



FDA Approves Vitrakvi® (larotrectinib), the First Ever TRK Inhibitor, for Patients with Advanced Solid Tumors Harboring an NTRK Gene Fusion(1,2)

November 26, 2018

- First treatment with a tumor-agnostic indication at the time of initial FDA approval
- 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 (N=55)²
- Adverse events (AE) of any grade observed in 20% or more 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%)²

STAMFORD, Conn. and WHIPPANY, N.J., Nov. 26, 2018 (GLOBE NEWSWIRE) -- The U.S. Food and Drug Administration (FDA) today approved Vitrakvi® (larotrectinib), the first ever oral TRK inhibitor, for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.^{1,2} 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. Vitrakvi 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, Vitrakvi demonstrated an ORR of 75 percent (N=55) (95% CI, 61%, 85%), including a 22 percent complete response (CR) rate.²

"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 that can act as an oncogenic driver, promoting cell proliferation and survival in tumor cell lines.² Vitrakvi, developed by Bayer and Loxo Oncology, Inc., is a CNS active TRK inhibitor designed to inhibit these proteins.² TRK fusions can be found in many types of solid tumors and affect both children and adults.¹ In the clinical trials that were the basis for this approval, Vitrakvi showed clinical benefit across numerous unique tumor types, including lung, thyroid, melanoma, GIST, colon, soft tissue sarcoma, salivary gland and infantile fibrosarcoma.²

"Today's approval of Vitrakvi is the culmination of years of hard work and research by many people to bring the first ever 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."

Vitrakvi® (larotrectinib) has warnings and precautions of neurotoxicity, hepatotoxicity and embryo-fetal toxicity.² The most



common adverse events observed in more than 20 percent of patients, regardless of attribution, were increased ALT, increased AST, anemia, fatigue, nausea, dizziness, cough, vomiting, constipation, and diarrhea.² The majority of adverse events occurring in greater than or equal to 10 percent of patients were grade 1 or 2.²

TRK fusion cancer occurs across a broad range of tumor types with varying frequency in both adult and pediatric patients.¹ It 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).² Patients eligible for treatment with Vitrakvi should be selected based on the presence of an *NTRK* gene fusion in their tumor.²

"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. "The approval of Vitrakvi is a testament to the relentless prioritization of biology in the drug development process. 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."

The FDA reviewed Vitrakvi 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 Vitrakvi Breakthrough Therapy Designation, Rare Pediatric Disease Designation and Orphan Drug Designation.

"We welcome the FDA approval of Vitrakvi 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 options for patients."

Vitrakvi will be available in oral capsules as well as a liquid formulation for adults and children.² For more information, visit www.vitrakvi.com.

Bayer to Provide Comprehensive Value and Access Programs

Bayer is committed to ensuring that patients in the U.S. who are prescribed Vitrakvi 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 ProgramTM and the TRAK AssistTM patient support program.

The Vitrakvi Commitment Program will refund the cost of Vitrakvi 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 Vitrakvi from an in-network specialty pharmacy.

The TRAK AssistTM patient support program provides comprehensive reimbursement support and patient assistance services. For more information and eligibility requirements, please call 1-844-634-TRAK (8725).

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.

"Express Scripts applauds Bayer for its thoughtful approach to patient access. The Vitrakvi Commitment Program represents a significant advance to patient access," said Steve Miller, M.D., chief medical officer, Express Scripts. "We look forward to working together to help those who will benefit from this medicine have affordable access to it."

Clinical Trial Results

The FDA approval of Vitrakvi[®] (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).² In pooled study results, Vitrakvi 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.² Seventy-three percent of responding patients (N=41) had a duration of response (DOR) lasting six months or greater at the time of data cut-off.² Median DOR (range 1.6+, 33.2+) and progression-free survival



(PFS) had not been reached at the time of analysis.^{2,3} Median time to response was 1.84 months.³ 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 2.² 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%).² In October 2018, updated efficacy and safety data on larotrectinib were presented at the [ESMO 2018 Congress](#) (European Society for Medical Oncology).

Vitrakvi will be available in the U.S. market immediately. Bayer submitted a Marketing Authorization Application (MAA) in the European Union in August 2018.

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

About Vitrakvi® (larotrectinib)

Vitrakvi is an oral TRK inhibitor for the treatment of adult and pediatric patients with solid tumors with an *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.² This indication is 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. 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.^{1,2}

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 are jointly developing 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 not been approved by the European Medicines Agency.

About TRK Fusion Cancer

TRK fusion cancer occurs when an *NTRK* gene fuses with another unrelated gene, producing an altered TRK protein.² The altered protein, or TRK fusion protein, becomes constitutively active or overexpressed, triggering a signaling cascade.² 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.² TRK fusion cancer is not limited to certain types of tissues and can occur in any part of the body.¹ 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).^{1,2}

Important Safety Information

Neurotoxicity: Among the 176 patients who received VITRAKVI, neurologic adverse reactions of any grade occurred in 53% of patients, including Grade 3 and Grade 4 neurologic adverse reactions in 6% and 0.6% of patients, respectively. The majority (65%) of neurological adverse reactions occurred within the first three months of treatment (range 1 day to 2.2 years). Grade 3 neurologic adverse reactions included delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). Grade 4 encephalopathy (0.6%) occurred in a single patient. Neurologic adverse reactions leading to dose modification included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%).²

Advise patients and caretakers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dose when resumed.²



Hepatotoxicity: Among the 176 patients who received VITRAKVI, increased transaminases of any grade occurred in 45%, including Grade 3 increased AST or ALT in 6% of patients. One patient (0.6%) experienced Grade 4 increased ALT. The median time to onset of increased AST was 2 months (range: 1 month to 2.6 years). The median time to onset of increased ALT was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients.²

Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed.²

Embryo-Fetal Toxicity: VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily.²

Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI.²

Most Common Adverse Reactions (?20%): The most common adverse reactions (?20%) were: increased ALT (45%), increased AST (45%), anemia (42%), fatigue (37%), nausea (29%), dizziness (28%), cough (26%), vomiting (26%), constipation (23%), and diarrhea (22%).²

Drug Interactions: Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors (including grapefruit or grapefruit juice), strong CYP3A4 inducers (including St. John's wort), or sensitive CYP3A4 substrates. If coadministration of strong CYP3A4 inhibitors or inducers cannot be avoided, modify the VITRAKVI dose as recommended. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.²

Lactation: Advise women not to breastfeed during treatment with VITRAKVI and for 1 week after the final dose.²

Please see the [full Prescribing Information](#).

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 now includes five oncology 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.us.



About Loxo Oncology

Loxo Oncology is a biopharmaceutical company focused on the development and commercialization of highly selective medicines for patients with genomically defined cancers. Our pipeline focuses on cancers that are uniquely dependent on single gene abnormalities, such that a single drug has the potential to treat the cancer with dramatic effect. We believe that the most selective, purpose-built medicines have the highest probability of maximally inhibiting the intended target, with the intention of delivering best-in-class disease control and safety. Our management team seeks out experienced industry partners, world-class scientific advisors and innovative clinical-regulatory approaches to deliver new cancer therapies to patients as quickly and efficiently as possible. For more information, please visit the company's website at www.loxooncology.com.

© 2018 Bayer and Loxo Oncology, Inc. All rights reserved.

Bayer, the Bayer Cross and Vitrakvi are registered trademarks of Bayer and Vitrakvi Commitment Program and TRAK Assist are trademarks of Bayer.

Bayer Media Contact:

Rose Talarico, Tel. +1 862.404.5302

E-Mail: rose.talarico@bayer.com

Loxo Oncology, Inc. Contacts

Company:

Lauren Cohen

E-Mail: lcohen@loxooncology.com

Investors:

Peter Rahmer

Endurance Advisors, LLC

Tel. +1 415.515.9763

E-Mail: prahmer@enduranceadvisors.com

Media:

Dan Budwick

1AB Media

Tel. +1 973-271-6085

E-Mail: dan@1abmedia.com

Forward-Looking Statements

This press release contains "forward-looking" statements within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. Forward-looking statements can be identified by words such as: "anticipate," "intend," "plan," "goal," "seek," "believe," "project," "estimate," "expect," "strategy," "future," "likely," "may," "should," "will" and similar references to future periods. These statements are subject to various known and unknown risks, uncertainties and other factors that could cause actual results to differ materially from what we expect. Examples of forward-looking statements include, among others, statements we make regarding the timing and success of Loxo Oncology's clinical trials or the collaboration between Bayer and Loxo Oncology, the potential therapeutic benefits and economic value of larotrectinib or other product candidates, and timing of future filings. Further information on potential risk factors that could affect our business and its financial results are detailed in Bayer's public reports which are available on the Bayer website at www.bayer.com, and Loxo Oncology's most recent Quarterly Report on Form 10-Q, and other reports as filed from time to time with the Securities and Exchange Commission. Neither the Bayer Group or Loxo Oncology undertakes any obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.



References

1. Vaishnavi A, Le AT, Doebele RC. TRKKing down an old oncogene in a new era of targeted therapy. *Cancer Discov.* 2015;5(1):25-34.
2. Vitrakvi[®] (larotrectinib) capsules and solution for oral use [Prescribing Information]. Stamford, CT: Loxo Oncology Inc.; November 2018.
3. Data on file, Stamford, CT: Loxo Oncology, Inc.; 2018.

[loxo.jpg](#)

Image not found or type unknown

Loxo Oncology, Inc.