA of Darmstadt, Germany, is the world's oldest pharmaceutical and chemical company – since 1668, the name has stood for innovation, business success and responsible entrepreneurship. Holding an approximately 70 percent interest, the founding family remains the majority owner of the company to this day.