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Investor News

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U.S. FDA approves Larotrectinib, the first TRK inhibitor, for patients with advanced solid tumors harboring an NTRK gene fusion

- First treatment with a tumor-agnostic indication at the time of initial FDA approval
- Larotrectinib approved under the brand name Vitrakvi®
- 75% overall response rate (ORR) (95% CI, 61%, 85%) [22% complete response (CR) and 53% partial response (PR)] across various solid tumors in adults and children
- Adverse events (AEs) of any grade observed in more than 20 percent of patients, regardless of attribution, included increased ALT (45%), increased AST (45%), anemia (42%), fatigue (37%), nausea (29%), dizziness (28%), cough (26%), vomiting (26%), constipation (23%), and diarrhea (22%)

Leverkusen, Germany, November 27, 2018 – The U.S. Food and Drug Administration (FDA) has approved larotrectinib, the first oral TRK inhibitor, under the brand name Vitrakvi®. The approval is 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. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Larotrectinib is the first treatment to receive a tumor-agnostic indication at the time of initial FDA approval. In clinical trials of patients with TRK fusion cancer, larotrectinib demonstrated an ORR of 75 percent (N=55) (95% CI: 61, 85%), including a 22 percent complete response (CR) rate.

“The FDA approval of larotrectinib marks an important milestone in how we treat cancers that have an *NTRK* gene fusion – a rare driver of cancer. I have seen firsthand how treatment with larotrectinib, which is designed specifically for this oncogenic driver, can deliver clinically meaningful responses in patients with TRK fusion cancer, regardless of

patient age or tumor type," said David Hyman, M.D., chief of the Early Drug Development Service at Memorial Sloan Kettering Cancer Center and a global principal investigator for a larotrectinib clinical trial. "We now have the first therapy approved for this genomic alteration, regardless of cancer type."

NTRK gene fusions are genomic alterations that result in constitutively-activated chimeric TRK fusion proteins, which act as an oncogenic driver, promoting cell proliferation and survival in tumor cell lines. Larotrectinib, developed by Bayer and Loxo Oncology, Inc., is a CNS active TRK inhibitor designed to inhibit these proteins. TRK fusions can be found in many types of solid tumors and affect both children and adults. In the clinical trials that were the basis for this approval, larotrectinib showed clinical benefit across numerous unique tumor types, including lung, thyroid, melanoma, GIST, colon, soft tissue sarcoma, salivary gland and infantile fibrosarcoma.

"The first approval of larotrectinib is the culmination of years of hard work and research by many people to bring the first treatment to patients with TRK fusion cancer. TRK fusions are rare, but occur across many different tumor types. In this era of precision medicine, we are delivering on Bayer's commitment to advance the future of cancer care while providing value for patients and physicians," said Robert LaCaze, Member of the Executive Committee of Bayer's Pharmaceuticals Division and Head of the Oncology Strategic Business Unit at Bayer. "It is very rewarding to provide a therapy specifically for patients with advanced solid tumors harboring an *NTRK* gene fusion."

"We are grateful to the investigators, research teams and patients who contributed to and participated in the larotrectinib clinical trials that supported this approval," said Josh Bilenker, M.D., chief executive officer of Loxo Oncology. "It is now even more critical to screen patients of all ages with advanced solid tumors for actionable genomic insights that could benefit their care or aid in their referral to clinical trials."

TRK fusion cancer is diagnosed through the identification of *NTRK* gene fusions using specific tests, including those that employ next-generation sequencing (NGS) and fluorescence in situ hybridization (FISH). Patients eligible for treatment with larotrectinib should be selected based on the presence of an *NTRK* gene fusion in their tumor.

"We welcome the FDA approval of larotrectinib and the innovations in genomic testing that make such precision medicine a reality," said Andrea Stern Ferris, president and chief executive officer of the LUNGevity Foundation. "We're seeing scientific

advancements, like genomic testing capable of detecting an *NTRK* gene fusion, beginning to transform the treatment of cancer and provide new treatment options for patients."

The FDA reviewed larotrectinib under Priority Review, which is reserved for medicines that could provide significant improvements in the safety or effectiveness of the treatment for serious conditions. The FDA previously granted larotrectinib Breakthrough Therapy Designation, Rare Pediatric Disease Designation and Orphan Drug Designation. Bayer submitted a Marketing Authorization Application in the European Union in August 2018 and additional filings in other countries are underway.

Larotrectinib will be available in the U.S. market in oral capsules as well as a liquid formulation for adults and children.

Bayer to Provide Comprehensive Value and Access Programs

Bayer is committed to ensuring eligible patients in the U.S. who are prescribed larotrectinib are able to access the medication and receive the support they may need. As part of this commitment, Bayer is providing two comprehensive programs, the Vitrakvi Commitment Program™ and the TRAK Assist™ patient support program. The first one will refund the cost of larotrectinib to payers, patients and third-party organizations paying on behalf of patients, in the event eligible patients do not experience clinical benefit within 90 days of treatment initiation. Eligible patients include those who have tested positive for an *NTRK* gene fusion, have not received clinical benefit within 90 days of treatment initiation, and received larotrectinib from an in-network specialty pharmacy.

The TRAK Assist™ patient support program provides comprehensive reimbursement support and patient assistance services. Additionally, the Bayer US Patient Assistance Foundation, a charitable organization that helps eligible patients get their Bayer prescription medicine at no cost, is an additional resource for patients in need of financial assistance.

Clinical Trial Results

The FDA approval of larotrectinib is based on pooled data across the Phase I adult trial, Phase II NAVIGATE trial and Phase I/II pediatric SCOUT trial (N=55). In pooled study results, larotrectinib demonstrated an overall response rate (ORR) of 75 percent (95% CI,

61%, 85%) by blinded independent review committee (with 22 percent of patients achieving a complete response and 53 percent of patients achieving a partial response) across various tumor types, including soft tissue sarcoma, salivary gland, infantile fibrosarcoma, thyroid, lung, melanoma, colon, GIST, cholangiocarcinoma, appendix, breast and pancreas. Seventy-three percent of responding patients (n=41) had a duration of response (DOR) lasting 6 months or greater at the time of data cut-off. Median DOR (range 1.6+, 33.2+) and progression-free survival (PFS) had not been reached at the time of analysis. Median time to response was 1.84 months.

In the safety database (N=176), which included patients with and without an *NTRK* gene fusion, the majority of adverse events (AEs) reported in greater than or equal to 10 percent of patients were grade 1 or 2. AEs of any grade observed in more than 20 percent of patients included increased ALT (45 percent), increased AST (45 percent), anemia (42 percent), fatigue (37 percent), nausea (29 percent), dizziness (28 percent), cough (26 percent), vomiting (26 percent), constipation (23 percent), and diarrhea (22 percent).

In October 2018, updated efficacy and safety data on larotrectinib were presented at the ESMO 2018 Congress (European Society for Medical Oncology).

For additional information about the larotrectinib clinical trials, please refer to www.clinicaltrials.gov or visit www.loxooncologytrials.com.

About larotrectinib
Larotrectinib is an oral TRK inhibitor for the treatment of patients with cancers that harbor an *NTRK* gene fusion. Research suggests that the *NTRK* genes can become abnormally fused to other genes, producing a TRK fusion protein that can lead to the growth and survival of solid tumors in various sites of the body.

In November 2017, Bayer and Loxo Oncology entered into an exclusive global collaboration for the development and commercialization of the TRK inhibitors larotrectinib and LOXO-195. Bayer and Loxo Oncology will jointly develop the two products with Loxo Oncology leading the ongoing clinical studies as well as the filing in the U.S., and Bayer leading ex-U.S. regulatory activities and worldwide commercial activities. In the U.S., Bayer and Loxo Oncology will co-promote the products.

Larotrectinib has been approved in the U.S. under the brand name Vitrakvi®. It has not been approved by the European Medicines Agency or any other health authority outside the U.S.

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, GI 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 compounds 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 agriculture. Its products and services are designed to benefit people and improve their quality of life. At the same time, the Group aims to create value through innovation, growth and high earning power. Bayer is committed to the principles of sustainable development and to its social and ethical responsibilities as a corporate citizen. In fiscal 2017, the Group employed around 99,800 people and had sales of EUR 35.0 billion. Capital expenditures amounted to EUR 2.4 billion, R&D expenses to EUR 4.5 billion. For more information, go to www.bayer.com.

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Forward-Looking Statements
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