For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

WARNING: To be sold by retail under the prescription of an Oncologist only.

Entrectinib Capsule 100mg

Entrectinib Capsule 200mg

ROZLYTREK®

रॉज़्लिट्रेक ®

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent, Tyrosine Kinase inhibitor

ATC Code: L01EX14

1.2 TYPE OF DOSAGE FORM AND STRENGTHS

Dosage form: Hard Capsules

Strengths: 100 mg and 200 mg

1.3 ROUTE OF ADMINISTRATION

Oral

1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

1.5 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: Lactose anhydrous, Microcrystalline cellulose, Tartaric acid, Hypromellose, Crospovidone, Magnesium stearate, Colloidal silicon dioxide.
Capsule Shell- Body: Hypromellose, Titanium dioxide, FD&C Yellow #6; Cap: Hypromellose, Titanium dioxide (E171, CI77891), FD&C Yellow #6 (E110, CI15985), Colorant, Printing Ink

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

ROZLYTREK is a kinase inhibitor indicated for the treatment of:

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive.
- Adult and pediatric patients 12 years of age and older with solid tumors that:
  - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation,
  - are metastatic or where surgical resection is likely to result in severe morbidity and
  - have progressed following treatment or have no satisfactory alternative therapy.

2.2 DOSAGE AND ADMINISTRATION

General

Patient Selection

Solid Tumors

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

NSCLC
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.

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 until disease progression or unacceptable toxicity

Pediatric patients 12 Years and Older (Adolescents)
The recommended dosage of Rozlytrek is based on body surface area (BSA) as shown in Table 1 below. Take Rozlytrek orally once daily with or without food until disease progression or unacceptable toxicity.

Table 1: Dosing in Pediatric Patients 12 Years and Older (Adolescents)

Body surface area (BSA)	Recommended Dosage Once daily dose
1.11-1.50 m^2	400mg
≥ 1.51 m^2	600mg

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

Pediatric Patients
Table 3 provides specific dose reduction advice for pediatric patients. For pediatric 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 pediatric dose. Rozlytrek treatment should be permanently discontinued if patients are unable to tolerate the lowest reduced dose.

Table 3: Dose Reduction Schedule for pediatric patients

Action	**Pediatric Patients 12 Years and Older with BSA of 1.11 to 1.50 m2 (Orally once daily)**	**Pediatric Patients 12 Years and Older with BSA of 0.91 to 1.10 m2 (Orally once daily)**
First dose reduction	400 mg	300 mg
Second dose reduction*	200 mg	200 mg

*For a subsequent modification, permanently discontinue Rozlytrek in patients who are unable to tolerate Rozlytrek after two dose reductions.

Dose Modifications for Specific Adverse Reactions
Recommendations for Rozlytrek dose modifications for adults and pediatric patients for specific adverse reactions are provided in Table 4.

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 ≤ Grade 2 or to baseline, then resume treatment at same dose level or reduced dose, as clinically needed.
Cognitive Disorders	Grade ≥ 2	• Withhold Rozlytrek until recovery to ≤ 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; signs/symptoms of serious arrhythmia	• Permanently discontinue Rozlytrek
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 2.8 *Interactions with Other Medicinal Products and other forms of Interaction).*

Pediatric patients
The concomitant use of strong or moderate CYP3A inhibitors in pediatric patients should be avoided. (See section 2.8 *Interactions with Other Medicinal Products and other forms of Interaction).*

Concomitant CYP3A inducers:
Co-administration of Rozlytrek with CYP3A inducers in adult and pediatric patients should be avoided. (See section 2.8 *Interactions with Other Medicinal Products and other forms of Interaction.*)

2.2.1 Special Dosage Instructions

Pediatric use

Pediatric patients must have the ability to swallow whole Rozlytrek capsules. Dosage for patients is based on body surface area (mg/m^2) with a maximum daily dose of 600 mg (see Table 1 for pediatric dosing).

Geriatric use

No dose adjustment of Rozlytrek is required in patients ≥ 65 years of age. (See section *3.2.5 Pharmacokinetics in Special Populations)*.

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 2.5 *Use in Special Populations* and section 3.2.5 *Pharmacokinetics in Special Populations).*

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 2.5 *Use in Special Populations* and section 3.2.5 *Pharmacokinetics in Special Populations).*

Other Special Patient Populations

Ethnicity

No dose adjustment is necessary for patients of different ethnicities *(*see section 3.2.5 *Pharmacokinetics in Special Populations)*.

2.3 Contraindications

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

2.4 Warnings and Precautions

2.4.1 General

Congestive Heart Failure

Congestive heart failure (CHF) has been reported across clinical trials with Rozlytrek (see Table 5 in section 2.6.1 *Undesirable Effects*). 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 2.2 *Dosage and Administration.*

Cognitive Disorders

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with Rozlytrek (see section 2.6.1 *Undesirable Effects* for description of events). 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 2.2 *Dosage and Administration*.

Patients should be counseled 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 2.4.3 *Ability to drive and use machine)s.*

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 pediatric 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 pediatric 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 2.6.1 *Undesirable Effects)*.

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 2.2 *Dosage and Administration.*

Embryo-fetal toxicity

Based on the findings in animal studies, Rozlytrek may cause fetal harm when administered to a pregnant woman. When administrated 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 3.3.4 *Reproductive toxicity)*.

Female patients receiving Rozlytrek should be advised of the potential harm to the fetus. Female patients of reproductive potential, must use highly effective contraceptive methods during treatment and for 5 weeks following the last dose of Rozlytrek. (See section 2.5.1 *Females and Males of Reproductive potential*).

2.4.2 Drug Abuse and Dependence

Not applicable.

2.4.3 Ability to Drive and Use Machines

Rozlytrek may influence 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 2.4 *Warnings and Precautions* and section 2.6 *Undesirable effects*).

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Fertility

See section 3.3.3 *Impairment of fertility.*

Pregnancy testing

Female patients of reproductive potential should have medically supervised pregnancy testing prior to initiating Rozlytrek therapy.

Contraception

Female patients of reproductive potential, must use highly effective contraceptive methods during treatment and for 5 weeks following the last dose of Rozlytrek. Based on the potential for genotoxicity, male patients with female partners of child-bearing potential must use highly effective contraceptive methods during treatment and for 3 months following the last dose of Rozlytrek (See section 3.3.2 *Genotoxicity*).

2.5.2 Pregnancy

Female patients of reproductive potential must be advised to avoid pregnancy while receiving Rozlytrek (see section 2.4 *Warnings and Precautions*). There is no available data on the use of Rozlytrek in pregnant

women. Based on animal studies with Entrectinib (see section 3.3 *Nonclinical Safety*) and its mechanism of action, Rozlytrek may cause fetal harm when administered to a pregnant woman. Patients receiving Rozlytrek should be advised of the potential harm to the fetus. Female patients should be advised to contact the doctor, should pregnancy occur.

Labor and Delivery

The safe use of Rozlytrek during labor and delivery has not been established.

2.5.3 Lactation

It is not known whether Entrectinib or its metabolites are excreted in human breast milk. No studies have been conducted to assess the effects of Rozlytrek on milk production or its presence in breast milk. As the potential for harm to the nursing infant is unknown, mothers should be advised to discontinue breast-feeding during treatment with Rozlytrek.

2.5.4 Paediatric Use

The safety and efficacy of Rozlytrek have been studied in pediatric patients. See section *2.4.1 Warnings and Precautions,* 2.6.1 *Undesirable Effects, Clinical Trials* and section 3.1.2 *Clinical/Efficacy Studies.* In addition, use of Rozlytrek in pediatric patients is supported by extrapolation of evidence from clinical trials in adults to pediatric population, based on population pharmacokinetic data demonstrating similar drug exposure in adults and pediatric patients. See section 2.2.1 *Special Dosage Instructions,* section 3.1.2 *Clinical/Efficacy Studies,* and section 3.2.5 *Pharmacokinetics, Special Populations.*

Rozlytrek was associated with a higher incidence of skeletal fractures in the pediatric patients compared to adult patients. See section 2.4.1 *Warnings and Precautions* and 2.6.1 *Undesirable Effects, Clinical Trials*.

2.5.5 Geriatric 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 2.2.1 *Special Dosage Instructions* and section 3.2.5 *Pharmacokinetics, Special Populations.*

2.5.6 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 2.2.1 *Special Dosage Instructions, Renal Impairment* and section 3.2.5 *Pharmacokinetics, Special Populations.*

2.5.7 Hepatic Impairment

See section 2.2.1 *Special Dosage Instructions* and section 3.2.5 *Pharmacokinetics, Special Populations.*

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

Summary of the safety profile

The overall safety profile of Rozlytrek is based on an integrated safety population of 853 patients (762 adult and 91 pediatric patients) across 5 clinical trials (ALKA, STARTRK-1, STARTRK-2, STARTRK-NG and TAPISTRY). The safety of Rozlytrek was evaluated as integrated analyses of these 5 clinical trials and is shown in Table 5. The median duration of exposure to Rozlytrek was 8.6 months.

The integrated safety population includes of 91 paediatric patients.The median duration of exposure to Rozlytrek was 11.1 months.

Of these, 21 patients were 28 days to < 2 years , 55 patients were >/= 2 to < 12 years old, and 15 patients were >=12 to < 18 years old.

Tabulated summary of adverse drug reactions from clinical trials

Table 5 summarizes the adverse drug reactions (ADRs) occurring in adult and pediatric patients treated with Rozlytrek. Adverse drug reactions from clinical trials are listed by MedDRA system organ class. The following categories of frequency have been used: very common ≥1/10, common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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=853*		*Frequency Category (All Grades)*
	All Grades (%)	*Grade ≥ 3 (%)*	
Infections and Infestations			
Urinary tract infection	***15.7***	***2.7***	***Very common***
Lung infections[8]	***14.4***	***6.1****	***Very common***
Blood and Lymphatic System Disorders			
Anemia	***33.4***	***9.7***	***Very common***
Neutropenia[10]	***15.8***	***6.1***	***Very common***
Metabolism and Nutrition Disorders			
Weight increased	***34.1***	***10.6***	***Very common***
Hyperuricemia	***16.4***	***2.3***	***Very common***
Decreased appetite	***13.0***	***0.7***	***Very common***
Dehydration	***6.6***	***1.1***	***Common***
Tumor lysis syndrome	***0.2***	***0.2****	***Uncommon***
Nervous System Disorders			

Dizziness[5]	***36.5***	***1.9***	***Very common***
Dysgeusia	***35.8***	***0.2***	***Very common***
Dysasthesia[3]	***24.9***	***0.4***	***Very common***
Cognitive Disorders[1]	***23.3***	***3.6***	***Very common***
Peripheral Sensory Neuropathy[2]	***16.2***	***1.1***	***Very common***
Headache	***16.1***	***0.6***	***Very common***
Ataxia[4]	***15.1***	***1.5***	***Very common***
Sleep disturbances[16]	***12.8***	***0.4***	***Very common***
Mood disorders[17]	***9.4***	***0.6***	***Common***
Syncope	***5.0***	***3.5***	***Common***
Eye Disorders			
Vision Blurred[13]	***11.7***	***0.2***	***Very common***
Cardiac Disorders			
Congestive Heart Failure[9]	***5.4***	***2.5****	***Common***
Electrocardiogram QT prolonged	***3.6***	***0.9***	***Common***
Vascular Disorders			
Hypotension[15]	***15.9***	***2.3***	***Very common***
Respiratory, Thoracic and Mediastinal Disorders			
Dyspnea	***23.8***	***4.9****	***Very common***
Cough	***21.1***	***0.4***	***Very common***
Gastrointestinal Disorders			
Constipation	***42.3***	***0.4***	***Very common***
Diarrhea	***37.9***	***2.2***	***Very common***
Nausea	***30.0***	***0.6***	***Very common***
Vomiting	***25.1***	***1.1***	***Very common***
Abdominal pain	***11.6***	***0.6***	***Very common***
Dysphagia	***10.7***	***0.6***	***Very common***
Hepatobiliary Disorders			
AST increased	***21.1***	***2.9***	***Very common***

ALT increased	***20.2***	***3.2***	***Very common***
Skin and Subcutaneous Tissue Disorders			
Rash[12]	***13.4***	***1.2***	***Very common***
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	***21.0***	***0.7***	***Very common***
Myalgia	***19.7***	***0.8***	***Very common***
Fractures[11]	***11.3***	***3.4***	***Very common***
Muscular weakness	***10.4***	***1.3***	***Very common***
Renal and Urinary Disorders			
Blood creatinine increased	***31.5***	***1.2***	***Very common***
General Disorders and Administration Site Conditions			
Fatigue[14]	***43.5***	***5.0***	***Very common***
Edema[6]	***34.3***	***1.8***	***Very common***
Pain[7]	***25.6***	***1.5***	***V ery common***
Pyrexia	***23.8***	***0.9***	***V ery common***
Dyspnea	***27.0***	***5.8****	***very common***
Cough	***21.4***	***0.6***	***very common***
Blood Disorders			
Anemia	***28.2***	***9.7***	***very 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***

ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
******* *Grades 3 to 5, inclusive of fatal adverse reactions (including 4 reactions of pneumonia, 3 reactions of dyspnea,1 reaction of cardiac failure and 1 reaction of tumour lysis syndrome)*
1 *Includes preferred terms: cognitive disorder, confusional state,memory impairment, disturbance in attention, , amnesia, mental status changes, hallucination, delirium,disorientation, brain fog, attention deficit hyperactivity disorder, 'hallucination visual', 'hallucination auditory', mental impairmentand 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: acetabulum fracture, ankle fracture, avulsion fracture, bursitis, cartilage injury, clavicalclavicle fracture, compression fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, fracture, fractured sacrum, hand fracture, hip fracture, humerus fracture, ilium fracture, jaw fracture, joint injury, limb fracture, lower limb fracture, lumbar vertebral fracture, osteoporaticosteoporotic fracture, pathological fracture, pelvic fracture, rib fracture, spinal compression fracture, spinal fracture, spondylolisthesis, sternal fractures, stress fracture, synovial rupture, thoracic vertebral fracture, tibia fracture, ulna fracture, wrist 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

Cognitive disorders

A variety of cognitive symptoms were reported across clinical trials (see section 2.4.1 *General (Warnings and Precautions)*]. These included events reported as cognitive disorders (6.4 %), confusional state (6.2 %), memory impairment (4.9%), disturbance in attention (4.1 %), amnesia (2.3 %), mental status changes (0.9 %), hallucination (0.8%), delirium (0.8%), disorientation (0.5%), brain fog (0.4%), attention

deficit hyperactivity disorder (0.2%), hallucination visual (0.2%), auditory hallucination (0.1%), mental impairment (0.1%) and mental disorder (0.1%). Grade 3 events were reported in 3.6% of patients. Adult patients who had brain metastases at baseline had a higher frequency of these events (30.0 %) compared to those without brain metastases (22.6 %). In the pediatric population, Grade 1 disturbance in attention was reported in 2.2 % (2/91) patients and Grade 2 disturbance of attention in 2.2 % (2/91) patients.

Fractures

Fractures were experienced by 9.1 % (69/762) of adult patients and 29.7 % (27/91) of pediatric patients. In general, there was inadequate assessment for tumor involvement at the site of fracture; however, radiologic abnormalities possibly indicative of tumour involvement were reported in some patients. In both adult and pediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft) and some fractures occurred in the setting of a fall or other trauma.

The median time to fracture was 8.1 months (range: 0.26 months to 43.34 months) in adults. Rozlytrek was interrupted due to fractures in 26.1 % (18/69) of adult patients that experienced fractures. Two adult patients discontinued Rozlytrek due to fractures. Rozlytrek dose was reduced for 2 adult patients due to fractures

A total of 52 fracture events were reported in 27 pediatric patients, with 14 patients who experienced more than one occurrence of fracture.
In pediatric patients, all fractures occurred in patients less than 12 years of age. Fractures resolved in 85.2% (23/27) of pediatric patients.The median time to fracture was 4.3 months (range: 2 months to 28.7 months) in pediatric patients. Rozlytrek was interrupted 18.5% (5/27) of pediatric patients who experienced fractures. Six pediatric patients discontinued Rozlytrek due to fractures. Rozlytrek dose was reduced for one pediatric patient. Twelve patients experienced Grade 2 fractures and 10 patients experienced Grade 3 fractures. Seven of the Grade 3 fractures were serious.

Ataxia

Ataxia (including events of ataxia, balance disorder, and gait disturbances) was reported in 15.1% of patients. The median time to onset for ataxia was 0.46 months (range: 0.03 months to 65.48 months) and the median duration was 0.72 months (range: 0.03 months to 11.99 months). The majority of patients (55.8 %) recovered from ataxia. Ataxia related adverse events were observed more frequently in elderly patients (24.2 %) compared to patients below 65 years of age (11.8%).

Syncope

Syncope events were reported in 5.0 % 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 853 patients who received Entrectinib across clinical trials, 47 (7.2 %) patients with at least one post-baseline ECG assessment experienced QTcF interval prolongation of > 60 ms after starting Entrectinib, and 27 (4.1 %) patients had a QTcF interval of $\geq$ 500 ms.

Peripheral sensory neuropathy

Peripheral sensory neuropathy was reported in 16.2 % of patients. The median time to onset was 0.71 months (range 0.03 months to 81.97 months) and the median duration was 0.92 months (range: 0.07 months to 41 months). 48.6% of patients recovered from peripheral neuropathy.

Eye Disorders

Eye disorders reported across clinical trials included events of vision blurred (9.0 %), visual impairment (1.9 %), and diplopia (1.8 %). The median time to onset for eye disorders was 1.89 months (range: 0.03 months to 49.61 months). The median duration of eye disorders was 1.18 months (range 0.03 months to 14.98 months). 54% of patients 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 5 clinical trials.

Table 6: Rozlytrek Treatment-emergent shifts from baseline in key laboratory abnormalities(integrated safety population)

Laboratory Test Abnormality[1]	**Rozlytrek NCI-CTCAE Grade N= 853 [2]**	
	Change from Baseline All Grades (%)	**Change from Baseline to Grade 3 or 4 (%)[3]**
Chemistry		
Increased Blood Creatinine	78.8	8.5
Hyperuricemia	57.2	19.9
Increased AST	51.0	2.5
Increased ALT	47.5	2.4
Hematology		
Decreased Neutrophils	34.2	8.3
Decreased Hemoglobin	64.8	11.9

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=815 for Blood Creatinine ; N=824 for AST; N=825 for ALT; N=675 for Hyperuricemia; N=769 for Neutrophils; N=792 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

Pediatric patients
The overall safety profile observed was generally similar between pediatric patients and adults. Rozlytrek was associated with a higher incidence of skeletal fractures in pediatric patients compared to adult patients. Adverse reactions and laboratory abnormalities of Grade 3 to 4 severity occurring more frequently (at least a 5% increased incidence) in pediatric patients (n=91) compared to adult patients (n=762) were neutropenia (19.8% vs 4.5%), weight increased (18.7% vs 9.6%), and bone fractures (11% vs 2.5%) and lung infection (11% vs 5.5%). No Grade 5 events were observed in the 91 patients in the expanded pediatric safety population. Grade 3 to 4 events that occurred at a frequency ≥ 5% were neutropenia (19.8%), weight increased (18.7%), fractures (11%), lung infection (11%), and anemia (8.8%).

2.6.2 Post Marketing Experience

Not applicable

2.7 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.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effects of Entrectinib on others 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 AUCinf (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 Cmax by approximately 28% and overall exposure by approximately 18% (GMR with/without Entrectinib for Cmax (90% CI) was 128% (98.2%, 167%) and AUCinf (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 AUCinf (90% CI) of 112% (111%, 113%) and Cmax (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 AUCinf (90% CI) was 23.3% (18.4%, 29.5%) and Cmax (90% CI) was 44.4% (35.3%, 55.9%).

Co-administration of Rozlytrek with CYP3A inducers should be avoided (see section *2.2 Dosage and Administration*).

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 AUCinf (90% CI) was 604% (454%, 804%) and Cmax (90% CI) was 173% (137%, 218%).

Co-administration of strong and moderate CYP3A inhibitors (including, but not limited to, anti-fungal agents, anti-retroviral agents) 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 2.2 *Dosage and Administration.*

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 AUCinf (90%CI) was 74.5% (64.7%, 85.9%) and Cmax (90% CI) was 76.5% (67.6%, 86.6%).

Therefore, no dose adjustments are required when Rozlytrek is co-administered with PPIs or other drugs 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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 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 tumorigenic 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 tumor cell apoptosis. Entrectinib demonstrates potent inhibition of cancer cell lines harboring *NTRK, ROS1* and *ALK* fusion genes, irrespective of tumor type. Entrectinib has anti-tumor potency in *NTRK* and *ROS1* fusion-driven tumor models, driving tumor regressions across multiple tumor 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- tumor activity in three TRKA-driven intracranial tumor models and one ALK-driven intracranial tumor 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.

3.1.2 Clinical / Efficacy Studies

***NTRK* fusion-positive solid tumors**

Efficacy in Adult patients

The efficacy of Rozlytrek in the treatment of *NTRK* fusion-positive solid tumors in adult patients was evaluated by combining the results from 3 single-arm, open label clinical trials (ALKA, STARTRK-1 and STARTRK-2) and one multi-cohort, open label clinical trial (TAPISTRY)

Study ALKA was a Phase I single arm, open-label study in patients ≥ 18 years of age with solid tumors 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 tumors 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 tumors with *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangements. Patients received 600 mg Rozlytrek once daily in 4-week cycles. The TAPISTRY study is a multi-center Phase II, open label study in adult and pediatric patients to evaluate the safety and efficacy of targeted therapies or immunotherapy in patients with unresectable, locally advanced or metastatic solid tumors with specific oncogenic genomic alterations, including *NTRK* fusion-positive or *ROS1* fusion-positive tumors. Patients received doses from 20 mg to 600 mg 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 Tumors (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 242 adult patients with confirmed *NTRK* fusion-positive solid tumors treated with Rozlytrek, not previously treated with a TRK inhibitor, presenting with measurable disease at baseline as assessed by investigator, and with ≥ 12 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: 47.5 % males, median age of 58 years (range: 19 to 92 years), 49.4 % white Caucasian, 36.5 % Asian, 3.3 % Hispanic or Latino and 61.9 % never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (42.1%), 1 (50 %), or 2 (7.9%). Most patients (95.5 %) had metastatic disease [most common sites being lung (62.8 %), lymph nodes (49.2 %), liver (33.1%), bone (31%) and brain (16.5 %)], 4.5 % patients had locally advanced disease, and 37.2 % patients had no prior systemic therapies. The overall median duration of follow-up was 35.1 months.

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

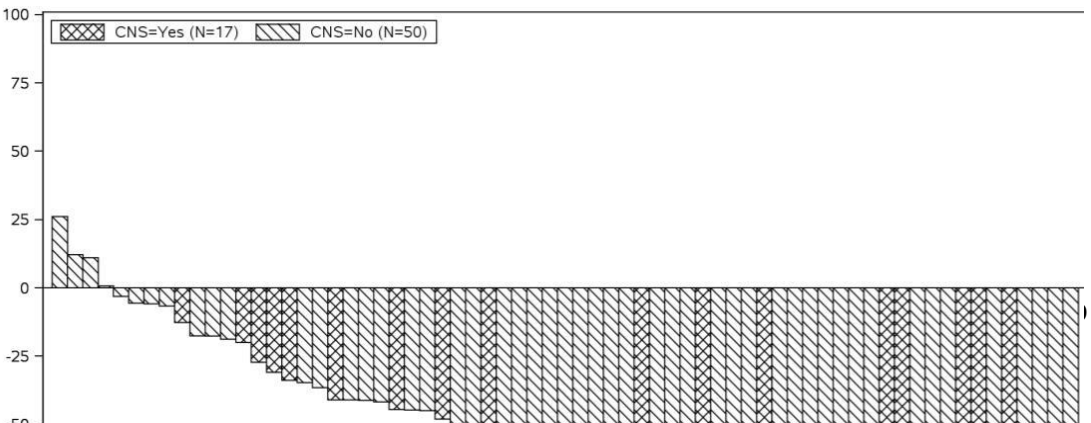
Table 7: Overall efficacy by BICR in Adults with *NTRK*-fusion positive Solid Tumors

Efficacy Endpoints	Rozlytrek **N=242**
Primary endpoints *(BICR-assessed, RECIST 1.1)*	
ORR	
Number of responders	152/242
ORR% (95% CI***)	62.8% (56.4 ,68.9)
Complete Response, n (%)	41 (16.9 %)
Partial Response, n (%)	111 (45.9 %)
DOR *	
Number (%) of patients with events	86/152 (56.6 %)
Median, months (95% CI)	22 (16.6,30.4)
6-month durable response % (95% CI)	85 (80, 91)
9-month durable response % (95% CI)	78 (71, 84)
12-month durable response % (95% CI)	69 (62, 77)

Secondary endpoints *(BICR-assessed, RECIST 1.1)*	
CBR** Number of CR+PR+SD 6 months/Number of patients Number of patients with clinical benefit CBR% (95% CI***)	 169/242 69.8 % (63.6, 75.6)
PFS * Number (%) of patients with events/ Median, months (95% CI)	 155/242 (64.0 %) 15.6 (12.0, 20.4)
Time to CNS Progression*	
Number (%) of patients with events	116/242 (47.9 %)
Median, months (95% CI)	28.6 (23.4, 37.1)
Overall Survival*	
Number (%) of patients with events	108/242 (44.6 %)
Median, months (95% CI)	38.2 (31.6, 56.5)
CR: complete response; PR: partial response; . *Median and event-free rates based on Kaplan-Meier estimates. **Clinical benefit rate: proportion of patients with complete response, partial response, stable disease, or non CR/non PD for 6 months. ***Confidence Intervals (CI) calculated using the Clopper-Pearson method.	

As shown in Figure 1, most adult patients with *NTRK*-fusion positive solid tumors experienced tumor 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 Tumors, shaded by CNS metastases at baseline



SLD: Sum of Longest Diameter

Of the 242 adult patients with *NTRK*-fusion positive solid tumors in the efficacy evaluable analysis set, 41 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 Tumors with CNS Metastases at Baseline

Secondary Endpoint *(BICR-assessed, RECIST 1.1)*	**CNS Metastases at Baseline (by Investigator)-**	
	Yes N=41	**No N=201**
ORR		
Number of responders	27	125
ORR% (95% CI*)	65.9 (49.41, 79.92)	62.2 % (55.10, 68.92 ,
Complete Response, n (%)	(9.8%)	37 (18.4 %)
Partial Response, n (%)	23 (56.1 %)	88 (43.8 %)
DOR		
Number of patients with events	22 (81.5 %)	64 (51.2 %)
Median, months (95% CI)	16.6 (12.9, 29.,)	27.1 (16.7, 47.8)
PFS		
Number of patients with events	33 (80.5 %)	122 (60.7 %)
Median, months (95% CI)	13.8 (6.5, 28.3)	15.7 (13.7, 20.8)

CR: complete response; PR: partial response;
Confidence Intervals (CI) calculated using the Clopper-Pearson method.

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

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

Tumor Type	Patients (N=242)	ORR		DOR
		n (%)	95% CI	Range (months)

All	242	152 (62.8)	(56.4, 68.9)	3 to 74*
Sarcoma	46	29 (63.0)	(47.6, 76.8)	2.8, 68.6*
Non-small cell lung cancer	60	38 (63.3)	(49.9, 75.4)	3.1, 71.6
Salivary (MASC)	38	32 (84.2)	(68.8, 94)	2.8, 73.5*
Breast cancer (secretory)	12	10 (83.3)	(51.6, 97.9)	5.5, 69.9*
Breast cancer (non-secretory)	2	NE, PR	NA	4.2
Breast cancer (NOS)	2	NE, NE	NA	NA
Breast cancer (Ductal)	1	PD	NA	NA
Thyroid cancer	33	20 (60.6)	(42.1, 77.1)	5.6, 60.7
Colorectal cancer	17	6 (35.3)	(14.2, 61.7)	5.6*, 24*
Neuroendocrine cancers	8	5 (62.5)	(24.5, 91.5)	7.4, 31.1
Head and neck	5	3 (60.0)	(14.7, 94.7)	4.0, 56.5*
Pancreatic cancer	6	4 (66.7)	(22.3, 95.7)	5.6*, 12.9
Unknown primary cancer	3	1 (33.3)	(0.8, 90.6)	9.1
Ovarian cancer	1	Non CR/PD	NA	NA
Endometrial carcinoma	1	PR	NA	38.2
Cholangiocarcinoma	1	PR	NA	9.3
Gastrointestinal cancer (other)	1	CR	NA	30.4
Gastrointestinal cancer (non-CRC)	1	PD	NA	NA
Neuroblastoma	1	NE	NA	NA
Prostate cancer	1	PD	NA	NA
Penile cancer	1	PD	NA	NA
Adrenal cancer	1	PD	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; NOS: not otherwise specified; CRC: colorectal cancer; CR: complete response; PR: partial response; PD: progressive disease; NE:Not estimable.

Intracranial Response

Of the 242 adult patients with *NTRK*-fusion positive solid tumors in the efficacy evaluable analysis set, 36 patients had CNS metastases at baseline as assessed by BICR, including 20 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 Tumors with CNS Metastases at Baseline by BICR

Secondary Endpoint *(BICR-assessed, RECIST 1.1)*	**CNS Metastases at Baseline (by BICR)**	
	Measurable disease N=20	**All patients N= 36**
IC-ORR		
Responders	14	19
IC-ORR% (95% CI*)	70.0 % (45.7, 88.1)	52.8% (35.5,69.6)
Complete Response n (%)	7 (35 %)	12 (33.3%)
Partial Response n (%)	7 (35 %)	7 (19.4%)
IC-DOR		
Number of patients with events (%)	11 (78.6 %)	14 (73.7 %)
Median, months (95% CI)	19.7 (7.4, 26.6)	17.2 (7.4, 26.6)
IC-PFS		
Number of patients with events (%)	14 (70 %)	27 (75.0 %)
Median, months (95% CI)	17.9 (6.4, 26.7)	12.3 (7, 20)

IC-ORR derived using RECIST 1.1 criteria applied only to CNS lesions.
*Confidence Intervals (CI) calculated using the Clopper-Pearson method.

Primary CNS tumors

In the three trials conducted, a total of 16 adult patients with CNS primary tumors received treatment with Rozlytrek. These patients were followed up for at least 12 months. The assessment of IC-ORR, DOR, and PFS was done by BICR using the Response Assessment in Neuro-Oncology Criteria (RANO). Out of the 16 patients, two achieved an objective response according to RANO. One patient with glioma showed a partial response and had a DOR of 2.8 months and PFS of 6.3 months. The second patient with glioblastoma also had a partial response and had a DOR of 9.2 months and PFS of 10.8 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 Lung Cancer Module (QLQ-LC13), and the Colorectal Cancer Module (QLQ-CR29). Both STARTRK-2 and TAPISTRY evaluated PROs of the treatment impact on symptoms, functioning, and HRQoL based on the EORTC Core Quality of Life Questionnaire (QLQ-C30).

Most safety evaluable patients indicated that the symptoms commonly associated with Rozlytrek treatment (lack of appetite, nausea, diarrhea and vomiting) were of low severity, if present. Efficacy evaluable patients with *NTRK*-fusion positive NSCLC (n=53) reported low-to-moderate lung-related symptoms at baseline with clinically meaningful improvement in coughing and pain in the arm or shoulder while receiving Rozlytrek. Patients with mCRC (n=14) reported low-to-moderate CRC symptoms burden at baseline, with improvement in abdominal pain and maintenance of baseline scores for other symptoms over time. Moderate- to-high functioning and overall HRQoL was reported at baseline for patients with *NTRK* fusion-positive solid tumors, and this was maintained while receiving Rozlytrek, as measured by the EORTC QLQ-C30.

Efficacy in Pediatric patients

The efficacy of Rozlytrek in pediatric patients with *NTRK* fusion-positive solid tumors was evaluated combining the results from 2 clinical trials (STARTRK-NG and TAPISTRY . The study STARTRK-NG is a multi-center Phase I/II, open- label dose-escalation and expansion study in pediatric patients with relapsed or refractory solid tumors, including primary CNS tumors, with or without *NTRK*, *ROS1* or *ALK* molecular alterations.The study included a dose escalation segment and a dose expansion segment. In the dose expansion segment, patients received 20 mg to 600 mg once daily in repeated 4-week cycles.

Patients received 20 mg to 600 mg once daily in repeated 4-week cycles. See section *3.1.2 Clinical / Efficacy Studies*, NTRK fusion-positive solid tumors, Efficacy in Adult patients for TAPISTRY study details. The range of survival follow up was 1 month to 66.0 months .

The range of survival follow up was 1 month to 66.0 months.

The primary efficacy outcome measure was ORR as assessed by BICR according to RECIST v1.1 for extra-cranial tumors and according to RANO for primary CNS tumors. The secondary efficacy outcome measures included DOR as evaluated by BICR, time to first objective response (CR or PR), CBR, PFS and OS.

The pooled efficacy analysis set included 44 pediatric patients (less than 18 years of age) with confirmed NTRK fusion-positive solid tumors treated with at least one dose of Rozlytrek, not previously treated with a TRK inhibitor, presenting with measurable or evaluable disease at baseline, and with ≥ 6 months of follow up. NTRK fusion-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.

Of the 44 pediatric patients, the baseline demographic and disease characteristics were: 45.5% males, median age of 4 years (range: 2 months to 15 years), 52.3% white Caucasian, 34.1% Asian, and 9.1% Hispanic or Latino, with a median BSA of 0.73 m2 (range: 0.2-1.9 m2). At baseline, 23.8% of patients had metastatic disease, 76.2% of patients had locally advanced disease, and 43.2% of patients had no prior systemic therapies. The majority of patients had received prior treatment for their cancer including surgery (n=24), radiotherapy (n=8) and/or systemic therapy (n=25). The sites for metastatic disease included other (4 patients), brain (3 patients) and lung (32 patients). 45.5% of patients had primary CNS tumors. The overall median duration of follow-up was 24.2 months.

Efficacy results from pediatric patients with NTRK fusion-positive solid tumors are summarized in Table 11.

Table 11: Overall Efficacy in Pediatric patients with *NTRK* fusion-positive Solid Tumors assessed by BICR

Efficacy Endpoints	Rozlytrek **N=44**
Primary endpoints**	

ORR	
Number of responders	32/44
ORR% (95% CI****)	72.7 % (57.21, 85.04)
Complete Response, n (%)	20 (45.5 %)
Partial Response, n (%)	12 (27.3 %)
Secondary endpoints*	
DOR *	
Number (%) of patients with events	6/32 (18.8 %)
Median, months (95% CI)	NE (25.4, NE)
6-month durable response % (95% CI)	97 (90, 100)
9-month durable response % (95% CI)	97 (90, 100)
12-month durable response % (95% CI)	84 (70, 99)
Time to first objective response Median, months [range]	1.86 [1.1, 5.5]
CBR***	
Number of patients with clinical benefit	38/44
CBR% (95% CI****)	86.4 % (72.65, 94.83)
PFS *	
Number (%) of patients with events	11/44 (25.0 %)
Median, months (95% CI)	NE (27.2 , NE)
Overall Survival*	
Number (%) of patients with events	7/44 (15.9 %)
Median, months (95% CI)	NE (35.7, NE)

CR: complete response; PR: partial response; NE: not estimable.
*Median and event-free rates based on Kaplan-Meier estimates
**Includes patients with measurable or evaluable disease. BICR analysis by RECIST v1.1 for solid tumors (24 patients) and by RANO criteria for primary CNS tumors (20 patients)
***Clinical benefit rate: proportion of patients with complete response, partial response, stable disease or non CR/non PD for 6 months
****Confidence Intervals (CI) calculated using the Clopper-Pearson method.

Objective response rate and duration of response by tumor type in pediatric patients with NTRK-fusion positive solid tumors is presented in Table 12.

Table 12:Efficacy by tumor type, in pediatric patients with *NTRK* fusion-positive solid tumors

Tumor Type	Patients (N=44)	ORR		DOR
		n (%)	95% CI	Range (months)
All	44	32 (72.7)	(57.21,85.04)	3.7*, 42.4*
Primary CNS**	20	10 (50.0)	(27.2, 72.8)	5.5, 42.3*
Infantile fibrosarcoma	11	10 (90.9)	(58.72, 99.77)	5.7*, 24.0*
Spindle Cell	8	8 (100.0)	(63, 100)	5.4*, 23.0*
Sarcoma (other)	2	1 (50.0)	(1.26, 98.74)	3.7 *
Melanoma	1	CR	NA	42.4*
Kidney	1	PR	NA	9.2*
Thyroid	1	CR	NA	11.1*

* Censored
** Median time to first objective response for patients with primary CNS tumors was 1.86 months and range of time to first objective response was 1.7 months to 1.9 months
ORR: Objective Response Rate; DOR: Duration of Response; NA: not applicable due to small number or lack of response; CR: complete response;PR: partial response; PD: progressive disease

Figure 2: Best percentage change from baseline in tumor size (BICR assessment) in pediatric patients with NTRK-fusion positive solid tumors (primary CNS and non-CNS), shaded by response

SLD: Sum of Longest Diameter, SPD: Sum of Products of Greatest Diameters

Only patients with available baseline and post-baseline values for SLD or SPD were included in the plot

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 13.

Table 13: Overall Efficacy by BICR in patients with ROS1-positive NSCLC

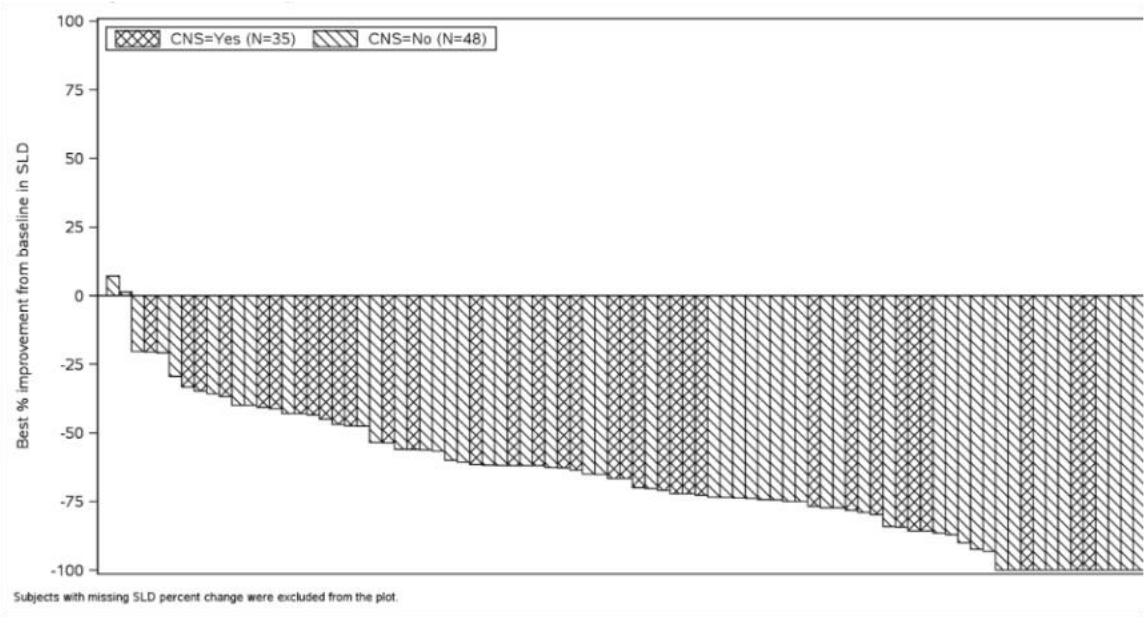
Efficacy Endpoint	Rozlytrek **N= 94**
Primary endpoints *(BICR-assessed, RECIST 1.1)*	
ORR	
Number of responders	69/94
ORR% (95% CI****)	73.4 (63.3, 82.0)
Complete Response, n (%)	11 (11.7%)
Partial Response, n (%)	58 (61.7%)
DOR *	
Number (%) of patients with events	36/69 (52.2%)
Median, months (95% CI)	16.5 (14.6, 28.6)**
6-month durable response % (95% CI)	82 (72, 91)
9-month durable response % (95% CI)	79 (69, 89)
12-month durable response % (95% CI)	66 (54, 78)
Secondary endpoints *(BICR-assessed, RECIST 1.1)*	
CBR***	
Number of patients with clinical benefit	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.
*Median and event-free rates based on Kaplan-Meier estimates
**not a robust estimate
*** Clinical benefit rate: proportion of patients with complete response, partial response, stable disease or non CR/non PD for 6 months
****Confidence Intervals (CI) calculated using the Clopper-Pearson method.

Most ROS1-positive NSCLC patients treated with Rozlytrek experienced tumor 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 14.

Table 14: Efficacy in ROS1-positive NSCLC Patients with CNS metastases at Baseline

Secondary Endpoints	**CNS Metastases at Baseline (by Investigator)**

(BICR-assessed, RECIST 1.1)		
	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)
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 15 and Figure 3 below.

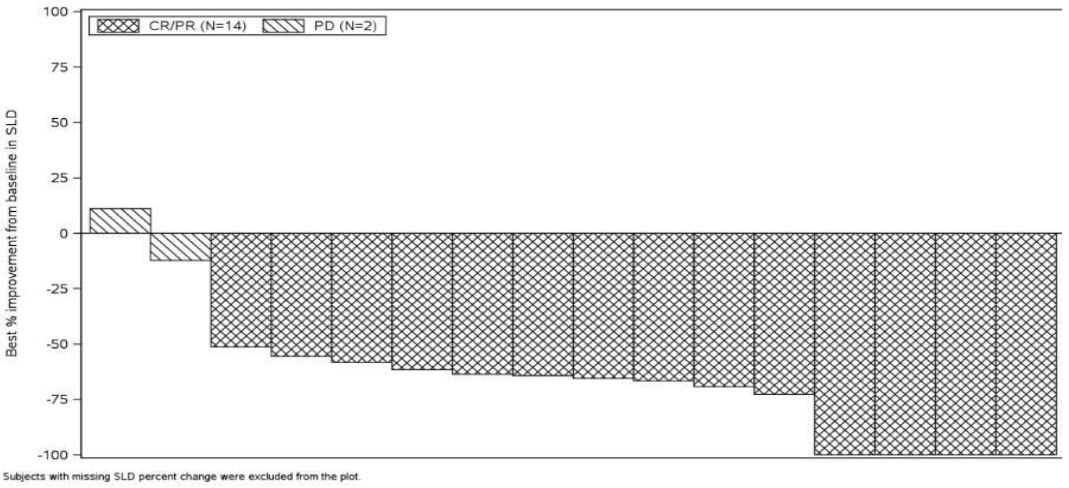
Table 15: Intracranial Efficacy in ROS1-positive NSCLC patients with CNS metastases at baseline by BICR

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% CI)	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 Tumor 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.

3.1.3 IMMUNOGENICITY

Not applicable.

3.2 Pharmacokinetic Properties

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

Following administration of a single 600 mg dose of Entrectinib, the estimated Entrectinib mean (± SD) Cmax was 1990 (± 1050) nM and AUC_{0-24} 33900 (± 15800) nM*h and for M5 Cmax was 765 (± 598) nM and AUC_{0-24} 13300 (± 10200) nM*h . At steady-state the estimated Entrectinib mean Cmax was 3490 (± 1600) nM and AUC_{0-24} 62800 (±29100) nM*h and for M5 Cmax was 1340 (± 934) nM and AUC0-24 25500 (±29100) nM*h. The population PK model estimated mean accumulation at steady-state following 600 mg once daily administration of Entrectinib was 1.89 (±0.381) and 2.01 (± 0.437) for M5.

3.2.1 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 (Tmax) 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 AUCinf (90%CI) was 115% (107, 124) and for Cmax (90%CI) was 106% (98.9, 115) [9]. Entrectinib can be administered with or without food (see section *2.2 Dosage and Administration*).

3.2.2 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]-labelled Entrectinib, the geometric mean volume of distribution (Vz/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.

3.2.3 Metabolism

Entrectinib is metabolized predominantly by CYP3A4 (~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.

3.2.4 Elimination

Following administration of a single dose of [^{14}C]-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 Cmax, 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.

3.2.5 Pharmacokinetics in Special Populations

Pediatric 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 pediatric patients.

Data obtained from population pharmacokinetic analyses show that a dose of 300 mg/m^2 of Rozlytrek once daily in pediatric 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 pediatric patients with BSA $\geq$ 1.51 m^2 with 600 mg of Rozlytrek once daily.

Geriatric 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 [41, 42].

Ethnicity

Following a single oral dose of Rozlytrek in Japanese and Caucasian healthy volunteers, no clinically relevant differences in the exposure of Rozlytrek were observed. Based on population pharmacokinetics analysis, there was no relationship between systemic exposure of Entrectinib and race/ethnicity (Asian, Japanese, white and other ethnicities). No dose adjustment is required for patients of different race/ethnicities. See section *2.2.1 Special Dosage Instructions*.

3.3 Nonclinical Safety

3.3.1 Carcinogenicity

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

3.3.2 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.

3.3.3 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.

3.3.4 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.

3.3.5 Other

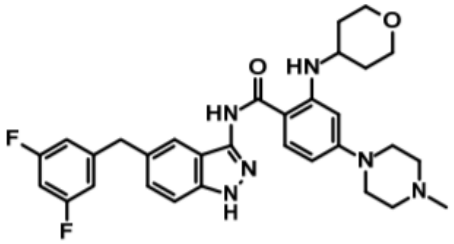
In a 13-week juvenile rat toxicology study from post-natal day 7 to day 97 (approximately equivalent to neonate to 16 years of age in humans), effects on growth and development were observed in the dosing and recovery phases including decreased body weight gain and delayed sexual maturation (at $\geq$ 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 $\geq$ 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.

4 DESCRIPTION

Entrectinib is a kinase inhibitor. The molecular formula for Entrectinib is $C_{31}H_{34}F_2N_6O_2$ and the molecular weight is 560.64 Daltons. The chemical name is N-[5-(3,5- difluorobenzyl)-1H-indazol-3-yl]-4-(4 methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino) benzamide. The chemical structure of Entrectinib is as follows:



Entrectinib is white to pale pink powder. Rozlytrek (Entrectinib) capsules for oral use are supplied as printed hard-shell capsules containing 100 mg (yellow opaque HPMC capsule) or 200 mg of Entrectinib (orange opaque HPMC capsule). Inactive ingredients are tartaric acid, lactose anhydrous, hypromellose, crospovidone, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The yellow opaque capsule shell contains hypromellose, titanium dioxide, and yellow iron oxide. The orange opaque capsule shell contains hypromellose, titanium dioxide, and FD&C yellow #6. The printing ink contains shellac, propylene glycol, strong ammonia solution, and FD&C blue #2 aluminum lake.

5 PATIENT COUNSELLING INFORMATION

Congestive Heart Failure

Inform patients of the risks of CHF and advise patients to contact their healthcare provider immediately for any new or worsening signs or symptoms of CHF [see Warnings and Precautions].

Central Nervous System Effects

Advise patients to inform their healthcare provider if they experience new or worsening central nervous system symptoms. Instruct patients not to drive or operate hazardous machinery if they are experiencing CNS adverse reactions [see Warnings and Precautions].

Skeletal Fractures

Inform patients that bone fractures have been reported in patients taking Rozlytrek. Advise patients to report symptoms such as pain, changes in mobility, or deformity to their healthcare provider [see Warnings and Precautions].

Hepatotoxicity

Advise patients that they will need to undergo laboratory tests to monitor liver function and to immediately

report symptoms of hepatotoxicity [see Warnings and Precautions].

Hyperuricemia

Advise patients to inform their healthcare provider if they experience signs or symptoms associated with hyperuricemia [see Warnings and Precautions].

QT Interval Prolongation

Inform patients of the risks of QT interval prolongation and to advise patients to contact their healthcare provider immediately for any symptoms of QT interval prolongation [see Warnings and Precautions].

Vision Disorders

Advise patients to inform their healthcare provider if they experience visual changes [see Warnings and Precautions].

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].
- Advise females of reproductive potential to use effective contraception during treatment with Rozlytrek and for 5 weeks after the final dose.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose.

Lactation

Advise females not to breastfeed during treatment with Rozlytrek and for 1 week after the final dose [see Use in Specific Populations].

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Advise patients to avoid grapefruit juice while taking Rozlytrek [see Drug Interactions].

Administration

- Advise patients to swallow Rozlytrek capsules whole.
- Instruct patients if they miss a dose to make up that dose unless the next dose is due within 12 hours.
- Instruct patients if they vomit immediately after taking a dose of Rozlytrek to take a dose as soon as possible [Dosage and Administration].

6 PHARMACEUTICAL PARTICULARS

6.1 Storage

Storage: Do not store above 30°C. Store in the original package and keep the bottle tightly closed in order to protect from moisture.
Keep out of the reach of children.

6.2 Special Instructions for Use, Handling and Disposal

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.

6.3 Packs

Capsules 100mg	30
Capsules 200mg	90

6.4 Shelf life

Shelf life- 36 months

This medicine should not be used after the expiry date (Expiry) shown on the pack.

6.5 Incompatibilities

No text

7 DETAILS OF MANUFACTURER

Manufactured by: F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4058 Basel Switzerland at-
F. Hoffmann-La Roche Ltd, Wurmisweg, CH-4303, Kaiseraugst, Switzerland

Imported and Marketed by:

Roche Products (India) Pvt. Ltd.,
C/O. Parekh Integrated Services
Pvt. Ltd, Gala No. B1, 2nd Floor, Warehouse No. 6, BGR Logistics Park, NH-3, Bhiwandi (Thane Z5), Maharashtra (India) –421302

8. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Permission No.: IMP-ND-103/2022

9. DATE OF REVISION

Current at September:2024, Version 4.0