

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Rozlytrek® 100 mg hard capsules

Rozlytrek® 200 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: Entrectinib

Each 100 mg hard capsule contains 100 mg entrectinib.

Each 200 mg hard capsule contains 200 mg entrectinib.

Excipients with known effect: Lactose

Each hard capsule contains 65 mg lactose (see section 4.4)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard Capsules

Rozlytrek 100 mg hard capsules

Size 2 (18 mm in length), hard capsule with yellow opaque body and cap with ENT 100 imprinted in blue on the body.

Rozlytrek 200 mg hard capsules

Size 0 (21.7 mm in length), hard capsule with orange opaque body and cap with ENT 200 imprinted in blue on the body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Solid tumours

Rozlytrek is indicated for the treatment of adult and paediatric patients with neurotrophic tyrosine receptor kinase (*NTRK*) fusion-positive locally advanced or metastatic solid tumours, who have progressed following prior therapies, or as initial therapy when there are no acceptable standard therapies.

Non-small cell lung cancer (NSCLC)

Rozlytrek is indicated for the treatment of patients with *ROS1*-positive, locally advanced or metastatic NSCLC.

4.2 Posology and method of administration

General

Treatment with Rozlytrek should be initiated by a physician experienced in the use of anticancer medicinal products.

Patient Selection

NTRK gene fusion-positive solid tumours

A validated assay is required for the selection of patients with *NTRK* fusion-positive locally advanced or metastatic solid tumours. *NTRK* fusion-positive status should be established prior to initiation of Rozlytrek therapy.

ROS1- positive non-small cell lung cancer

A validated assay is required for the selection of patients with *ROS1*-positive locally advanced or metastatic NSCLC. *ROS1*-positive status should be established prior to initiation of Rozlytrek therapy.

Recommended Dosage

Rozlytrek hard capsules can be taken with or without food, swallowed whole and must not be opened or dissolved.

Adults

The recommended dose of Rozlytrek for adults is 600 mg given orally, once daily (see section 5.2).

Paediatric patients

The recommended dose of Rozlytrek for paediatric patients 12 years and older who can swallow capsules is 300 mg/m² orally, once daily (see Table 1). (See section 5.2).

Table 1: Recommended dosing for Paediatric patients

Body surface area (BSA)	Once daily dose
0.43 - 0.50 m ²	100 mg
0.51 - 0.80 m ²	200 mg
0.81 - 1.10 m ²	300 mg
1.11 - 1.50 m ²	400 mg
≥ 1.51m ²	600 mg

Duration of Treatment

It is recommended that patients are treated with Rozlytrek until disease progression or unacceptable toxicity.

Delayed or Missed Doses

If a planned dose of Rozlytrek is missed, patients can make up that dose unless the next dose is due within 12 hours. If vomiting occurs immediately after taking a dose of Rozlytrek, patients may repeat that dose.

Dose Modifications

Management of adverse events may require temporary interruption, dose reduction, or discontinuation of treatment with Rozlytrek, based on the prescriber's assessment of the patient's safety or tolerability.

Adults

For adults, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability. Table 2 provides general dose reduction advice for adult patients. Rozlytrek treatment should be permanently discontinued if patients are unable to tolerate a dose of 200 mg once daily.

Table 2: Dose Reduction Schedule for Adult patients

Dose reduction schedule	Dose level
Starting Dose	600 mg once daily
First dose reduction	400 mg once daily
Second dose reduction	200 mg once daily

Paediatric Patients

Table 3 provides specific dose reduction advice for paediatric patients. For paediatric patients, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability.

For some patients an intermittent dosing schedule is required to achieve the recommended reduced total weekly paediatric dose. Rozlytrek treatment should be permanently discontinued if patients are unable to tolerate the lowest reduced dose.

Table 3: Dose Reduction Schedule for paediatric patients

Starting Dose once daily	First dose reduction	Second dose reduction
100 mg	100 mg, once/day for 5 days each week*	100 mg, once/day for 3 days each week**
200 mg	200 mg, once/day for 5 days each week*	100 mg, once/day for 5 days each week*
300 mg	200 mg once daily	100 mg once daily
400 mg	300 mg once daily	200 mg, once/day for 5 days each week*
600 mg	400 mg once daily	200 mg once daily
*5 days each week: Monday, Wednesday, Friday, Saturday, and Sunday		
**3 days each week: Monday, Thursday and Saturday		

Dose Modifications for Specific Adverse Reactions

Recommendations for Rozlytrek dose modifications for adults and paediatric patients for specific adverse reactions are provided in Table 4. (See section 4.4 and section 4.8).

Table 4: Recommended dose modifications for specified Adverse Drug Reactions for Adult and Paediatric Patients

Adverse Drug Reaction	Severity *	Dose modification
Anemia or Neutropenia	Grade 3 or Grade 4	Withhold Rozlytrek until recovery to $\leq$ Grade 2 or to baseline, then resume treatment at same dose level or reduced dose, as clinically needed.
Cognitive Disorders	Grade $\geq$ 2	- Withhold Rozlytrek until recovery to $\leq$ Grade 1 or to baseline, then resume treatment at reduced dose. - If event recurs, further reduce dose. - For prolonged, severe, or intolerable events, discontinue as clinically appropriate.
Transaminase Elevations	Grade 3	- Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline. - Resume at same dose if resolution occurs within 4 weeks. - Permanently discontinue if adverse reaction does not resolve within 4 weeks. - Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks.

	Grade 4	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline. • Resume at reduced dose if resolution occurs within 4 weeks. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Permanently discontinue for recurrent Grade 4 events.
	ALT or AST elevation greater than 3 times ULN with total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis	• Permanently discontinue Rozlytrek.
Hyperuricemia	Symptomatic or Grade 4	• Initiate urate-lowering medication • Withhold Rozlytrek until improvement of signs or symptoms • Resume Rozlytrek at same or reduced dose
Congestive Heart Failure	Grade 2 or 3	• Withhold Rozlytrek until recovered to less than or equal to Grade 1 • Resume at reduced dose
	Grade 4	• Withhold Rozlytrek until recovered to less than or equal to Grade 1 • Resume at reduced dose or discontinue as clinically appropriate
QT Interval Prolongation	QTc 481 to 500 ms	• Withhold Rozlytrek until recovered to baseline • Resume treatment at same dose
	QTc greater than 500 ms	• Withhold Rozlytrek until QTc interval recovers to baseline • Resume at same dose if factors that cause QT prolongation are identified and corrected • Resume at reduced dose if other factors that cause QT prolongation are not identified
	Torsade de pointes; polymorphic ventricular tachycardia;	• Permanently discontinue Rozlytrek

	signs/symptoms of serious arrhythmia	
Other clinically relevant adverse reactions	Grade 3 or 4	• Withhold Rozlytrek until adverse reaction resolves or improvement to Grade 1 or baseline • Resume at the same or reduced dose, if resolution occurs within 4 weeks • Consider permanent discontinuation if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events
*Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)		

Dose Modifications for Specific Drug Interactions

Concomitant strong or moderate CYP3A inhibitors:

Adults

The concomitant use of strong or moderate CYP3A inhibitors and Rozlytrek in adults should be avoided or limited to 14 days or less. If concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, Rozlytrek dose should be reduced to 100 mg once daily for use with strong CYP3A inhibitors and to 200 mg once daily for use with moderate CYP3A inhibitors.

After discontinuation of the concomitant strong or moderate CYP3A inhibitors, Rozlytrek dose that was taken prior to initiating the strong or moderate CYP3A inhibitor can be resumed. A wash out period may be required for CYP3A4 inhibitors with long half-life. (See section 4.5).

Paediatric patients

The concomitant use of strong or moderate CYP3A inhibitors in paediatric patients should be avoided. (See section 4.5).

Concomitant CYP3A inducers:

Co-administration of Rozlytrek with CYP3A inducers in adult and paediatric patients should be avoided. (See section 4.5)

Special Dosage Instructions

Paediatric use

Paediatric patients must have the ability to swallow whole Rozlytrek capsules. Dosage for patients is based on body surface area (mg/m²) with a maximum daily dose of 600 mg (see Table 1 for paediatric dosing).

Geriatric use

No dose adjustment of Rozlytrek is required in patients ≥ 65 years of age. (See section 5.2).

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. The safety and efficacy of Rozlytrek have not been studied in patients with severe renal impairment. However, since entrectinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment. (See sections 4.4 and section 5.2).

Hepatic Impairment

No dose adjustment is required in patients with underlying mild, moderate or severe hepatic impairment based on a study in subjects with hepatic impairment. (See section 4.4 and section 5.2).

4.3 Contraindications

Rozlytrek is contraindicated in patients with a known hypersensitivity to entrectinib or any of the excipients

4.4 Special Warnings and precautions for use

Congestive Heart Failure

Congestive heart failure (CHF) has been reported across clinical trials with Rozlytrek (see Table 5 in section 4.8). These reactions were observed in patients with or without a history of cardiac disease and resolved upon treatment with diuretics and/or dose reduction/interruption of Rozlytrek.

For patients with symptoms or known risk factors of CHF, left ventricular ejection fraction (LVEF) should be assessed prior to initiation of Rozlytrek treatment. Patients receiving Rozlytrek should be carefully monitored and those with clinical signs and symptoms of CHF, including shortness of breath or edema, should be evaluated and treated as clinically appropriate.

Based on the severity of CHF, Rozlytrek treatment should be modified as described in Table 4 in section 4.2.

Cognitive Disorders

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with Rozlytrek, (see section 4.8). Patients should be monitored for signs of cognitive changes.

Based on the severity of the cognitive disorder, Rozlytrek treatment should be modified as described in Table 4 in section 4.2.

Patients should be counselled on the potential for cognitive changes with Rozlytrek treatment. Patients should be instructed not to drive or use machines until symptoms resolve, if they experience symptoms of cognitive disorders. (See section 4.7).

Fractures

Rozlytrek increases the risk of fractures (see description of selected ADRs). Patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures should be evaluated promptly. In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in paediatric patients' fractures occurred in patients with minimal or no trauma. There are no data on the effects of Rozlytrek on healing of known fractures and the risk of occurrence of future fractures. In the majority of paediatric patients, treatment was continued with Rozlytrek and the fracture healed.

QTc Interval Prolongation

QT interval prolongation has been observed in patients treated with Rozlytrek in clinical trials (see section 4.8).

Use of Rozlytrek should be avoided in patients with congenital long QT syndrome and in patients taking medications that are known to prolong QT interval. Assessment of ECG at baseline and periodic monitoring of ECGs and electrolytes are recommended.

Based on the severity of QTc prolongation, Rozlytrek treatment should be modified as described in Table 4 in section 4.2.

Embryo-foetal toxicity

Based on the findings in animal studies, Rozlytrek may cause foetal harm when administered to a pregnant woman. When administered to pregnant rats, Rozlytrek caused maternal toxicity and developmental toxicities at exposures 2.3-fold the human exposure by AUC at the recommended dose. (See section 4.6).

Female patients of reproductive potential, must use highly effective contraceptive methods during treatment and for 5 weeks following the last dose of Rozlytrek. Female patients receiving Rozlytrek should be advised of the potential harm to the foetus. (See section 4.6).

Drug Abuse and Dependence

Not applicable.

Use in Special Populations

Elderly Use

No differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients. No dose adjustment is required in patients ≥ 65 years of age. See section 4.2 and section 5.2.

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment based on population pharmacokinetic analysis. The safety and efficacy of Rozlytrek in patients with severe renal impairment have not been studied. See section 4.2 and section 5.2.

Hepatic Impairment

See section 4.2 and section 5.2.

Paediatric Use

The safety and efficacy of Rozlytrek have been studied in paediatric patients. See section 4.4 and 4.8. In addition, use of Rozlytrek in paediatric patients is supported by extrapolation of evidence from clinical trials in adults to paediatric population, based on population pharmacokinetic data demonstrating similar drug exposure in adults and paediatric patients. See section 4.2 and section 5.2.

Rozlytrek was associated with a higher incidence of skeletal fractures in the paediatric patients compared to adult patients. See section 4.4 and section 4.8.

Sugar

Rozlytrek contains lactose. Patients with the rare hereditary conditions of lactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take Rozlytrek.

Rozlytrek contains lactose which may influence the glycaemic control of patients with diabetes mellitus.

Sunset yellow FCF (E110)

Rozlytrek 200 mg hard capsules contain sunset yellow FCF (E110), which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

Effects of entrectinib on other drugs

CYP substrates

Based on the *in vitro* studies in human liver microsomes, entrectinib exhibits inhibitory potential toward CYP3A.

In vitro studies indicate that entrectinib and its major active metabolite, M5, do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 at clinically relevant concentrations.

In vitro results indicate entrectinib has weak induction potential toward CYP3A and CYP2C8/9.

In a clinical study, co-administration of multiple doses of entrectinib and midazolam, a sensitive CYP3A substrate, increased the systemic exposure of midazolam by approximately 50% indicating a weak inhibitory effect of entrectinib on the metabolism of midazolam (Geometric mean ratio (GMR) with/without entrectinib for AUC_{inf} (90% CI) was 150% (129%, 173%)).

Therefore, no dose adjustment is required when Rozlytrek is co-administered with CYP3A substrates.

P-gp substrates

In vitro data suggest that entrectinib has inhibitory potential towards P-gp.

In a clinical study, co-administration of a single oral dose of entrectinib with a sensitive P-gp substrate, digoxin, increased the digoxin C_{max} by approximately 28% and overall exposure by approximately 18% (GMR with/without entrectinib for C_{max} (90% CI) was 128% (98.2%, 167%) and AUC_{inf} (90% CI) was 118% (106%, 132%)). The renal clearance of digoxin was similar between treatments of digoxin alone and digoxin co-administered with entrectinib, indicating minimal effect of entrectinib on renal clearance of digoxin.

These results indicate that entrectinib is a weak P-gp inhibitor and that no clinically significant interaction exists between digoxin, as a P-gp substrate, and entrectinib. Therefore, no dose adjustment is required when Rozlytrek is co-administered with P-gp substrates.

BCRP substrates

As with P-gp, a mild inhibition of BCRP was observed in *in vitro* studies. Given that no clinically significant interaction was observed with the P-gp substrate digoxin, an interaction with BCRP is not predicted. No dose adjustment is required when Rozlytrek is co-administered with BCRP substrates.

Other transporter substrates

In vitro data indicate that entrectinib has weak inhibitory potential toward organic anion-transporting polypeptide (OATP) 1B1 and multidrug and toxin extrusion protein 1 (MATE1).

Oral Contraceptive

Physiologically-based pharmacokinetic simulation of the effects of co-administration of multiple oral doses of entrectinib with ethinyl estradiol, an oral contraceptive, predicted no drug-drug interaction. GMR with/without entrectinib for AUC_{inf} (90% CI) of 112% (111%, 113%) and C_{max} (90% CI) was 112% (111%, 113%).

Therefore Rozlytrek can be co-administered with an oral contraceptive.

Effects of other drugs on entrectinib

Based on *in vitro* data, CYP3A4 is the predominant enzyme mediating the metabolism of entrectinib and formation of its major active metabolite M5.

CYP3A inducers

Co-administration of multiple oral doses of rifampin, a strong CYP3A inducer, with a single oral dose of entrectinib reduced the systemic exposure of entrectinib by 77%. GMR with/without rifampin for AUC_{inf} (90% CI) was 23.3% (18.4%, 29.5%) and C_{max} (90% CI) was 44.4% (35.3%, 55.9%). Co-administration of Rozlytrek with CYP3A inducers should be avoided (see section 4.2).

CYP3A inhibitors

Co-administration of a single oral dose of entrectinib with multiple oral doses of itraconazole, a strong CYP3A4 inhibitor, increased the systemic exposure of entrectinib by 500%. GMR with/without itraconazole for AUC_{inf} (90% CI) was 604% (454%, 804%) and C_{max} (90% CI) was 173% (137%, 218%).

Co-administration of strong and moderate CYP3A inhibitors (including, but not limited to, anti-fungal medicines, anti-retroviral medicines) with Rozlytrek should be avoided or limited to 14 days. If concurrent use is unavoidable, dose adjustment of Rozlytrek is required as described in section 4.2.

Medicinal products that increase gastric pH

The aqueous solubility of entrectinib in vitro is pH dependent. In a clinical study, administration of entrectinib with lansoprazole (a proton pump inhibitor (PPI)), resulted in a 25% decrease in entrectinib systemic exposure which is not clinically relevant. GMR with/without lansoprazole for AUC_{inf} (90%CI) was 74.5% (64.7%, 85.9%) and C_{max} (90% CI) was 76.5% (67.6%, 86.6%).

Therefore, no dose adjustments are required when Rozlytrek is co administered with PPIs or other medicines that raise gastric pH (e.g., H2 receptor antagonists or antacids).

Effect of transporters on Entrectinib disposition

Based on the in vivo brain-to-plasma concentration ratio (≥ 0.6) at steady-state in rats and dogs as well as lack of sensitivity to a P-gp inhibitor in vitro in a P-gp expressing cell assay, entrectinib is considered a poor substrate of P-gp. M5 is a substrate of P-gp.

Entrectinib is not a substrate of BCRP but M5 is a substrate of BCRP. Entrectinib and M5 are not substrates of OATP1B1 or OATP1B3.

4.6 Fertility, pregnancy and lactation

Pregnancy

Female patients of reproductive potential must be advised to avoid pregnancy while receiving Rozlytrek (see section 4.4). There is no available data on the use of Rozlytrek in pregnant women. Based on animal studies with entrectinib (see section 5.3) and its mechanism of action, Rozlytrek may cause foetal harm when administered to a pregnant woman. Patients receiving Rozlytrek should be advised of the potential harm to the foetus. Female patients should be advised to contact the medical practitioner, should pregnancy occur.

Breastfeeding

Mothers should not breastfeed their infants when taking Rozlytrek.

Fertility

No fertility studies in animals have been performed to evaluate the effect of entrectinib. Except for dose dependent decreases in prostate weight in male dogs, no effects of entrectinib on reproductive organs were observed in the repeat-dose toxicology studies in rats and dogs at approximately 2.4-fold and 0.6-fold, respectively, the human exposure by AUC at the recommended human dose.

4.7 Effects on ability to drive and use machines

Rozlytrek has moderate influence on the ability to drive and use machines. Patients should be instructed not to drive or use machines until the symptoms resolve, if they experience cognitive adverse reactions, syncope, blurred vision, or dizziness, during treatment with Rozlytrek. (See section 4.4 and section 4.8).

4.8 Undesirable effects

Clinical Trials

Summary of the safety profile

For the clinical development program of Rozlytrek, a total of 504 patients have received Rozlytrek in 4 clinical trials (ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG). The safety of Rozlytrek was evaluated as integrated analyses of these 4 clinical trials. The median duration of exposure to Rozlytrek was 5.5 months.

The safety of Rozlytrek in adult patients has been evaluated in a total of 475 patients with NTRK-fusion positive, ROS1-positive or ALK-positive solid tumours, in studies ALKA, STARTRK-1, STARTRK-2.

The safety of Rozlytrek has been evaluated in 29 paediatric patients with solid tumours (27 patients enrolled in STARTRK-NG, and 2 patients enrolled in STARTRK-2). Of these, 1 patient was less than 1 year old, 21 patients were 2 to 11 years old, 7 patients were 12 to 17 years old.

Tabulated summary of adverse drug reactions from clinical trials

Table 5 summarizes the adverse drug reactions (ADRs) occurring in adult and paediatric patients treated with Rozlytrek. ADRs from clinical trials (Table 5) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$).

Table 5 Summary of adverse drug reactions occurring in patients treated with Rozlytrek in clinical trials (integrated safety population)

System Organ Class Adverse Reaction	Rozlytrek N=504		Frequency Category (All Grades)
	All Grades (%)	Grade ≥ 3 (%)	
General Disorders and Administration Site Conditions			
Fatigue ¹⁴	45.0	5.0	very common
Edema ⁶	37.3	1.4	very common
Pain ⁷	24.4	1.6	very common
Pyrexia	20.0	0.8	very common
Gastrointestinal Disorders			
Constipation	42.9	0.4	very common
Diarrhoea	33.5	2.6	very common
Nausea	32.1	0.8	very common
Vomiting	23.2	1.2	very common
Abdominal pain	11.1	0.6	very common
Dysphagia	10.1	0.4	very common
Nervous System Disorders			
Dysgeusia	42.3	0.4	very common
Dizziness ⁵	39.7	1.2	very common
Dysaesthesia ³	29.0	0.2	very common
Cognitive Disorders ¹	24.2	4.4	very common
Headache	17.5	1.0	very common
Peripheral Sensory Neuropathy ²	15.7	1.0	very common
Ataxia ⁴	15.7	0.8	very common
Sleep disturbances ¹⁶	13.5	0.4	very common
Mood disorders ¹⁷	9.1	0.6	common
Syncope	4.6	3.0	common
Respiratory Disorders			
Dyspnea	27.0	5.8*	very common
Cough	21.4	0.6	very common
Blood Disorders			
Anemia	28.2	9.7	very common
Neutropenia ¹⁰	11.3	4.4	very common
Metabolism and Nutritional Disorders			
Weight increased	26.4	7.3	very common
Decreased appetite	11.9	0.2	very common
Hyperuricemia	9.1	1.8	common
Dehydration	7.9	1.0	common

Tumour lysis syndrome	0.2	0.2*	uncommon
Renal and urinary disorders			
Blood creatinine increased	25.4	0.6	very common
Musculoskeletal Disorders			
Myalgia	19.6	0.6	very common
Arthralgia	19.0	0.6	very common
Muscular weakness	12.3	1.2	very common
Fractures ¹¹	6.2	2.4	common
Hepatobiliary Disorders			
AST increased	17.5	3.6	very common
ALT increased	16.1	3.4	very common
Infections and Infestations			
Lung infection ⁸	13.1	6.0*	very common
Urinary tract infection	12.7	2.6	very common
Eye Disorders			
Vision Blurred ¹³	11.9	0.4	very common
Skin and Subcutaneous Tissue Disorders			
Rash ¹²	11.5	1.4	very common
Vascular Disorders			
Hypotension ¹⁵	16.5	2.4	very common
Cardiac Disorders			
Congestive Heart Failure ⁹	3.0	2.2	common
Electrocardiogram QT prolonged	2.0	0.6	common
ALT: Alanine aminotransferase AST: Aspartate aminotransferase * Grades 3 to 5, inclusive of fatal adverse reactions (including 2 reactions of pneumonia, 2 reactions of dyspnea, and 1 reaction of tumour lysis syndrome) ¹ Includes preferred terms: cognitive disorder, confusional state, disturbance in attention, memory impairment, amnesia, mental status changes, hallucination, delirium, 'hallucination visual' and mental disorder. ² Includes the preferred terms: neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy ³ Includes the preferred terms: paresthesia, hyperesthesia, hypoesthesia, dysesthesia ⁴ Includes the preferred terms: ataxia, balance disorder, gait disturbances ⁵ Includes the preferred terms: dizziness, vertigo, dizziness postural ⁶ Includes the preferred terms: face edema, fluid retention, generalized edema, localized edema, edema, edema peripheral, peripheral swelling ⁷ Includes the preferred terms: back pain, neck pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity ⁸ Includes the preferred terms: bronchitis, lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, upper respiratory tract infection ⁹ Includes the preferred terms: acute right ventricular failure, cardiac failure, cardiac failure congestive, chronic right ventricular failure, ejection fraction decreased, pulmonary edema ¹⁰ Includes the preferred terms: neutropenia, neutrophil count decreased ¹¹ Includes the preferred terms: humerus fracture, foot fracture, ankle fracture, femoral neck fracture, stress fracture, fibula fracture, fracture, rib fracture, spinal fracture, wrist fracture, femur fracture, pathological fracture ¹² Includes the preferred terms: rash, rash maculopapular, rash pruritic, rash erythematous, rash papular ¹³ Includes the preferred terms: diplopia, vision blurred, visual impairment ¹⁴ Includes the preferred terms: fatigue, asthenia ¹⁵ Includes the preferred terms: hypotension, orthostatic hypotension ¹⁶ Includes the preferred terms: hypersomnia, insomnia, sleep disorder, somnolence ¹⁷ Includes the preferred terms: anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation			

Description of selected adverse drug reactions from clinical trials

Cognitive disorders

A variety of cognitive symptoms were reported across clinical trials. These included events reported as cognitive disorders (6.3%), confusional state (7.3%), disturbance in attention (3.8%), memory impairment (4.2%), amnesia (2.8%), mental status changes (1.2%), hallucination (1.0%), delirium

(0.8%), hallucination visual (0.4%) and mental disorder (0.2%). Grade 3 events were reported in 4.4% of patients. In the paediatric population, 3.4% (1/29) paediatric patients experienced disturbance in attention of Grade 1 severity. Patients who had brain metastases at baseline had a higher frequency of these events (29.7%) compared to those without brain metastases (23.1%).

Fractures

Fractures were experienced by 5.3% (N=475) of adult patients and 20.7% (N=29) of paediatric patients. In general, there was inadequate assessment for tumour involvement at the site of fracture; however, radiologic abnormalities possibly indicative of tumour involvement were reported in some patients. In both adult and paediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). In 2 paediatric patients, bilateral femoral neck fractures occurred. No patients discontinued Rozlytrek due to fractures.

In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area. The median time to fracture was 3.42 months (range: 0.26 months to 18.5 months) in adults. Rozlytrek was interrupted due to fractures in 36.0% of adult patients that experienced fractures.

In paediatric patients, all fractures occurred in patients with minimal or no trauma. The median time to fracture was 3.38 months (range: 1.77 months to 7.39 months) in paediatric patients. Rozlytrek was interrupted due to fractures in 33.3% of paediatric patients that experienced fractures.

Ataxia

Ataxia (including events of ataxia, balance disorder, and gait disturbances) was reported in 15.7% of patients. The median time to onset for ataxia was 0.36 months (range: 0.03 months to 28.19 months) and the median duration was 0.66 months (range: 0.03 months to 11.99 months). The majority of patients (67.1%) recovered from ataxia. Ataxia related adverse events were observed more frequently in elderly patients (23.8%) compared to patients below 65 years of age (12.8%).

Syncope

Syncope events were reported in 4.6% of patients. In some patients, syncope was reported with concurrent hypotension, dehydration, or QTc prolongation and in other patients no other concurrent related conditions were reported.

QTc interval prolongation

Among the 504 patients who received entrectinib across clinical trials, 17 (4.0%) patients with at least one post-baseline ECG assessment experienced QTcF interval prolongation of > 60 ms after starting entrectinib, and 12 (2.8%) patients had a QTcF interval of $\geq$ 500 ms.

Peripheral sensory neuropathy

Peripheral sensory neuropathy was reported in 15.7% of patients. The median time to onset was 0.49 months (range 0.03 months to 20.93 months) and the median duration was 0.76 months (range: 0.07 months to 6.01 months). The majority of patients (55.7%) recovered from peripheral neuropathy.

Eye Disorders

Eye disorders reported across clinical trials included events of vision blurred (8.5%), diplopia (2.6%), and visual impairment (1.6%). The median time to onset for eye disorders was 1.87 months (range: 0.03 months to 21.59 months). The median duration of eye disorders was 1.02 months (range 0.03 months to 14.49 months). The majority of patients (61.7%) recovered from the eye disorder events.

Laboratory Abnormalities

The following table provides treatment-emergent shifts from baseline in laboratory abnormalities occurring in patients treated with Rozlytrek across the 4 clinical trials.

Table 6 Rozlytrek Treatment-emergent shifts from baseline in key laboratory abnormalities

Laboratory Test Abnormality ¹	Rozlytrek NCI-CTCAE Grade N= 504 ²	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or 4 (%) ³
Chemistry		
Increased Blood Creatinine	94.8	3.1
Hyperuricemia	50.8	6.8
Increased AST	43.3	3.3
Increased ALT	38.4	3.1
Hematology		
Decreased Neutrophils	27.8	6.3
Decreased Hemoglobin	65.7	9.2
AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase ¹ Based on number of patients with available baseline and at least one on-treatment test value ² N=480 for Blood Creatinine ; N=478 for AST; N=479 for ALT; N=382 for Hyperuricemia; N=457 for Neutrophils; N=487 for Hemoglobin ³ Patients with change from baseline values of Grade of 0–2 to a post-baseline value of Grade 3 or Grade 4 at any time		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no experience with overdose in clinical trials with Rozlytrek. Patients who experience overdose should be closely supervised and supportive care instituted. There are no known antidotes for Rozlytrek.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX14

Mechanism of Action

Entrectinib is a potent inhibitor of receptor tyrosine kinases TRKA, TRKB and TRKC (encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes NTRK1, NTRK2 and NTRK3, respectively), proto-oncogene tyrosine-protein kinase ROS (ROS1; encoded by the gene ROS1), and anaplastic lymphoma kinase (ALK; encoded by the gene ALK). The major active metabolite of entrectinib, M5, showed similar in vitro potency and activity.

Fusion proteins that include TRK, ROS1 or ALK kinase domains drive tumourigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation. Entrectinib potently inhibits the TRK kinases, ROS1 and ALK, leading to inhibition of downstream signaling pathways, cell proliferation and induction of tumour cell apoptosis. Entrectinib demonstrates potent inhibition of cancer cell lines harboring NTRK, ROS1 and ALK fusion genes, irrespective of tumour type. Entrectinib has anti-tumour potency in NTRK and ROS1 fusion-driven tumour models, driving tumour regressions across multiple tumour types, including sarcomas, head

and neck carcinoma, non-small cell lung carcinoma (NSCLC), colorectal cancer (CRC), acute myeloid leukemia (AML), and gliomas.

Entrectinib is a CNS penetrant molecule that showed brain-to-plasma concentration ratios of 0.4 - 2.2 in multiple animal species (mice, rats and dogs). It has demonstrated potent anti-tumour activity in three TRKA-driven intracranial tumour models and one ALK-driven intracranial tumour model. These data are consistent with entrectinib dosing resulting in sufficient brain exposure achieving target pharmacological activities at steady-state and at clinically relevant systemic exposures.

Clinical / Efficacy Studies

NTRK fusion-positive solid tumours

Efficacy in Adult patients

The efficacy of Rozlytrek in the treatment of *NTRK* fusion-positive solid tumours in adult patients was evaluated by combining the results from 3 single-arm, open label clinical trials (ALKA, STARTRK-1 and STARTRK-2) through a pre-specified integrated analysis.

Study ALKA was a Phase I single arm, open-label study in patients ≥ 18 years of age with solid tumours with *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations to determine the maximum tolerated dose. Study STARTRK-1 was a Phase I multi-center single arm, open label study in patients ≥ 18 years of age with solid tumours with *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations. The study included a dose escalation segment and a dose expansion segment. In the dose expansion segment, patients received 600 mg daily in repeated 4-week cycles and the primary objective was to evaluate the recommended Phase 2 dose. Study STARTRK-2 was a multicenter, international Phase II single-arm basket study in patients with solid tumours with *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangements. Patients received 600 mg Rozlytrek once daily in 4-week cycles.

The primary efficacy outcome measures in the integrated analyses were objective response rate (ORR) and duration of response (DOR) as evaluated by Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. The secondary efficacy outcome measures included clinical benefit rate (CBR), progression-free survival (PFS), time to central nervous system (CNS) progression, overall survival (OS), and in patients presenting with CNS metastases at baseline - intracranial (IC) ORR, IC-DOR, and IC-PFS (also evaluated by BICR using RECIST v1.1).

The efficacy evaluable analyses set comprised a total of 74 adult patients with confirmed *NTRK* fusion-positive solid tumours treated with Rozlytrek, not previously treated with a TRK inhibitor, presenting with measurable disease at baseline as assessed by investigator, and with ≥ 6 months of follow up. *NTRK* fusion-positive status was determined by a validated nucleic acid-based test performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited laboratory, prior to enrollment in the study.

The baseline demographic and disease characteristics of the efficacy evaluable population were: 47.3% males, median age of 57 years (range: 21 to 83 years), 70.0% white Caucasian, 17.6% Asian, 5.5% Hispanic or Latino and 59.7% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (40.5%), 1 (45.9%), or 2 (13.5%). Most patients (97.3%) had metastatic disease [most common sites being lung (60.8%), lymph nodes (52.7%) and brain (25.7%)], 2.7% patients had locally advanced disease, and 27% patients had no prior systemic therapies. The overall median duration of follow-up was 14.2 months.

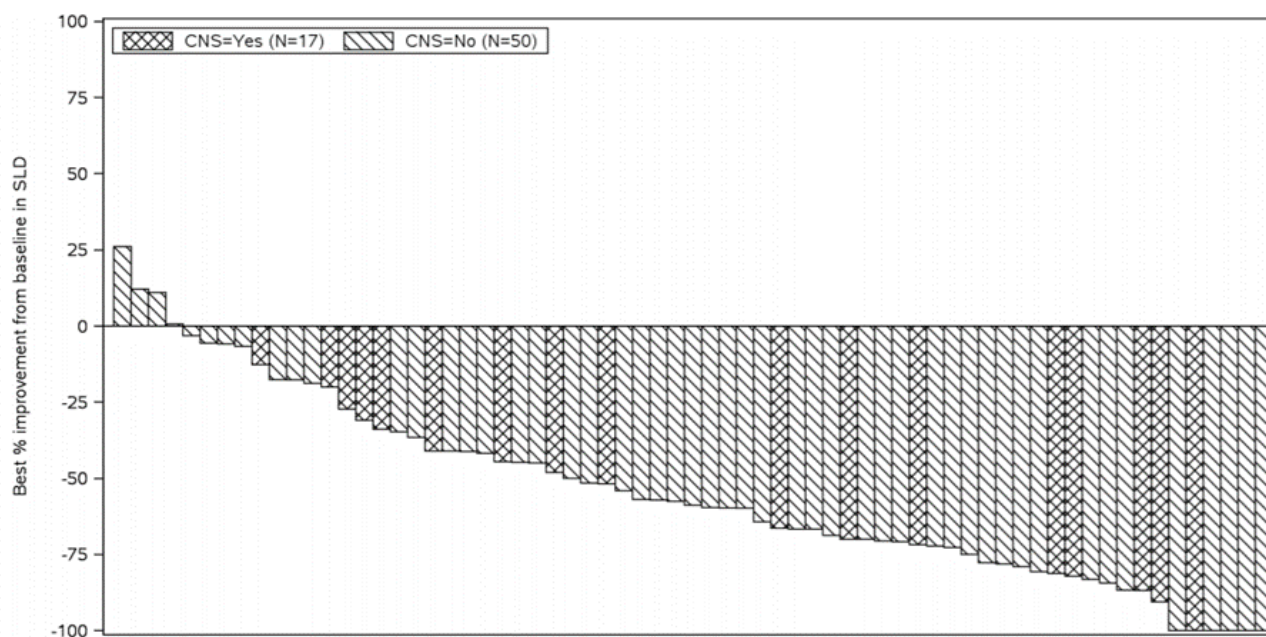
Efficacy results from patients with *NTRK*-fusion positive solid tumours are summarized in Table 7.

Table 7: Overall efficacy by BICR in Adults with NTRK-fusion positive Solid Tumours

Efficacy Endpoints	Rozlytrek N=74
Primary endpoints (BICR-assessed, RECIST 1.1)	
ORR	
Number of CR+PR	47/74
ORR% (95% CI)	63.5% (51.5, 74.4)
Complete Response, n (%)	5 (6.8%)
Partial Response, n (%)	42 (56.8%)
Stable Disease, n (%)	9 (12.2%)
Progressive Disease, n (%)	6 (8.1%)
DOR *	
Number (%) of patients with events	21/47 (44.7%)
Median, months (95% CI)	12.9 (9.3, NE)
6-month durable response % (95% CI)	0.71 (0.58, 0.85)
9-month durable response % (95% CI)	0.65 (0.51, 0.8)
12-month durable response % (95% CI)	0.55 (0.39, 0.72)
Secondary endpoints (BICR-assessed, RECIST 1.1)	
CBR	
Number of CR+PR+SD 6 months/Number of patients	50/74
CBR% (95% CI)	67.6% (55.7, 78.0)
PFS *	
Number (%) of patients with events/Number of patients	41/74 (55.4%)
Median, months (95% CI)	11.2 (8.0, 15.7)
Time to CNS Progression	
Number (%) of patients with events	27/74 (36.5%)
Median, months (95% CI)	16.8 (14.3, NE)
Overall Survival	
Number (%) of patients with events	24/74 (32.4%)
Median, months (95% CI)	23.9 (16.0, NE)
CR: complete response; PR: partial response; NE: not estimable. Confidence Intervals (CI) calculated using the Clopper-Pearson method. *Median and percentiles based on Kaplan-Meier estimates	

As shown in Figure 1, most adult patients with NTRK-fusion positive solid tumours experienced tumour shrinkage, as assessed by BICR according to RECIST 1.1.

Figure 1: Best percentage change in the sum of target lesions from baseline (BICR Assessment) in Adults with NTRK-fusion positive Solid Tumours, shaded by CNS metastases at baseline



SLD: Sum of Longest Diameter

Of the 74 adult patients with NTRK-fusion positive solid tumours in the efficacy evaluable analysis set, 19 patients were identified by the Investigator to have CNS metastases at baseline. Efficacy results by BICR according to RECIST v 1.1 in this subgroup of patients with CNS metastases at baseline are summarized in Table 8.

Table 8: Efficacy in Adults with NTRK-fusion positive Solid Tumours with CNS Metastases at Baseline

Secondary Endpoint (BICR-assessed, RECIST 1.1)	CNS Metastases at Baseline (by Investigator)	
	Yes N=19	No N=55
ORR		
Number of CR+PR	11	36
ORR% (95% CI)	57.9% (33.50, 79.75)	65.5% (51.42, 77.76)
Complete Response, n (%)	0	5 (9.1%)
Partial Response, n (%)	11 (57.9%)	31 (56.4%)
Stable Disease, n (%)	4 (21.1%)	5 (9.1%)
Progressive Disease, n (%)	1 (5.3%)	5 (9.1%)
DOR		
Number of patients with events	5 (45.5%)	16 (44.4%)
Median, months (95% CI)	6.0 (4.2, NE)	12.9 (9.3, NE)
PFS		
Number of patients with events	12 (63.2%)	29 (52.7%)
Median, months (95% CI)	6.7 (4.5, NE)	13.7 (10.1, 16.0)

CR: complete response; PR: partial response; NE: not estimable.
Confidence Intervals (CI) calculated using the Clopper-Pearson method.

Objective response rate and duration of response by tumour type in all efficacy evaluable adult patients with *NTRK*-fusion positive solid tumours is presented in Table 9.

Table 9: Efficacy by Tumour Type, in adults with *NTRK*-fusion positive Solid Tumours

Tumour Type	Patients (N=74)	ORR		DOR Range (months)
		n (%)	95% CI	
All	74	47 (63.5)	(51.5, 74.4)	1.4* to 26.0*
Sarcoma	16	9 (56.3)	(29.9, 80.3)	2.8, 15.1
Non-small cell lung cancer	13	9 (69.2)	(38.6, 90.9)	1.4*, 25.9*
Salivary (MASC)	13	12 (92.3)	(64.0, 99.8)	2.8, 22.1*
Breast cancer (secretory)	4	4 (100)	(39.8, 100)	5.5, 20.3*
Breast cancer (non-secretory)	2	NE, PR	NA	4.2
Thyroid cancer	7	3 (42.9)	(9.9, 81.6)	5.6, 10.9*
Colorectal cancer	7	2 (28.6)	(3.7, 71)	7.9*, 15.2
Neuroendocrine cancers	4	2 (50.0)	(6.8, 93.2)	1.9*, 9.2*
Pancreatic cancer	3	2 (66.7)	(9.4, 99.2)	7.1, 12.9
Ovarian cancer	1	Non CR/PD	NA	NA
Endometrial carcinoma	1	PR	NA	26.0*
Cholangiocarcinoma	1	PR	NA	9.3
Gastrointestinal cancer (other)	1	PR	NA	5.6*
Neuroblastoma	1	NE	NA	NA

* Censored
ORR: Objective Response Rate; DOR: Duration of Response; MASC: mammary analogue secretory carcinoma; NA: not applicable due to small number or lack of response; CR: complete response; PR: partial response; PD: progressive disease; NE: Not estimable.

Intracranial Response

Of the 74 adult patients with *NTRK*-fusion positive solid tumours in the efficacy evaluable analysis set, 16 patients had CNS metastases at baseline as assessed by BICR, including 8 patients with measurable CNS lesions. Intracranial ORR, DOR, and PFS assessed by BICR according to RECIST version 1.1 in this subgroup of patients with measurable CNS lesions at baseline are summarized in Table 10.

Table 10: Intracranial Efficacy in Adults with *NTRK*-fusion positive Solid Tumours with CNS Metastases at Baseline by BICR

Secondary Endpoint (BICR-assessed, RECIST 1.1)	CNS Metastases at Baseline (by BICR)	
	Measurable disease N=8	All patients N=16
IC-ORR		
Responders	5	8
IC-ORR% (95% CI)	62.5% (24.5, 91.5)	50% (24.7, 75.4)
Complete Response n (%)	1 (12.5%)	4 (25%)
Partial Response n (%)	4 (50%)	4 (25%)
IC-DOR		
Number of patients with events (%)	2 (40%)	4 (50%)
Median, months (95%)	NE (5.0, NE)	8.0 (6.7, NE)
IC-PFS		
Number of patients with events (%)	4 (50%)	10 (62.5%)
Median, months (95% CI)	10.1 (2.8, NE)	8.9 (5.9, 14.3)

NE: not estimable.
IC-ORR derived using RECIST 1.1 criteria applied only to CNS lesions.
Confidence Intervals (CI) calculated using the Clopper-Pearson method.

Primary CNS tumours

Across the three trials, seven adult patients with CNS primary tumours were treated with Rozlytrek with a minimum of 6 months of follow-up. IC-ORR, DOR and PFS were assessed by BICR according to Response Assessment in Neuro-Oncology Criteria (RANO). One patient had an objective response with a DOR of 2.79 months and PFS of 6.34 months.

Patient Reported Outcomes

Study STARTRK-2 evaluated patient-reported outcomes (PRO) of the treatment impact on symptoms, functioning and health-related quality of life (HRQoL) based on the EORTC Core Quality of Life Questionnaire (QLQ-C30), Lung Cancer Module (QLQ-LC13), and the Colorectal Cancer Module (QLQ-CR29).

Most safety evaluable patients indicated that the symptoms commonly associated with Rozlytrek treatment (lack of appetite, nausea, diarrhoea and vomiting) were of low severity, if present. Efficacy evaluable patients with *NTRK*-fusion positive NSCLC (n=12) reported moderate lung-related symptoms at baseline with qualitative trends towards improvement while receiving Rozlytrek. Patients with mCRC (n=7) reported low abdominal symptoms burden at baseline, which generally remained low over time. Qualitative trends towards improvements in functioning (moderate to high at baseline) and maintenance of HRQoL (high at baseline) were observed for patients with *NTRK* fusion-positive solid tumours while receiving Rozlytrek as measured by the Physical function, Role function and Global Health Status from the EORTC QLQ-C30.

Efficacy in Paediatric patients

The efficacy of Rozlytrek in paediatric patients with *NTRK* fusion-positive solid tumours was evaluated in study STARTRK-NG (ST-NG). This study is a multi-center Phase I/II, open-label dose-escalation and expansion study in paediatric patients with relapsed or refractory solid tumours, including primary CNS tumours, with or without *NTRK*, *ROS1* or *ALK* molecular alterations. Patients received 250 mg/m² to 750 mg/m² once daily of Rozlytrek in 4-week cycles. The range of survival follow up was 6.9 months to 18.0 months.

Table 11 summarizes the efficacy of Rozlytrek in 7 paediatric patients (less than 18 years of age) with *NTRK* fusion-positive solid tumours as assessed by the BICR according to RECIST version 1.1 for extra-cranial tumours and according to RANO for CNS primary tumours. Efficacy data in paediatric patients with *NTRK* fusion-positive solid tumours is further supported by extrapolation from results in the respective adult populations.

Table 11: Efficacy in Paediatric patients with *NTRK* fusion-positive Solid Tumours assessed by BICR

Tumour Type	Best Overall Response	Duration of Response (months)
Infantile fibrosarcoma	PR	13.6*
Infantile fibrosarcoma	CR ^b	6.5*
Epithelioid glioblastoma ^a	CR ^b	9.7*
High grade glioma ^a	PR ^b	14.3*
Metastatic melanoma	PR ^b	12.9*
Anaplastic ganglioglioma ^a	CR ^b	5.5
Ganglioneuroblastoma of the CNS ^a	PR ^b	3.7*
^a Primary CNS tumours (assessment was by RANO criteria) ^b Patient was still receiving entrectinib treatment at the time of the clinical cutoff date (1 May 2019) * censored observation		

ROS1-positive NSCLC

The efficacy of Rozlytrek in the treatment of ROS1 positive locally advanced or metastatic NSCLC was evaluated by combining the results from 3 single-arm, open label clinical trials (ALKA, STARTRK-1 and STARTRK-2) described above, through a pre-specified integrated analysis.

The primary efficacy outcome measures in the integrated analyses were ORR and DOR, as evaluated by BICR according to RECIST v1.1. The secondary efficacy outcome measures included CBR, PFS, time to CNS progression, OS, and in patients presenting with CNS metastases at baseline - IC-ORR, IC-DOR, and IC-PFS (also evaluated by BICR using RECIST v1.1).

The efficacy evaluable analyses set comprised a total of 94 patients with histologically confirmed ROS1-positive NSCLC treated with Rozlytrek, not previously treated with a ROS1-inhibitor, presenting with measurable disease at baseline as assessed by the investigator, and with ≥ 12 months of follow up. ROS1-positive status was determined by a validated nucleic acid-based test performed at a CLIA-certified or equivalently accredited laboratory, prior to enrollment in the study.

The baseline demographic and disease characteristics of the efficacy evaluable population were: 36.2% males, median age of 53 years (range: 27 to 86 years), 79.8% patients <65 years of age, 48.9% white Caucasian, 43.6% Asian, 5.3% Black, 2.4% Hispanic or Latino and 59.6% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (37.2%), 1 (51.1%), or 2 (11.7%). Most patients (98.9%) had metastatic disease with 42.6% having brain metastases [other common sites were lung (57.4%) and lymph nodes (75.5%)], 1.1% patients had locally advanced disease, and 33% patients had no prior systemic therapies. The overall median duration of follow-up was 20.9 months.

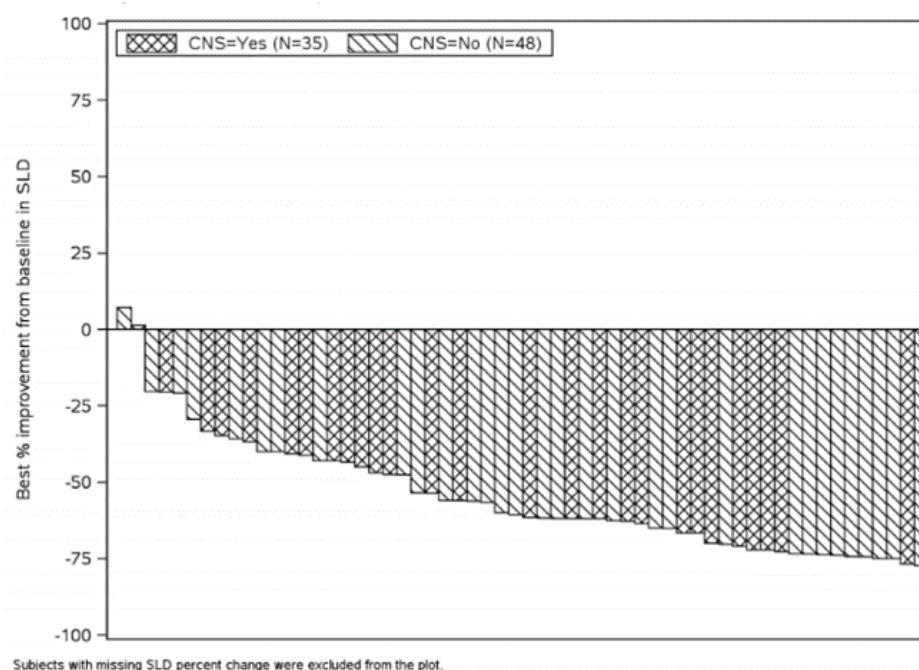
Efficacy results from patients with ROS1-positive NSCLC are summarized in Table 12.

Table 12: Overall Efficacy by BICR in patients with ROS1-positive NSCLC

Efficacy Endpoint	Rozlytrek N= 94
Primary endpoints (BICR-assessed, RECIST 1.1)	
ORR	
Number of CR+PR	69/94
ORR% (95% CI)	73.4 (63.3, 82.0)
Complete Response, n (%)	11 (11.7%)
Partial Response, n (%)	58 (61.7%)
Stable Disease, n (%)	6 (6.4%)
Progressive Disease, n (%)	8 (8.5%)
DOR *	
Number (%) of patients with events	36/69 (52.2%)
Median, months (95% CI)	16.5 (14.6, 28.6)**
6-month durable response % (95% CI)	0.82 (0.72, 0.91)
9-month durable response % (95% CI)	0.79 (0.69, 0.89)
12-month durable response % (95% CI)	0.66 (0.54, 0.78)
Secondary endpoints (BICR-assessed, RECIST 1.1)	
CBR	
Number of CR+PR+SD 6 months	70/94
CBR% (95% CI)	74.5% (64.4, 82.9)
PFS*	
Number (%) of patients with events	54/94 (57.4%)
Median, months (95% CI)	16.8 (12.0, 21.4)
Time to CNS Progression	
Number (%) of patients with events	40/94 (42.6%)
Median, months (95% CI)	24.8 (16.1, NE)
Overall Survival	
Number (%) of patients with events	25/94 (26.6%)
Median, months (95% CI)	NE (28.3, NE)
CR: complete response; PR: partial response; NE: not estimable. Confidence Intervals (CI) calculated using the Clopper-Pearson method. *Median and percentiles based on Kaplan-Meier estimates **not a robust estimate	

Most ROS1-positive NSCLC patients treated with Rozlytrek experienced tumour shrinkage of their defined target lesions, as assessed by BICR according to RECIST 1.1. See Figure 2.

Figure 2: Best percentage change in the sum of target lesions from baseline (BICR Assessment) in patients with ROS1-positive NSCLC, shaded by CNS metastases at baseline



SLD: Sum of Longest Diameter

Of the 94 patients with ROS1-positive NSCLC in the efficacy evaluable analysis set, 40 patients were identified by the Investigator to have CNS metastases at baseline. Efficacy results by BICR according to RECIST v 1.1 in this subgroup of patients with CNS metastases at baseline are summarized in Table 13.

Table 13: Efficacy in ROS1-positive NSCLC Patients with CNS metastases at Baseline

Secondary Endpoints (BICR-assessed, RECIST 1.1)	CNS Metastases at Baseline (by Investigator)	
	Yes N=40	No N=54
ORR		
Number of CR+PR	27/40	42/54
ORR% (95% CI)	67.5% (50.9, 81.4)	77.8% (64.4, 88.0)
Complete Response, n (%)	4 (10.0)	7 (13.0)
Partial Response, n (%)	23 (57.5)	35 (64.8)
Stable Disease, n (%)	2 (5.0)	4 (7.4)
Progressive Disease, n (%)	6 (15.0)	2 (3.7)
DOR		
Number of patients with events	14/27 (51.9%)	22/42 (52.4%)
Median, months (95% CI)	16.5 (9.6, NE)	24.6 (13.9, 34.8)
PFS		
Number of patients with events	25/40 (62.5%)	29/54 (53.7%)
Median, months (95% CI)	11.9 (6.3, 21.1)	21.1 (14.8, 30.8)
CR: complete response; PR: partial response; NE: not estimable. Confidence Intervals (CI) calculated using the Clopper-Pearson method.		

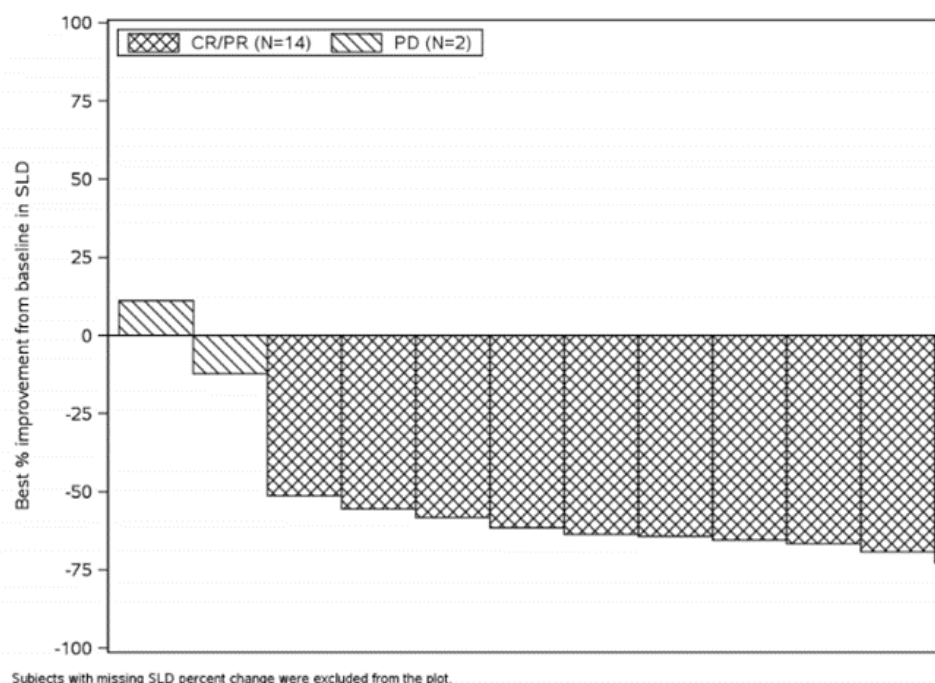
Intracranial Response

Of the 94 patients with ROS-1 positive NSCLC in the efficacy evaluable analysis set, 34 patients had CNS metastases at baseline as assessed by BICR, including 18 patients with measurable CNS lesions. Intracranial ORR, DOR, and PFS assessed by BICR according to RECIST version 1.1 in this subgroup of patients with measurable CNS lesions at baseline are summarized in Table 14 and Figure 3 below.

Table 14: Intracranial Efficacy in ROS1-positive NSCLC patients with CNS metastases at baseline by BICR

Secondary Endpoint (BICR-assessed, RECIST 1.1)	CNS Metastases at Baseline (by BICR)	
	Measurable disease N=18	All patients N=34
IC-ORR		
Responders	14	17
IC-ORR% (95% CI)	77.8% (52.4, 93.6)	50% (32.4, 67.6)
Complete Response n (%)	2 (11.1%)	5 (14.7%)
Partial Response n (%)	12 (66.7%)	12 (35.3%)
IC-DOR		
Number of patients with events (%)	10 (71.4%)	11 (64.7%)
Median, months (95%)	12.9 (5.3, 16.5)	12.9 (5.6, 22.1)
IC-PFS		
Number of patients with events (%)	13 (72.2%)	25 (73.5%)
Median, months (95% CI)	7.7 (4.6, 17.4)	7.7 (4.6, 15.7)
NE: not estimable. IC-ORR derived using RECIST 1.1 criteria applied only to CNS lesions. Confidence Intervals (CI) calculated using the Clopper-Pearson method.		

Figure 3: Intracranial Activity- Best Percent Change from Baseline in Tumour Sum in ROS1-positive NSCLC Patients with Measurable CNS metastases at Baseline by BICR



SLD: Sum of Longest Diameter

Patients without measurable CNS disease at baseline or without post-baseline measurements were excluded from the plot

Patient Reported Outcomes

Patients with ROS1-positive NSCLC reported rapid and durable clinically meaningful improvement (change from baseline of ≥ 10 points on a 0-100 scale) in lung-cancer symptoms (cough, dyspnea, chest pain) as measured by the EORTC QLQ LC13. Patients maintained their day-to-day function resulting in an improvement in HRQoL while on Rozlytrek treatment (evaluated by the Physical function, Role function and Global Health Status from the EORTC QLQ-C30). In addition, most patients, indicated that the symptoms commonly associated with Rozlytrek treatment (lack of appetite, nausea, diarrhoea and vomiting) were of low severity, if present.

Immunogenicity

Not applicable.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters for entrectinib and its major active metabolite (M5), have been characterized in patients with NTRK-positive solid tumours and ROS1-positive NSCLC, and healthy subjects.

Following administration of a single 600 mg dose of entrectinib, the estimated entrectinib mean ($\pm$ SD) C_{max} was 1990 ($\pm$ 1050) nM and AUC_{0-24} 33900 ($\pm$ 15800) nM $\cdot$ h and for M5 C_{max} was 765 ($\pm$ 598) nM and AUC_{0-24} 13300 ($\pm$ 10200) nM $\cdot$ h. At steady-state the estimated entrectinib mean C_{max} was 3490 ($\pm$ 1600) nM and AUC_{0-24} 62800 ($\pm$ 29100) nM $\cdot$ h and for M5 C_{max} was 1340 ($\pm$ 934) nM and AUC_{0-24} 25500 ($\pm$ 29100) nM $\cdot$ h.

The population PK model estimated mean accumulation at steady-state following 600 mg once daily administration of entrectinib was 1.89 ($\pm$ 0.381) and 2.01 ($\pm$ 0.437) for M5.

Absorption

Following a single 600 mg oral administration of Rozlytrek to patients with NTRK-fusion positive and ROS1 positive NSCLC under fed conditions, entrectinib was rapidly absorbed reaching time-to-maximum plasma concentration (T_{max}) after approximately 4 - 6 hours. Based on population pharmacokinetic analysis, steady-state was achieved within 5 days for entrectinib with 600 mg once daily dosing.

The estimated absolute bioavailability of entrectinib based on physiologically based pharmacokinetic (PBPK) modeling was 55%.

No clinically significant effect of food on entrectinib bioavailability was observed. Following a single 600 mg oral administration of Rozlytrek to healthy subjects under fasting conditions and following a high fat, high calorie meal, the GMR under fed/fasted condition for AUC_{inf} (90% CI) was 115% (107, 124) and for C_{max} (90%CI) was 106% (98.9, 115). Entrectinib can be administered with or without food (see section 2.2).

Distribution

Entrectinib and its major active metabolite M5 are highly bound to human plasma proteins independent of drug concentrations. In human plasma, entrectinib and M5 had similar protein binding with $>99\%$ bound at a clinically relevant concentration.

After a single oral dose of [^{14}C]-labeled entrectinib, the geometric mean volume of distribution (V_z/F) was 860 L, suggesting extensive distribution into tissues. Population pharmacokinetic analysis estimated volume of distribution of 551 L and 81.1 L for entrectinib and M5, respectively.

Metabolism:

Entrectinib is metabolized predominantly by CYP3A4 ($\sim 76\%$). Minor contributions from several other CYPs and UGT1A4 were estimated at $<25\%$ in total. The active metabolite M5 (formed by CYP3A4) and the direct N-glucuronide conjugate, M11 (formed by UGT1A4), are the two major circulating metabolites identified.

Elimination:

Following administration of a single dose of [¹⁴C]-labeled entrectinib administered orally to healthy subjects, the majority of radioactivity was excreted in feces (82.9%) with minimal excretion in urine (3.06%). In feces, 35.7% and 22.1% of the dose was excreted as unchanged entrectinib and M5, respectively, indicating hepatic clearance is the major route of elimination.

Entrectinib and M5 account for approximately 73% of radioactivity in systemic circulation at C_{max}, and approximately half of total radioactivity AUC_{inf}.

Population PK analysis estimated a CL/F of 19.6 L/h and 52.4 L/h for entrectinib and M5, respectively. The elimination half-lives of entrectinib and M5 were estimated to be 20 and 40 hours, respectively.

Pharmacokinetics in Special Populations

Paediatric Population

Non-compartmental analysis and population pharmacokinetic modeling approaches demonstrated that the pharmacokinetics of entrectinib and M5 were comparable in adults and children allowing extrapolation of data in adults to paediatric patients.

Data obtained from population pharmacokinetic analyses show that a dose of 300 mg/m² of Rozlytrek once daily in paediatric patients' results in a similar systemic exposure attained in adults treated with 600 mg of Rozlytrek, once daily. Population pharmacokinetic analysis data support dosing of paediatric patients with BSA ≥ 1.51 m² with 600 mg of Rozlytrek once daily.

Elderly Population

No differences in entrectinib exposure were noted in patients older than 65 years and younger adults based on pharmacokinetic analysis.

Renal impairment

Negligible amounts of entrectinib and the active metabolite M5 are excreted unchanged in urine (~3 % of the dose) indicating renal clearance plays a minor role in the elimination of entrectinib. Population pharmacokinetic data obtained in patients with mild and moderate impairment show that pharmacokinetics of entrectinib are not significantly affected in renal impairment. No formal pharmacokinetic study has been conducted and no population pharmacokinetic data was collected in patients with severe renal impairment. However, since entrectinib elimination via the kidney is negligible, no dose adjustment is required in patients with renal impairment.

Hepatic impairment

The pharmacokinetics of entrectinib were studied in subjects with hepatic impairment due to cirrhosis and subjects with normal hepatic function. Following administration of a single oral dose of 100 mg entrectinib, the AUC_{inf} GMRs (90%CI) of entrectinib were 1.57 (1.03, 2.41) for the mild (Child-Pugh A), 1.54 (1.06, 2.24) for the moderate (Child-Pugh B), and 1.80 (1.22, 2.66) for the severe (Child-Pugh C) hepatic impaired groups compared to the normal hepatic function group. The combined AUC_{last} of entrectinib and M5 showed no relevant change in the hepatic impaired groups compared to the normal hepatic function group. The AUC_{last} GMRs (90%CI) were 1.30 (0.889, 1.89) for the mild, 1.24 (0.886, 1.73) for the moderate, and 1.39 (0.988, 1.95) for the severe hepatic impaired groups compared to the normal hepatic function group.

In addition to the modest increases in entrectinib exposure observed, the variability in systemic exposure was high and observed exposures overlapped across all the study groups.

No dose adjustment is required in patients with underlying mild, moderate or severe hepatic impairment.

5.3 Preclinical safety data

Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of entrectinib.

Genotoxicity

Entrectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay. Entrectinib was not clastogenic in the in vivo micronucleus assay in rats and did not induce DNA-damage in a comet assay in rats. A potential for abnormal chromosome segregation (aneugenicity) has been detected under in vitro conditions in cultured human peripheral blood lymphocytes (HPBL) but was not detected in the in vivo micronucleus assay in rats.

Impairment of Fertility

No fertility studies in animals have been performed to evaluate the effect of entrectinib. With the exception of dose dependent decreases in prostate weight in male dogs, no effects of entrectinib on reproductive organs were observed in the repeat-dose toxicology studies in rats and dogs at approximately 2.4-fold and 0.6-fold, respectively, the human exposure by AUC at the recommended human dose.

Reproductive Toxicity

In an embryo-fetal developmental study in rats, maternal toxicity (decreased body weight gain and food consumption) and fetal malformations (including body closure defects and malformations of the vertebrae and ribs), were observed at 200 mg/kg/day of entrectinib, which represents approximately 2-fold the human exposure by AUC at the recommended dose. Lower fetal weights and reduced skeletal ossification were observed at exposures equivalent to 0.7 times the human exposure by AUC at the recommended dose.

Other

In a 13-week juvenile rat toxicology study from post-natal day 7 to day 97 (approximately equivalent to neonate to 16 years of age in humans), 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) and decreased femur length (at 16 mg/kg/day, approximately 0.3 times the human exposure by AUC at the recommended dose).

Entrectinib penetrates the CNS with brain-to-plasma concentration ratios of ~ 0.4 in mice, 0.6-1.5 in rats and 1.4-2.2 in dogs following repeated oral daily dosing. Consistent with being a weak P-gp substrate, entrectinib demonstrated high retention in the CNS following IV infusion in rats, achieving sufficient steady-state concentrations in the brain to cover target pharmacological activity at clinically relevant systemic exposure. M5 was also detected in a brain homogenate in rats following a single oral dose or an IV infusion of entrectinib for 5-6 hours, but the exposures of M5 were lower than entrectinib in both plasma and brain in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

Capsule content

Tartaric acid
Lactose
Hypromellose
Crospovidone
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Capsule shell

Hypromellose
Titanium dioxide (E171)

Yellow iron oxide (E172 – 100 mg hard capsule)
Sunset yellow FCF (E110 – 200 mg hard capsule)

Printing ink
Shellac
Propylene glycol
Indigo carmine aluminium lake (E132)

Contains sugar (lactose)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package and keep the bottle tightly closed to protect from moisture.

6.5 Nature and contents of container

Rozlytrek 100 mg hard capsules

HDPE bottles containing 30 hard capsules with a child-resistant, tamper-evident closure and silica gel desiccant integrated in the cap.

Rozlytrek 200 mg hard capsules

HDPE bottles containing 90 hard capsules with a child-resistant, tamper-evident closure and silica gel desiccant integrated in the cap.

6.6 Special precautions for disposal and other handling

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd
90 Bekker Road, Hertford Office Park,
Building E, Vorna Valley, Midrand,
Johannesburg, 1686
South Africa
Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

Rozlytrek 100 mg : 56/26/0575

Rozlytrek 200 mg : 56/26/0576

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Registration: 23 May 2023

10. DATE OF REVISION OF THE TEXT

Last revision: 17 October 2025

Registration number(s)



Rozlytrek 100 mg	Namibia: NS2 23/26/0029
Rozlytrek 200 mg	Namibia: NS2 23/26/0028

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