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Bayer receives positive CHMP opinion for precision oncology treatment larotrectinib with first ever tumor-agnostic indication in in Europe

- Recommendation for approval 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
- Upon approval, larotrectinib would be the first therapy in Europe with a tumor-agnostic indication
- CHMP opinion is based on pooled data showing that larotrectinib provides high and durable responses in adult and pediatric patients with TRK fusion cancer, including CNS tumors
- Larotrectinib showed a favorable safety profile, with the majority of adverse events being grade 1 or 2
- Final decision from the European Commission is anticipated within the next months

Leverkusen, Germany, July 26, 2019 – The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has recommended Bayer's precision oncology treatment larotrectinib for marketing authorization in the European Union (EU). The recommended indication is treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion, are locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatment options. The final decision of the European Commission on the marketing authorization is expected in the coming months. Larotrectinib, a first-in-class oral TRK inhibitor specifically developed to treat tumors that have an *NTRK* gene fusion, will be the first treatment to receive a tumor-agnostic indication in the EU. Larotrectinib is already approved in the U.S. as well as in Brazil and Canada.

The CHMP recommendation is based on pooled clinical trial data of 102 patients (93 patients from the primary analysis population and an additional 9 patients with primary central nervous [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, showing a high response rate with durable and rapid responses for larotrectinib. Results in the primary analysis population demonstrate an overall response rate (ORR) of 72% (95% CI: 62, 81), including a 16% complete response (CR) rate and a 55% partial response (PR) rate. In an additional analysis including primary CNS patients, the ORR was 67% (95% CI: 57, 76), including a 15% CR, and a 51% PR. In the pooled primary analysis set, the median duration of response was not reached at time of analysis with responses ranging from 1.6+ to 38.7+ months and 75% of patients having a duration of response of 12 months or longer. Ninety percent (95% CI: 83, 97) of patients treated were alive one year after the start of therapy. Median progression free survival had not been reached at the time of analysis. The safety of larotrectinib was evaluated in 125 patients with an *NTRK* gene fusion. The majority of adverse events (AEs) were grade 1 or 2; three percent of patients had to stop therapy due to treatment-emergent AEs. Dose reduction in the target population (n=125) was reported in 19 (15%) patients including 10 (8%) due to AEs. The majority of AEs leading to dose reduction occurred within the first three months of treatment.

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

"This positive CHMP recommendation for the first-ever tumor agnostic indication in Europe marks an important step towards delivering a first-of -its -kind precision medicine for children and adults with TRK fusion cancer in Europe," said Dr Scott Z Fields, Senior Vice President and Head of Oncology Development at Bayer. "Larotrectinib was specifically developed to treat patients with TRK fusion cancer, and has the potential to significantly improve treatment outcomes, regardless of tumor type or age. As

researchers learn more about tumor genomics, it becomes all the more important to ensure broad access to genomic testing to allow patients that have the potential to benefit from precision medicines to be identified and treated, moving us beyond a one-size fits all therapeutic approach."

High quality *NTRK* testing is key to identifying those patients who are most likely to benefit from larotrectinib. Only specific tests can identify *NTRK* gene fusions or TRK fusion proteins. Immunohistochemistry (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 larotrectinib should be selected based on the presence of an *NTRK* gene fusion in their tumor.

About larotrectinib

Larotrectinib was approved in November 2018 in the U.S. under the brand name Vitrakvi® for the treatment of adult and pediatric patients with solid tumors with a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation that are either metastatic or where surgical resection will likely result in severe morbidity, and have no satisfactory alternative treatments or have progressed following treatment. In the U.S., larotrectinib was approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Larotrectinib has also received regulatory approval in Brazil as well as Canada. Filings in other regions are underway or planned.

As detailed in data recently presented at ASCO 2019 which included a total of 139 patients across the three trials (detailed above) over a median follow-up time of 17.2 months, larotrectinib has the largest dataset and longest follow-up data of any TRK inhibitor.

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 to 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 five 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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Forward-Looking Statements
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