Summary of the Risk Management Plan for Vitrakvi®

Active substance: Larotrectinib

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Based on the EU-RMP v.2.1 for Vitrakvi® (dated 09 APR 2024)

VITRAKVI®
(Larotrectinib)
Risk Management Plan
Summary of the Risk Management Plan

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Vitrakvi® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Vitrakvi® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bayer (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Vitrakvi®.

The Summary of the Risk Management Plan for Vitrakvi® v2.0 is based on the Summary of Activities of the Risk Management Plan for Vitrakvi® (Larotrectinib) of the EU-RMP v2.1, dated 09 APR 2024.

Summary of the risk management plan for Vitrakvi®

This is a summary of the risk management plan (RMP) for Vitrakvi® (larotrectinib; LOXO-101). The RMP details important risks of Vitrakvi®, how these risks can be minimised, and how more information will be obtained about Vitrakvi®'s risks and uncertainties (missing information).

Vitrakvi®'s summary of medicinal product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vitrakvi® should be used.

This summary of the RMP for Vitrakvi® should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vitrakvi®'s RMP.

1. The Medicine and What it is used for

Vitrakvi® as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours 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.

Further information about the evaluation of the benefits of Vitrakvi®, including its plain-language summary, can be found in in the EPAR for Vitrakvi® (https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi).

2. Risks Associated with the Medicine and Activities to Minimise or further Characterise the Risks

Important risks of Vitrakvi®, together with measures to minimise such risks and the proposed studies for learning more about these risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and analysed regularly (e.g., via the periodic safety update report [PSUR]) so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Vitrakvi® is not yet available, it is listed under 'missing information' below.

2.1 List of Important Risks and Missing Information

Important risks of Vitrakvi® are risks that require special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vitrakvi®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None identified
Important potential risks	Severe neurologic reactions
	Severe drug-induced liver injury
	Serious infections secondary to neutropenia
	Impairment of neurodevelopment in paediatric patients
Missing information	Use in pregnancy and lactation
	Long-term safety

2.2 Summary of Important Risks

Important potential risk: Severe neurologic reactions	
Evidence for linking the risk to the medicine	Treatment-related adverse events (TRAEs) of dizziness, gait disturbance, paraesthesia were frequently observed in clinical studies.
Risk factors and risk groups	Primary central nervous system tumours or metastatic lesions, medical history of brain tumours, surgeries or head trauma, underlying neurological conditions, concomitant use of certain agents known for neurotoxicity.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC sections 4.8; 5.3) Routine risk communication recommending specific clinical measure to address the risk: • Caution patients about driving and operating machinery (SmPC 4.7) • Consider dose modification/s (SmPC 4.2; 4.4) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, in post-marketing experience, and as an Adverse Event of Special Interest (AESI) in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

Important potential risk: Severe drug-induced liver injury	
Evidence for linking the risk to the medicine	Elevation of liver enzymes, hyperbilirubinaemia and jaundice were reported in clinical trials with Vitrakvi®.
Risk factors and risk groups	Patients with impaired liver function at baseline, chronic liver conditions, concomitant administration of agents, and medications with known adverse hepatic effects.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC sections: 4.2; 4.8; 5.2) Routine risk communication recommending specific clinical measure to address the risk: • Liver function monitoring (SmPC 4.2; 4.4) • Consider dose modification/s (SmPC 4.2; 4.4) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures**: None

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Important potential risk: Severe drug-induced liver injury	
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, in post-marketing experience, and as an AESI in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

Important potential risk: Serious infections secondary to neutropenia	
Evidence for linking the risk to the medicine	In the overall clinical safety database (n=335), a total of 49 SAEs from SOC "Infections" were reported, and none were assessed as related to study medication. None of the cases of infections were reported in combination with neutropenia with the exception of a single patient (febrile neutropenia and sepsis). Neutropenia was observed in ongoing clinical trials in 17% of total cases (paediatric patients 29% vs adults 9%).
Risk factors and risk groups	Underlying haematological conditions, concomitant administration of agents with known haematotoxicity effects, immunosuppression, chronic infectous and inflammatory disease, exposure to infectous agents. Paediatric patients with complex past medical histories and / or neutropenia observable at baseline. Of note, 47% and 28% of so far Vitrakvi®-treated patients had received 1 or 2 and at least 3 prior systemic therapies, respectively. Hence, a certain effect on baseline bone marrow reserve in these patients, in particular in the paediatric population, can't be excluded.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 4.8) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, in post-marketing experience, and in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

Important potential risk: Impairment of neurodevelopment in paediatric patients	
Evidence for linking the risk to the medicine	No adverse events pertaining to HLGT: "Cognitive and attention disorders and disturbances", HLT: "Developmental motor skills disorders", HLT: "Developmental disorders cognitive", HLT: "Memory loss (excl dementia)", and HLT: "Mental impairment (excl dementia and memory loss" were reported in any of the Vitrakvi® clinical trials to date. Risk is also being evaluated in the context of the important potential risk "severe neurologic reactions". No further developmental data is currently available.

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Important potential risk: Impairment of neurodevelopment in paediatric patients	
Risk factors and risk groups	Malnutrition, prematurity, perinatal asphyxia (e.g., cerebral palsy), genetic disorders, chronic infections and medical conditions, - brain tumours (including benign), broncho-pulmonary dysplasia, microcephaly, hydrocephalus, sepsis, intranatal infections (e.g., Zika virus), environmental enteropathy and toxins, cardiac surgery, congenital heart disease, severe head trauma, neurodevelopment disruption (including psychosocial stress, violence).
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 5.3) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), in post-marketing experience, and in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

Missing information: Use in pregnancy and lactation	
Evidence for linking the risk to the medicine	Patient population has not been studied.
Risk factors and risk groups	Respective population in need of further characterisation. Potential increased risk of maternal toxicity, damage to the foetus, and nursing infants.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 5.3) Routine risk communication recommending specific clinical measure to address the risk: • Highly effective contraception in both males and females (SmPC 4.6) • Pregnancy test prior to treatment initiation (SmPC 4.6) • Discontinuation of breastfeeding in nursing mothers (SmPC 4.6) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, in post-marketing experience and in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

Missing information: Long-term safety	
Evidence for linking the risk to the medicine	Preliminary analysis of safety data on the 109 patients who reached the exposure to Vitrakvi® of >2 years, suggests that the majority of TEAEs are reported during the first 2 years of exposure. No further long-term safety data is available.
Risk factors and risk groups	Long-term exposure may increase the risk of occurrence of additional adverse events in adult and paediatric patients exposed to Vitrakvi® for a period of longer than 2 years.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 4.8). Prescription-only medicine. Specialist healthcare professional. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, in post-marketing experience, and in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

2.3 Post-authorisation Development Plan

2.3.1 Studies which are Conditions of the Marketing Authorisation

Study name **Status**	**Rationale and study objectives**
Study ON-TRK, A PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib Ongoing	To evaluate, under real-world conditions, the safety and effectiveness of Vitrakvi® in patients with locally advanced or metastatic TRK fusion cancer for whom a decision to treat with larotrectinib has been made before enrolment.
Study 20289 (NAVIGATE; formerly LOXO-TRK-15002), a Phase 2 multicentre, open-label study in patients 12 years of age and older with advanced cancer harbouring a fusion of *NTRK1*, *NTRK2*, or *NTRK3*. Ongoing	To determine the overall response rate as determined by an independent radiology review committee and measured by the proportion of subjects with best overall confirmed response of complete response or partial response by the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1), or Response Assessment in Neuro Oncology (RANO) criteria, as appropriate, following treatment with Vitrakvi® in subjects age 12 and older with an advanced cancer harbouring a fusion involving *NTRK1*, *NTRK2*, or *NTRK3* (collectively referred to as *NTRK* gene fusions) for each tumour-specific disease cohort. The study will also assess the safety profile and tolerability of Vitrakvi® for each tumour-specific disease cohort.

Study name **Status**	**Rationale and study objectives**
Study 20290 (SCOUT; formerly LOXO-TRK-15003), A Phase 1/2 study of the oral TRK inhibitor LOXO-101 in paediatric patients with advanced solid or primary central nervous system tumours. Ongoing	Phase I: To determine the safety of oral Vitrakvi®, including dose-limiting toxicity (DLT), in paediatric patients with advanced solid or primary central nervous system (CNS) tumours. Phase II: To determine the overall response rate (ORR) as determined by an independent radiology review committee and measured by the proportion of subjects with best overall confirmed response of complete response (CR) or partial response (PR) by the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1), or Response Assessment in Neuro-Oncology (RANO) criteria for primary CNS tumours, and International Neuroblastoma Response Criteria (INRC) for neuroblastoma as appropriate, following treatment with Vitrakvi® in paediatric subjects with an advanced cancer harbouring a fusion involving *NTRK1*, *NTRK2*, or *NTRK3* (collectively referred to as neurotrophic tyrosine kinase receptor [*NTRK*] fusions). In order to confirm the appropriate dose recommended in paediatric patients an updated PopPK model based on additional PK sampling in paediatric patients between 1 month and 6 years of age will be created. To collect long-term use safety and efficacy data in paediatric patients.

2.3.2 Other studies in Post-authorisation Development Plan

Study name **Status**	**Rationale and study objectives**
Patient Registry (EURACAN TRacKING) European Reference Network (ERN)-for adult rare solid cancers EURACAN Ongoing	Bayer AG supports a European adult registry (TRacKING) through the European Reference Network (ERN)-EURACAN, a European network focusing on rare adult solid cancers (http://euracan.eu/registries/tracking/) The objective of the TRacKING registry is to describe the management of adult patients with solid cancers harbouring an actionable fusion in real-life practice. The primary goal is the evaluation of overall survival. Among the secondary goals the clinical activity and safety of fusion-targeting treatments will be documented. The registry was launched in Q2 2021 for a 4-year period (2 years inclusion + 2 years follow-up. Bayer receives annual data updates in return for its support of the EURACAN registry.