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News Release

Not intended for U.S. and UK Media

Vitrakvi® (larotrectinib) receives first tumor-agnostic approval in EU

- Precision oncology treatment Vitrakvi® (larotrectinib) approved for the treatment of adults and children with locally advanced or metastatic solid tumors that have a rare genomic alteration called an *NTRK* gene fusion
- Vitrakvi, which was exclusively designed to treat TRK fusion cancer, is the first therapy in the EU with a tumor-agnostic indication
- Larotrectinib provides high response rates and durable responses in adults and children with TRK fusion cancer, including primary CNS tumors and brain metastases
- In studies, larotrectinib demonstrated an overall response rate of 72% including 16% complete responses, with 75% of patients still on treatment after one year
- Larotrectinib showed a favorable safety profile, with the majority of adverse events (AEs) being grade 1 or 2; only 3% of patients had to stop therapy due to treatment-emergent AEs

Berlin, September 23, 2019 – Bayer today announced that the European Commission has granted marketing authorization in the European Union (EU) for the precision oncology treatment Vitrakvi® (larotrectinib). The drug is indicated for the treatment of adult and pediatric patients with solid tumors that display a Neurotrophic Tyrosine Receptor Kinase (*NTRK*) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options. Vitrakvi, a first-in-class oral TRK inhibitor exclusively designed to treat tumors that have an *NTRK* gene fusion, is the first treatment in the EU to receive a tumor-agnostic indication. Vitrakvi has demonstrated high response rates and durable responses in adults and children with TRK fusion cancer, including central nervous system (CNS) tumors. It is already approved in the U.S., Brazil and Canada.

“With this first-ever tumor-agnostic approval in the EU, physicians in Europe now have the option to replace less tailored treatment approaches with a precision oncology treatment

exclusively designed to treat tumors that have an *NTRK* gene fusion – a rare cancer which affects both children and adults and occurs in varying frequencies across various tumor types," said Prof. Jesus Garcia-Foncillas, Director of the University Cancer Institute and the Department of Oncology at the University Hospital "Fundacion Jimenez Diaz" and Professor of Oncology at the Autonomous University of Madrid, Director of the Translational Oncology Division at the Health Research Institute FJD-UAM and Coordinator of the Comprehensive Cancer Program of four University Hospitals in Madrid. "Existing therapies commonly used to treat TRK fusion cancer patients such as chemotherapy or immuno-oncology therapies have shown limited efficacy, and may have significant side effects. With Vitrakvi, we have seen rapid, robust and durable responses with a consistent and manageable safety profile in patients with TRK fusion cancer, regardless of the age of the patient or where in the body the tumor is located."

The EMA approval of larotrectinib is based on pooled clinical trial data of 102 patients (93 patients from the primary analysis population and an additional 9 patients with primary CNS tumors) across the Phase I trial of adult patients, the Phase II NAVIGATE trial in adult and adolescent patients and the Phase I/II pediatric SCOUT trial. Results in the primary analysis population (n=93) demonstrate an overall response rate (ORR) of 72% (95% CI: 62, 81) including 16% complete responses (CR) and 55% partial responses (PR). In an additional analysis including primary CNS patients, the ORR was 67% (95% CI: 57, 76) including 15% CR, and 51% PR. In the pooled analysis set (n=102), neither the median duration of response nor median progression free survival had been reached at time of analysis. Responses ranged from 1.6+ to 38.7+ months and 75% of responding patients had a duration of response of 12 months or longer. At one year after the start of therapy, 88% (95% CI: 81, 95) of patients from the primary analysis population (n=93) were still alive. The safety of larotrectinib was evaluated in 125 patients with an *NTRK* gene fusion. Larotrectinib showed a favorable safety profile, with the majority of adverse events (AEs) being grade 1 or 2. Only 3% of patients had to stop therapy due to treatment-emergent AEs.

TRK fusion cancer is rare overall, affecting no more than a few thousand patients across Europe annually. It affects both children and adults and occurs in varying frequencies across various tumor types. TRK fusion cancer occurs when an *NTRK* gene fuses with another unrelated gene, producing an altered TRK protein. The altered protein, or TRK fusion protein, becomes constitutively active or overexpressed, triggering a signaling cascade. These TRK fusion proteins act as oncogenic drivers that fuel the spread and

growth of the patients' cancer, regardless of where it originates in the body. Larotrectinib, an oral, highly selective TRK inhibitor, was investigated in clinical trials across 29 different histologies of solid tumors including lung, thyroid, melanoma, gastrointestinal stromal tumors, colon, soft tissue sarcomas, salivary gland and infantile fibrosarcoma. The compound has shown efficacy in primary CNS tumors as well as patients with brain metastases, across age or tumor histology.

"The approval of Vitrakvi® in the EU, a first-of-its-kind treatment exclusively designed for adults and children with TRK fusion cancer, represents a meaningful advancement in the fight against cancer, as it treats the oncogenic driver that causes tumor spread and growth, rather than where the tumor originates in the body," said Robert LaCaze, Member of the Executive Committee of Bayer's Pharmaceuticals Division and Head of the Oncology Strategic Business Unit. "Cancer care is currently undergoing a paradigm shift and as this new era of precision oncology treatment unfolds, we are continuing our effort of delivering innovative medicines such as Vitrakvi, which can provide value to patients and their treating physicians around the world."

"As researchers learn more about tumor genomics, precision oncology treatments that directly address the genomic abnormality driving tumor growth become increasingly relevant for patients. We now have the tools to move beyond a one-size fits all treatment approach," said Marcia K. Horn, President and CEO of ICAN, the International Cancer Advocacy Network. "We welcome the approval of Vitrakvi for patients with TRK fusion cancer in the EU, which also underscores the importance of implementing consistent, widespread high quality molecular testing into the clinical practice to identify more patients through genomic insights and ultimately benefit their care."

Only specific tests can identify *NTRK* gene fusions or TRK fusion proteins, these include next generation sequencing (NGS), flourescense in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR) and Immunohistochemistry (IHC). IHC is a useful screening tool. However, IHC detects both the expression of the wildtype TRK protein as well as the TRK fusion protein; therefore, positive results need to be confirmed by more specific tests such as next-generation sequencing. Patients eligible for treatment with Vitrakvi should be selected based on the presence of an *NTRK* gene fusion in their tumor.

About Vitrakvi® (larotrectinib)

Larotrectinib was approved in September 2019 in the European Union under the brand name Vitrakvi® for the treatment of adult and pediatric patients with solid tumors that display a Neurotrophic Tyrosine Receptor Kinase (*NTRK*) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options. Vitrakvi has also received regulatory approval in the U.S, Brazil and Canada. Filings in other regions are underway or planned.

Larotrectinib patients have been treated for up to 38.7 months with many patients continuing treatment. To date, larotrectinib has the largest dataset (n=139) and experience in TRK fusion cancer patients.

Following the acquisition of Loxo Oncology by Eli Lilly and Company in February 2019, Bayer has obtained the exclusive licensing rights for the global development and commercialization, including in the U.S., for larotrectinib and the investigational TRK inhibitor BAY 2731954 (previously LOXO-195) progressing through clinical development.

About TRK Fusion Cancer

TRK fusion cancer occurs when an *NTRK* gene fuses with another unrelated gene, producing an altered TRK protein. The altered protein, or TRK fusion protein, becomes constitutively active or overexpressed, triggering a signaling cascade. These TRK fusion proteins act as oncogenic drivers promoting cell growth and survival, leading to TRK fusion cancer, regardless of where it originates in the body. TRK fusion cancer is not limited to certain types of tissues and can occur in any part of the body. TRK fusion cancer occurs in various adult and pediatric solid tumors with varying frequency, including lung, thyroid, gastrointestinal cancers (colon, cholangiocarcinoma, pancreatic and appendiceal), sarcoma, CNS cancers (glioma and glioblastoma), salivary gland cancers (mammary analogue secretory carcinoma) and pediatric cancers (infantile fibrosarcoma and soft tissue sarcoma).

About Oncology at Bayer

Bayer is committed to delivering science for a better life by advancing a portfolio of innovative treatments. The oncology franchise at Bayer includes six marketed products and several other assets in various stages of clinical development. Together, these

products reflect the company's approach to research, which prioritizes targets and pathways with the potential to impact the way that cancer is treated.

About Bayer

Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to benefit people by supporting efforts to overcome the major challenges presented by a growing and aging global population. At the same time, the Group aims to increase its earning power and create value through innovation and growth. Bayer is committed to the principles of sustainable development, and the Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2018, the Group employed around 117,000 people and had sales of 39.6 billion euros. Capital expenditures amounted to 2.6 billion euros, R&D expenses to 5.2 billion euros. For more information, go to www.bayer.com.

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