Summary of Risk Management Plan for Rozlytrek® (Entrectinib)

This is a summary of the risk management plan (RMP) for Rozlytrek. The RMP details important risks of Rozlytrek, how these risks can be minimized, and how more information will be obtained about Rozlytrek risks and uncertainties (missing information).

Rozlytrek SmPC and its package leaflet give essential information to healthcare professionals and patients on how Rozlytrek should be used.

This summary of the RMP for Rozlytrek 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 Rozlytrek RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Rozlytrek is authorized for the treatment of NTRK fusion-positive locally advanced or metastatic solid tumors and ROS1-positive, advanced non-small cell lung cancer (NSCLC) (see SmPC for the full indication). It contains entrectinib as the active substance, and it is given by oral administration.

Further information about the evaluation of Rozlytrek benefits can be found in Rozlytrek's EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Rozlytrek, together with measures to minimize such risks and the proposed studies for learning more about Rozlytrek risks, are outlined below.

Measures to minimize 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 authorized pack size: the amount of medicine in a pack is chosen so as 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 minimize its risks.

Together, these measures constitute *routine risk-minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, 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 Rozlytrek is not yet available, it is listed under “missing Information” below.

II.A List of Important Risks and Missing Information

Important risks of Rozlytrek are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 Rozlytrek. 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 about 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	• Congestive heart failure • QT prolongation • Fractures
Important potential risks	• Severe neurologic reactions • Neuro-developmental impairment in paediatric patients
Missing information	• Safety in long term use

II.B Summary of Important Risks

Important Identified Risk: Fractures	
Evidence for linking the risk to the medicine	Evidence is based on the safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]) one Phase I/II CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (504 patients) with, ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib
Risk factors and risk groups	In adult patients, the most common cause of fractures appears to be by accidental injury. It is known that entrectinib may cause dizziness and ataxia in patients, though this seemed to be a factor in few of the falls leading to the fractures.
Risk-minimization measures	**Routine risk-minimization measures**: SmPC Section 4.4 (Fractures) and Section 4.8 of the SmPC provide recommendations on risk management approach **Additional risk-minimization measures**: None
Additional pharmacovigilance activities	Risk of fractures continues to be further assessed through integrated safety analysis reports based on PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].

PAES=Post authorization efficacy study; SmPC=Summary of Product Characteristics.

Important Identified Risk: Congestive Heart Failure	
Evidence for linking the risk to the medicine	Evidence is based on the safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]) one Phase I/II (CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (504 patients) with, ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib
Risk factors and risk groups	Risk factors of heart failure include a medical history of coronary artery disease including a previous myocardial infarction, age >65 years, smoking, body mass index > 27 kg/m^2, sedentary life style, abnormality in lipidi profile, hypertension, diabetes, atrial fibrillation, valvular heart disease, alcohol abuse, infection, and cardiomyopathy of an unknown cause In addition, prior cancer treatments including the most commonly used chemotherapy agents (e.g., anthacyclines, cyclophosphamide and radiation therapy) and biologic and targeted therapy drugs, can induce cardiac disorders
Risk-minimization measures	**Routine risk-minimization measures**:

	SmPC Sections 4.2 (Dose modifications) and 4.4 (Congestive heart failure) and Section 4.8 (undesirable effects) provide recommendations on risk management approach **Additional risk-minimization measures**: None
Additional pharmacovigilance activities	Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY]

PAES=Post authorization efficacy study; SmPC=Summary of Product Characteristics.

Important Identified Risk: QT Prolongation	
Evidence for linking the risk to the medicine	Evidence is based on the safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]), one Phase I/II study (CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (504patients) with, ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib
Risk factors and risk groups	QTc prolongation appears to occur more frequently in females. Inherited genetic polymorphisms or mutations with low penetrance, involving the same gene loci associated with phenotypically expressed long-QT syndrome, may underlie individual idiosyncrasies to the acquired form in many, if not most, cases. Some individuals have QT prolongation throughout life without any manifest arrhythmias, while others are highly susceptible to symptomatic arrhythmias, particularly torsades de pointes. Risk factors for QTc prolongation may also include patients with pre-existing conditions such as history of cardiac dysrhythmia, electrolyte disturbances, cardiac ischemia, and the concomitant use of medications with the potential to prolong QTc.
Risk-minimization measures	**Routine risk-minimization measures**: SmPC Sections 4.2 (Dose modifications) and 4.4 (QTc prolongation) and Section 4.8 (undesirable effects) provide recommendations on risk management approach **Additional risk-minimization measures**: None
Additional pharmacovigilance activities	Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY]

PAES=Post authorization efficacy study; SmPC=Summary of Product Characteristics.

Important Potential Risk: Severe Neurological Reactions	
Evidence for linking the risk to the medicine	Evidence is based on the safety data from two Phase I/Ib studies (GO40783 [ALKA], GO40784 [STARTRK-1]), one Phase I/II study (CO40778 [STARTRK-NG]) and one Phase II study (GO40782 [STARTRK-2]) of entrectinib, in adults, adolescents, and children (504patients) with, ROS1, NTRK1/2/3 or ALK alterations or fusions who received at least one dose of entrectinib
Risk factors and risk groups	Patients with metastatic brain tumours can develop substantial cognitive disability, but the extent and type of cognitive dysfunction often varies from patient to patient because of differential tumour volume and location. In the entrectinib clinical trial programme, 96.3% of patients had metastatic disease and 22.2% had CNS metastases at baseline per investigator assessment. Chemotherapy-induced cognitive dysfunction is a common side effect and cause of morbidity in cancer patients and the majority (85.2%) of patients receiving entrectinib were previously treated with chemotherapy. Memory, attention, psychomotor function, processing speed, and executive function appear to be commonly affected.
Risk-minimization measures	**Routine risk-minimization measures**: SmPC Sections 4.2 (Dose modifications), 4.4 (Cognitive disorders) and 4.7 (Effects on ability to drive and use machines), provide recommendations on risk management approach **Additional risk-minimization measures**: None
Additional pharmacovigilance activities	Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY].

PAES=Post authorization efficacy study; SmPC=Summary of Product Characteristics.

Important Potential Risk: Neuro-developmental impairment in paediatric patients	
Evidence for linking the risk to the medicine	Evidence is based on a 13-week juvenile rat toxicology study animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood in humans). In addition to CNS and skin effects, and decreased RBC parameters, effects on growth and development were observed in the dosing and recovery phases including decreased body weight gain and delayed sexual maturation (at ≥ 4 mg/kg/day, approximately 0.1 times the human exposure by AUC at the recommended dose), deficits in neurobehavioral assessments including functional observational battery and learning and memory (at ≥ 8 mg/kg/day, approximately 0.2 times the human exposure by AUC at the recommended dose).
Risk factors and risk groups	Young children treated with entrectinib for an extended duration up to adult maturity.

Risk-minimization measures	**Routine risk-minimization measures:** Section 4.2 (Dose modifications), Section 4.4 (Cognitive disorder) and Section 5.3 (Juvenile rat toxicology study) of the SmPC provide recommendations on risk management approach. **Additional risk-minimization measures:** None
Additional pharmacovigilance activities	Risk continues to be further assessed as part of PAES CO40778 [STARTRK-NG], and BO41932 [TAPISTRY]

PAES=Post authorization efficacy study; SmPC=Summary of Product Characteristics.

Missing Information: Safety in long term use	
Risk factors and risk groups	Patients treated with entrectinib for greater than 12 months.
Risk-minimization measures	**Routine risk-minimization measures:** None **Additional risk-minimization measures:** None
Additional pharmacovigilance activities	Risk continues to be further assessed as part of PAESs GO40782 [STARTRK-2], CO40778 [STARTRK-NG], BO41932 [TAPISTRY].

PAES=Post authorization efficacy study.

II.C Post-Authorization Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorization

Study **Status**	**Rationale and objectives**	**Deadline**
[ANX] MO41552 Randomized, open-label, multicenter, Phase 3 study of entrectinib versus crizotinib in patients who have non-small cell lung cancer (NSCLC) harboring ROS1 gene rearrangements with and without central nervous system (CNS) metastases. Ongoing	In order to further characterize the efficacy of entrectinib in patients with baseline CNS disease, the MAH should conduct and submit the results of a randomized controlled trial versus crizotinib in treatment naïve ROS1 NSCLC patients. The primary endpoint will be PFS in the subgroup of patients with CNS metastases at baseline.	31 December 2027

Studies contributing to pooled analysis **Status**	**Rationale and objectives**	**Deadline**
[SOB] GO40782 (STARTRK-2) An open-label, multicenter, global Phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumours that harbor NTRK1/2/3, ROS1, or ALK gene rearrangements. Ongoing [SOB] CO40778 (STARTRK-NG) A phase 1/2, open-label, dose-escalation and expansion study of entrectinib (RXDX-101) in pediatrics with locally advanced or metastatic solid or primary central nervous system (CNS) tumors and/or who have no satisfactory treatment options. Ongoing [SOB] BO41932 (TAPISTRY) A Phase 2, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies	In order to further confirm the histology-independent efficacy of entrectinib in adult and paediatric patients, the MAH should submit a pooled analysis for an increased sample size of NTRK fusion-positive patients from the ongoing studies STARTRK-2, STARTRK-NG and any additional clinical trial conducted according to an agreed protocol. The MAH should submit the results of an interim safety and efficacy analysis of the NTRK efficacy-evaluable adult and paediatric patients including adolescents that are available as per integrated statistical analysis plan.	31 March 2027

Studies contributing to pooled analysis Status	Rationale and objectives	Deadline
or immunotherapy as single agents or in rational, specified combinations in patients with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations or who are TMB-high as identified by a validated NGS assay. Objective of cohort B is to evaluate the efficacy of entrectinib in patients with NTRK1/2/3 fusion-positive advanced or metastatic solid tumours. Ongoing		

ALK=Anaplastic lymphoma kinase; NTRK=neurotrophic receptor tyrosine kinase.

II.C.2 Other Studies in Post-Authorization Development Plan

Study Status	**Rationale and objectives**	**Deadline**
Integrated safety analysis report to assess risk of fracture based on GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY] studies (PAESs) Ongoing	Report to characterize the risk of fractures in paediatric patients where the following bone biomarkers will be assessed: Serial assessments of BMD with DXA; bone biomarkers in blood and assessment of potential impairment of bone growth with serial hand/wrist and knee X-rays Clinical summary of fracture events	Final integrated analysis report for bone biomarkers: 31 March 2025
		Interim report will include clinical summary of fracture events: With annual re-assessment
	Report to characterize the risk of fractures in adult patients where the following bone biomarkers will be assessed: Serial assessments of bone mineral density (BMD) with dual X-ray absorptiometry (DXA) and bone biomarkers in blood Clinical summary of fracture events	Final integrated analysis report for bone biomarkers: 31 March 2025
		Interim report will include clinical summary of fracture events: With annual re-assessment