PACK INSERT FOR MALAYSIA

ROZLYTREK®
100mg and 200mg Hard Capsules

Entrectinib

1. NAME OF THE MEDICINE

entrectinib

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:

Capsule fill mass: Lactose anhydrous, Microcrystalline cellulose, Tartaric acid, Hypromellose, Crospovidone, Magnesium stearate, Colloidal silicon dioxide

Capsule shell 100 mg: Hypromellose, Titanium dioxide (E171, CI77891), Yellow iron oxide (E172, CI77492), Printing Ink (shellac, propylene glycol, strong ammonia solution, and FD & C Blue #2 Aluminum Lake)

Capsule shell 200 mg: Hypromellose, Titanium dioxide (E171, CI77891), FD&C Yellow #6 (E110, CI15985), Printing Ink (shellac, propylene glycol, strong ammonia solution, and FD & C Blue #2 Aluminum Lake)

3. PHARMACEUTICAL FORM

Hard capsule.

Rozlytrek 100 mg are size 2 hard capsules with yellow body and cap with “ENT 100” imprinted in blue on the body.

Rozlytrek 200 mg are size 0 hard capsules with orange body and cap with “ENT 200” imprinted in blue on the body.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION(S)

Non-small cell lung cancer (NSCLC)
Rozlytrek is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours are ROS1-positive.

Solid tumours
Rozlytrek is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours 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 either progressed following treatment or have no satisfactory alternative therapy.

This indication is approved under conditional registration which is based on overall response rate and duration of response (see section 5.1 *Pharmacodynamic Properties; Clinical trials*). Continued approval for this indication may be based on the outcome of clinical benefit in a confirmatory trial.

4.2 DOSAGE AND ADMINISTRATION

General

Method of administration

Rozlytrek can be taken with or without food. Capsules should be swallowed whole. Capsules must not be opened or dissolved.

Patient selection

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.

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

Adults

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

Paediatric patients

The recommended dose of Rozlytrek for paediatric patients is based on body surface area (BSA) as shown in Table 1 (see section 5.2 *Pharmacokinetic Properties)*.

Table 1. Dosing in paediatric patients 12 years and older (adolescents)

Body surface area (BSA)	Recommended dosage (orally once daily)
Greater than 1.50 m^2	600 mg
1.11 to 1.50 m^2	500 mg
0.91 to 1.10 m^2	400 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 for adverse reactions

Management of adverse reactions may require temporary interruption, dose reduction, or discontinuation of treatment with Rozlytrek.

Recommended dose reductions are provided in Table 2. The dose of Rozlytrek may be reduced up to 2 times, after which Rozlytrek treatment should be permanently discontinued if patients are unable to tolerate the lowest reduced dose.

Table 2. Recommended doses when reduction is required

Dose level	**All adults, and paediatric patients with BSA greater than 1.50 m^2 (orally once daily)**	**Paediatric patients with BSA of 1.11 to 1.50 m^2 (orally once daily)**	**Paediatric patients with BSA of 0.91 to 1.10 m^2 (orally once daily)**
(Starting dose)	*(600 mg)*	*(500 mg)*	*(400 mg)*
Dose after first reduction	400 mg	400 mg	300 mg
Dose after second reduction	200 mg	200 mg	200 mg
Subsequently	Permanently discontinue Rozlytrek in patients who are unable to tolerate Rozlytrek after two dose reductions.		

Recommended dose modifications for specific adverse reactions are provided in Table 3. See sections 4.4 *Special Warnings and Precautions for Use* and 4.8 *Adverse Effects (Undesirable Effects*).

Table 3. Recommended dose modifications for specific adverse drug reactions

Adverse drug reaction	**Severity** *	**Dose modification**
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	• Permanently discontinue Rozlytrek.
Central nervous system effects	Intolerable Grade 2	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline. • Resume at same dose or reduced dose, as clinically appropriate.
	Grade 3	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline. • Resume at reduced dose.
	Grade 4	• Permanently discontinue Rozlytrek.
Hepatotoxicity	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 greater than 3 times the upper limit of normal (ULN) with concurrent total bilirubin greater than 1.5 times ULN (in the absence of	• Permanently discontinue Rozlytrek.

Adverse drug reaction	Severity *	Dose modification
	cholestasis or haemolysis).	
Hyperuricaemia	Symptomatic or Grade 4	• Initiate urate-lowering medication. • Withold Rozlytrek until improvement of signs or symptoms. • Resume Rozlytrek at same or reduced dose.
QT interval prolongation	QTc 481 to 500 ms	• Withhold Rozlytrek until recovered to baseline • Resume treatment at same dose
	QTc greater than 500 msec	• 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 <u>not</u> identified.
	Torsades de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	• Permanently discontinue Rozlytrek.
Vision disorders	Grade 2 or above	• Withhold Rozlytrek until improvement or stabilisation. • Resume at same dose or reduced dose, as clinically appropriate.
Anaemia or neutropenia	Grade 3 or Grade 4	• Withhold Rozlytrek until recovery to less than or equal to Grade 2. • Resume treatment at the same dose or reduced dose, as clinically appropriate.
Other clinically relevant adverse reactions	Grade 3 or 4	• Withhold ROZLYTREK until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline. • Resume at the same or 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.

*Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

<u>Dose modifications for specific medicine interactions</u>

Strong or moderate CYP3A inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors with Rozlytrek (see section 4.5 *Interactions with Other Medicines and Other Forms of Interactions*).

For adults and for paediatric patients 12 years and older who have a BSA greater than 1.50 m^2, if the concomitant use of strong or moderate CYP3A inhibitors with Rozlytrek cannot be avoided, the Rozlytrek dose should be reduced to:

- 100 mg once daily if it is a strong CYP3A inhibitor and
- 200 mg once daily if it is a moderate CYP3A inhibitor.

After discontinuation of a strong or moderate CYP3A inhibitor, and after an appropriate wash-out period (3 to 5 times the elimination half-life of the CYP3A inhibitor), the Rozlytrek dose that was taken prior to initiating the CYP3A inhibitor can be resumed.

For paediatric patients 12 years and older who have a BSA less than or equal to 1.50 m^2, the concomitant use of strong or moderate CYP3A inhibitors with Rozlytrek should be avoided altogether.

Avoid grapefruit products during treatment with Rozlytrek, as they contain inhibitors of CYP3A.

Strong or moderate CYP3A inducers
Avoid concomitant use of Rozlytrek with strong or moderate CYP3A inducers in adult and paediatric patients (See section 4.5 *Interactions with Other Medicines and Other Forms of Interactions*).

Drugs that prolong the QT interval
Avoid co-administration of Rozlytrek with other products known to prolong the QT/QTc interval (see section 4.4 S*pecial Warnings and Precautions for Use* and section 4.5 *Interactions with Other Medicines and Other Forms of Interactions*).

Dosing in special populations
Paediatric populations
Dosage for patients is based on body surface area (mg/m^2) (see Table 1 for paediatric dosing).

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment (CLcr 30 to < 90 mL/min calculated by Cockcroft-Gault equation). Rozlytrek has not been studied in patients with severe renal impairment (CLcr < 30 mL/min). However, since entrectinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment (see sections 4.4 *Special Warnings and Precautions for Use* and 5.2 *Pharmacokinetic Properties*).

Hepatic impairment
No dose adjustment is required in patients with underlying mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment, based on a study in subjects with hepatic impairment (see sections 4.4 *Special Warnings and Precautions for Use* and 5.2 *Pharmacokinetic Properties*). Patients with severe hepatic impairment should be carefully monitored for hepatic function and adverse reactions.

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 section 4.8 *Adverse Effects (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. Assess left ventricular ejection fraction (LVEF) prior to initiation of Rozlytrek in patients with symptoms or known risk factors for CHF. Monitor patients for clinical signs and symptoms of CHF, including shortness of breath and oedema. For patients with myocarditis, with or without a decreased ejection fraction, MRI or cardiac biopsy may be required to make the diagnosis. For patients with new onset or worsening CHF, withhold Rozlytrek, institute appropriate medical management, and reassess LVEF. Based on the severity of CHF, modify Rozlytrek treatment as described in Table 3 (see section 4.2 *Dosage and Administration*).

Central nervous system effects
A broad spectrum of central nervous system (CNS) adverse reactions were reported in clinical trials with Rozlytrek, including cognitive impairment, mood disorders, dizziness and sleep disturbances (see section

4.8 *Adverse Effects (Undesirable Effects)*). Monitor for signs of CNS adverse reactions, and advise patients and caregivers of these risks with Rozlytrek. Advise patients not to drive or operate hazardous machinery if they are experiencing CNS adverse reactions (see section 4.7 *Effects on Ability to Drive and Use Machines*). Based on the severity of the CNS effects, modify Rozlytrek treatment as described in Table 3 (see section 4.2 *Dosage and Administration*).

Skeletal fractures
Rozlytrek increases the risk of fractures (see section 4.8 *Adverse Effects (Undesirable Effects) – Description of selected adverse events*). Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures. In both adult and paediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area; in paediatric patients some fractures occurred with no trauma. There are no data on the effects of Rozlytrek on healing of known fractures and risk of future fractures. In the majority of paediatric patients treatment was continued with Rozlytrek and the fracture healed (see section 4.8 *Adverse Effects (Undesirable Effects))*.

Hepatotoxicity
Hepatic transaminase elevation was frequently reported in entrectinib clinical trials (see section 4.8 *Adverse Effects (Undesirable Effects)*), and hepatotoxicity is a known effect of other ROS1 inhibitors. Monitor liver function tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Based on the severity of hepatic enzyme elevation, modify Rozlytrek treatment as described in Table 3 (see section 4.2 *Dosage and Administration*).

Hyperuricaemia
Hyperuricaemia was frequently reported in entrectinib clinical trials (see *section* 4.8 *Adverse Effects (Undesirable Effects)*), and 34% of cases required medical intervention to reduce serum urate. Assess serum urate prior to initiating Rozlytrek and periodically during treatment. Monitor patients for signs and symptoms of hyperuricaemia. Initiate treatment with urate-lowering medications as clinically indicated and withhold Rozlytrek for signs and symptoms of hyperuricaemia, as described in Table 3 (see section 4.2 *Dosage and Administration*).

QTc interval prolongation
QT interval prolongation was observed in patients treated with Rozlytrek in clinical trials (see section 4.8 *Adverse Effects (Undesirable Effects)*). Monitor patients who have QTc interval prolongation or are at significant risk of developing it, including patients with congenital long QT syndrome, clinically significant bradyarrhythmias, severe or poorly controlled heart failure and patients taking medications that are associated with QT interval prolongation. Assess QT interval and electrolytes at baseline and periodically during treatment, adjusting frequency based upon risk factors such as congestive heart failure, electrolyte abnormalities, or concomitant medications. Based on the severity of any QT interval prolongation observed, modify Rozlytrek treatment as described in Table 3 (see section 4.2 *Dosage and Administration*).

Vision disorders
Vision changes were reported in 21% of patients treated with Rozlytrek in clinical trials (see *section* 4.8 *Adverse Effects (Undesirable Effects)*). For patients with new visual changes or changes that interfere with activities of daily living, modify Rozlytrek treatment as described in Table 3 (see section 4.2 *Dosage and Administration*).

Paediatric use
There is limited clinical experience with Rozlytrek in paediatric patients. Rozlytrek had effects on growth and development in juvenile rats (see section 5.3 *Preclinical Safety Data*).

The effectiveness of Rozlytrek in paediatric patients (12 years of age and older) was established based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumours harboring an NTRK gene fusion (ALKA, STARTRK-1, and STARTRK-2) and pharmacokinetic data in paediatric patients enrolled in STARTRK-NG. Rozlytrek doses based on body surface area in paediatric patients 12 years and older resulted in similar systemic exposure compared to that in adults who received a Rozlytrek dose of 600 mg (see sections 4.2 *Dosage and Administration*, 5.1 *Pharmacodynamic Properties – Clinical trials* and 5.2 *Pharmacokinetic Properties – Pharmacokinetics in special populations*).

The safety of Rozlytrek was evaluated in paediatric patients with unresectable or metastatic solid tumours with a NTRK gene fusion enrolled in one of three multi-centre, open-label clinical trials: STARTRK-NG (n=68); TAPISTRY (n=21) and STARTRK-2 (n=2). Patients received Rozlytrek 20 mg to 600 mg based on body surface area (BSA) orally or via enteral feeding tube once daily in 4-week cycles until unacceptable toxicity or disease progression. Among patients who received Rozlytrek, 62.6% were exposed for 6 months or longer and 48.4% were exposed for greater than one year.

The median age of paediatric patients who received Rozlytrek was 6 years (range: 0 to 17 years); 49.5% were female; 62.6% were White, 26.4% Asian, 5.5% Black or African American, and 5.5% were other races.

The overall safety profile was generally similar with that observed for adults. Rozlytrek was associated with a higher incidence of skeletal fractures in the paediatric patients compared to adult patients (see section 4.4 *Special Warnings and Precautions for Use* and 4.8 *Adverse Effects (Undesirable Effects) – Description of selected adverse events*).

The safety and effectiveness of Rozlytrek in paediatric patients with ROS1-positive NSCLC have not been established.

Use in 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} geometric mean ratio (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} geometric mean ratio (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. For the unbound entrectinib and M5, the $AUC_{last\ (fu)}$ geometric mean ratio (90% CI) were 1.91 (1.21, 3.02) for the mild, 1.57 (1.06, 2.31) for the moderate, and 2.34 (1.57, 3.48) for the severe hepatic impaired groups compared to the normal hepatic function group. Although the effect of hepatic impairment on unbound PK parameters generally followed a similar direction as total PK parameters, due to the high non-specific binding in buffer and high variability, results should be interpreted with caution. 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 (see also sections 4.2 *Dosage and Administration* and 5.2 *Pharmacokinetic properties*).

Use in renal impairment
Rozlytrek has not been studied in patients with severe (CLcr < 30 mL/min) renal impairment (see sections 4.2 *Dosage and Administration* and *5.2 Pharmacokinetic Properties*).

Use in the elderly
Of the 355 patients who received Rozlytrek across clinical trials, 25% were 65 years or older, and 5% were 75 years of age or older. Clinical studies of Rozlytrek did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients.

Effects on laboratory tests
See section 4.8 *Adverse Effects (Undesirable Effects) – Laboratory abnormalities*.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of entrectinib on other drugs

CYP substrates

Co-administration of a single 600 mg Rozlytrek dose with oral midazolam (a sensitive CYP3A substrate) in patients increased the midazolam AUC by 50% but reduced midazolam C_{max} by 21%. See section 4.2 *Dosage and Administration –Dose modifications for specific medicine interactions*.

Transporter substrates
Co-administration of a single 600 mg Rozlytrek dose with oral digoxin (a sensitive P-glycoprotein (P-gp) substrate) in patients increased digoxin C_{max} by 28% and AUC by 18%.

In vitro data indicates:

- Entrectinib is not a substrate of P-gp or BCRP, but M5 is a substrate of both.
- Entrectinib and M5 are not substrates of OATP1B1 or OATP1B3.

Oral contraceptives
Physiologically-based pharmacokinetic simulation does not predict a significant effect of entrectinib on the pharmacokinetics of ethinyl oestradiol.

Effects of other drugs on entrectinib

CYP3A inducers
Co-administration of a single oral 600 mg dose of entrectinib with rifampicin (a strong CYP3A inducer) reduced entrectinib AUC_{inf} by 77% and C_{max} by 56%. Co-administration of a moderate CYP3A inducer with Rozlytrek is predicted to reduce $AUC_{0\text{-}tau}$ by 56% and C_{max} by 43%. See section 4.2 *Dosage and Administration – Dose modifications for specific medicine interactions*.

CYP3A inhibitors
Co-administration of a single oral 100 mg dose of entrectinib with itraconazole (a strong CYP3A4 inhibitor) increased entrectinib AUC_{inf} by 504% (6-fold) and C_{max} by 73%. Co-administration of a moderate CYP3A inhibitor with Rozlytrek is predicted to increase entrectinib $AUC_{0\text{-}Tau}$ by 3-fold and C_{max} by 2.9-fold. See section 4.2 *Dosage and Administration – Dose modifications for specific medicine interactions*.

Medicinal products that increase gastric pH
Co-administration of a single oral 600 mg dose of entrectinib with lansoprazole (a proton pump inhibitor [PPI]) decreased entrectinib AUC_{inf} by 25% and C_{max} by 23%.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Dedicated toxicological fertility studies of entrectinib have not been performed. In general toxicology studies, with the exception of dose-dependent decreases in prostate weight in male dogs, no effects of entrectinib on reproductive organs were observed in rats or dogs at doses resulting in exposures up to approximately 3.2 times the human exposure (AUC) at the recommended human dose (600 mg).

Use in pregnancy - Category D
There are no available data on the use of Rozlytrek in pregnant women, but based on its mechanism of action, findings in animal studies (see below), and published clinical case reports of inherited NTRK pathway deficiencies (see below), Rozlytrek can cause embryo-fetal harm when administered to a pregnant woman. Advise all patients, including pregnant women, of the potential harm to a fetus.

Human data
Published reports of individuals with congenital mutations in TRK pathway proteins suggest that decreases in TRK-mediated signalling are correlated with obesity, developmental delays, cognitive impairment, insensitivity to pain, and anhidrosis.

Animal data
Administration of entrectinib to pregnant rats during the period of organogenesis at a dose of 200 mg/kg (resulting in exposures up to 2.7 times the human exposure (AUC) at the 600 mg dose) resulted in maternal toxicity (decreased body weight gain and food consumption) and resulted in fetal malformations including body closure defects (omphalocele and gastroschisis) and malformations of the vertebrae, ribs and limbs (micromelia and adactyly), but did not result in embryolethality. Lower fetal weights and reduced skeletal ossification occurred at doses ≥ 12.5 and 50 mg/kg, respectively (resulting in exposures equivalent to 0.2 and 0.9 times the human exposure (AUC) at the 600 mg dose, respectively).

Contraception in male and female patients
Rozlytrek can cause embryo-fetal harm when administered to a pregnant woman. Advise all patients of the potential harm to a fetus. Test for pregnancy in females of reproductive potential prior to initiating Rozlytrek. Advise female patients of reproductive potential to use highly effective contraceptive methods during treatment with Rozlytrek and for at least 5 weeks following the last dose.

Advise male patients with female partners of reproductive potential to use highly effective contraceptive methods during treatment with Rozlytrek and for 3 months following the last dose.

Use in lactation
There are no data on the presence of entrectinib or its metabolites in human milk or their effects on either the breastfed child or on milk production. Because of the potential for harm to the breastfed child, advise a lactating woman to discontinue breastfeeding during treatment with Rozlytrek and for 7 days after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Rozlytrek may influence the ability to drive and use machines. Advise patients not to drive or operate hazardous machinery if they are experiencing CNS adverse reactions (see sections 4.4 *Special Warnings and Precautions for Use* and 4.8 *Adverse Effects (Undesirable Effects)*).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile
The safety profile of Rozlytrek was characterised in a group of 355 patients, including 172 (48%) patients exposed for 6 months or longer and 84 (24%) patients exposed for 1 year or longer. Rozlytrek was studied in one dose-finding trial in adults [ALKA (n = 57)], one dose-finding and activity-estimating trial in adults [STARTRK-1 (n = 76)], one dose-finding and activity-estimating trial in paediatric and adult patients [STARTRK-NG (n = 16)], and one single arm, activity-estimating trial in adults [STARTRK-2 (n = 206)].

The population characteristics were: median age 55 years (range: 4 to 86 years); 5% (n = 17) were less than 18 years of age; 55% were female; and 66% were White, 23% were Asian, and 5% were Black; 3% were Hispanic/Latino. The most common tumours (≥ 5%) were lung (56%), sarcoma (8%), and colon (5%). ROS1 gene fusions were present in 42% and NTRK gene fusions were present in 20%. Most adults (75%) received Rozlytrek 600 mg orally once daily. The doses ranged from 100 mg/m^2 to 1600 mg/m^2 once daily in adults and 250 mg/m^2 to 750 mg/m^2 once daily in paediatric patients. Rozlytrek is not indicated for paediatric patients less than 12 years of age (see section 4.4 *Special Warnings and Precautions for Use – Paediatric use*).

Serious adverse reactions occurred in 39% of patients. The most frequent serious adverse reactions (≥ 2%) were pneumonia (3.9%), dyspnoea (3.7%), pleural effusion (3.4%), sepsis (2.5%), pulmonary embolism (2.3%), respiratory failure (2%), and pyrexia (2%).

Grade 3 or 4 adverse reactions occurred in 60% of patients; the most common (≥ 2%) were lung infection (5%), increased weight (7%), dyspnoea (6%), fatigue/asthenia (5%), cognitive disorders (4.5%), syncope (2.5%), pulmonary embolism (3.4%), hypoxia (3.4%), pleural effusion (3.1%), hypotension (2.8%), diarrhoea (2%), and urinary tract infection (2.5%).

Fatal events included dyspnoea (0.6%), pneumonia (0.6%), sepsis (0.6%), completed suicide (0.3%), large intestine perforation (0.3%) and tumour lysis syndrome (0.3%). One patient developed Grade 4 myocarditis after one dose of Rozlytrek which resolved after discontinuation of Rozlytrek and administration of high-dose corticosteroids.

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received Rozlytrek. The most frequent adverse reactions (< 1% each) that resulted in permanent discontinuation were pneumonia, cardio-respiratory arrest, dyspnoea, and fatigue.

Dose interruptions due to adverse reactions occurred in 46% of patients. The most frequent adverse reactions (≥ 2%) that resulted in interruption were increased blood creatinine (4%), fatigue (3.7%), anaemia

(3.1%), diarrhoea (2.8%), pyrexia (2.8%), dizziness (2.5%), dyspnoea (2.3%), nausea (2.3%), pneumonia (2.3%), cognitive disorder (2%) and neutropenia (2%).

Dose reductions due to adverse reactions occurred in 29% of patients who received Rozlytrek. The most frequent adverse reactions resulting in dose reductions (≥ 1%) were dizziness (3.9%), increased blood creatinine (3.1%), fatigue (2.3%), anaemia (1.7%), and increased weight (1.4%).

The most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, oedema, dizziness, diarrhoea, nausea, dysaesthesia, dyspnoea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia and vision disorders.

Tabulated summary of adverse drug reactions from clinical trials
Table 4 summarises the most common adverse drug reactions (ADRs) occurring in adult and paediatric patients treated with Rozlytrek.

Table 4. Adverse reactions that occurred in at least 10% of patients receiving Rozlytrek in clinical trials (ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG)

Adverse Reactions	Rozlytrek N = 355	
	All Grades (%)	Grade ≥ 3* (%)
General disorders and administration site conditions		
Fatigue[1]	48	5
Edema[2]	40	1.1
Pyrexia	21	0.8
Gastrointestinal		
Constipation	46	0.6
Diarrhoea	35	2.0
Nausea	34	0.3
Vomiting	24	0.8
Abdominal pain[3]	16	0.6
Nervous system disorders		
Dysgeusia	44	0.3
Dizziness[4]	38	0.8
Dysesthesia[5]	34	0.3
Cognitive impairment[6]	27	4.5
Peripheral sensory neuropathy[7]	18	1.1
Headache	18	0.3
Ataxia[8]	17	0.8
Sleep[9]	14	0.6
Mood disorders[10]	10	0.6
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	30	6*
Cough	24	0.3
Musculoskeletal and connective tissue disorders		
Myalgia[11]	28	1.1
Arthralgia	21	0.6
Muscular weakness	12	0.8
Back pain	12	1
Pain in extremity	11	0.3
Metabolism and nutrition disorders		
Increased weight	25	7
Decreased appetite	13	0.3
Dehydration	10	1.1
Eye disorders		

Adverse Reactions	Rozlytrek N = 355	
	All Grades (%)	Grade ≥ 3* (%)
Vision disorders[12]	21	0.8
Infections and infestations		
Urinary tract infection	13	2.3
Lung infection[13]	10	6*
Vascular disorders		
Hypotension[14]	18	2.8
Skin and subcutaneous tissue disorders		
Rash[15]	11	0.8

* Grades 3 – 5, inclusive of fatal adverse reactions, including 2 events of pneumonia and 2 events of dyspnoea.
[1]Includes fatigue, asthenia
[2] Includes face edema, fluid retention, generalized edema, localized edema, edema, edema peripheral, peripheral swelling
[3] Includes abdominal pain upper, abdominal pain, lower abdominal discomfort, abdominal tenderness
[4] Includes dizziness, vertigo, dizziness postural
[5] Includes paresthesia, hyperesthesia, hypoesthesia, dysesthesia, oral hypoesthesia, palmar-plantar erythrodysesthesia, oral paresthesia, genital hypoesthesia
[6] Includes amnesia, aphasia, cognitive disorder, confusional state, delirium, disturbance in attention, hallucinations, visual hallucination, memory impairment, mental disorder, mental status changes
[7] Includes neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy
[8] Includes ataxia, balance disorder, gait disturbances
[9] Includes hypersomnia, insomnia, sleep disorder, somnolence
[10] Includes anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation
[11] Includes musculoskeletal pain, musculoskeletal chest pain, myalgia, neck pain
[12] Includes blindness, cataract, cortical cataract, corneal erosion, diplopia, eye disorder, photophobia, photopsia, retinal hemorrhage, vision blurred, visual impairment, vitreous adhesions, vitreous detachment, vitreous floaters
[13] Includes lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection
[14] Includes hypotension, orthostatic hypotension
[15] Includes rash, rash maculopapular, rash pruritic, rash erythematous, rash papular

Clinically relevant adverse reactions that occurred in ≤ 10% of patients include dysphagia (10%), fall (8%), pleural effusion (8%), fractures (6%), hypoxia (4.2%), pulmonary embolism (3.9%), syncope (3.9%), congestive heart failure (3.4%), and QT prolongation (3.1%).

Description of selected adverse drug reactions

Congestive heart failure (CHF)

Among the 355 patients who received Rozlytrek across clinical trials, congestive heart failure (CHF) occurred in 3.4% of patients, including Grade 3 (2.3%). In clinical trials, cardiac monitoring was conducted using electrocardiograms (ECGs) and echocardiograms or multigated acquisition (MUGA) scans at baseline

and at specified time points during treatment with Rozlytrek. Study eligibility criteria excluded patients with symptomatic CHF, myocardial infarction, unstable angina, or coronary artery bypass graft within 3 months of study entry. Among the 12 patients with CHF, the median time to onset was 2 months (range: 11 days to 12 months). Rozlytrek was interrupted in 6 of these patients (50%) and discontinued in 2 of these patients (17%). CHF resolved in 6 patients (50%) following interruption or discontinuation of Rozlytrek and institution of appropriate medical management. In addition, myocarditis in the absence of CHF was documented in 0.3% of patients. See also section 4.4 *Special Warnings and Precautions for Use*.

Central nervous system effects

Among the 355 patients who received Rozlytrek across clinical trials, 96 (27%) experienced cognitive impairment; symptoms occurred within 3 months of starting Rozlytrek in 74 (77%). Cognitive impairment included cognitive disorders (8%), confusional state (7%), disturbance in attention (4.8%), memory impairment (3.7%), amnesia (2.5%), aphasia (2.3%), mental status changes (2%), hallucinations (1.1%), and delirium (0.8%). Grade 3 cognitive adverse reactions occurred in 4.5% of patients. Among the 96 patients with cognitive impairment, 13% required a dose reduction, 18% required dose interruption and 1% discontinued Rozlytrek due to cognitive adverse reactions.

Among the 355 patients who received Rozlytrek across clinical trials, 36 (10%) experienced mood disorders. The median time to onset of mood disorders was 1 month (range: 1 day to 9 months). Mood disorders occurring in ≥ 1% of patients included anxiety (4.8%), depression (2.8%) and agitation (2%). Grade 3 mood disorders occurred in 0.6% of patients. One completed suicide was reported 11 days after treatment had ended. Among the 36 patients who experienced mood disorders, 6% required a dose reduction, 6% required dose interruption and no patients discontinued Rozlytrek due to mood disorders.

Dizziness occurred in 136 (38%) of the 355 patients. Among the 136 patients who experienced dizziness, Grade 3 dizziness occurred in 2.2% of patients. Ten percent of patients required a dose reduction, 7% required dose interruption and 0.7% discontinued Rozlytrek due to dizziness.

Among the 355 patients who received Rozlytrek across clinical trials, 51 (14%) experienced sleep disturbances. Sleep disturbances included insomnia (7%), somnolence (7%), hypersomnia (1.1%), and sleep disorder (0.3%). Grade 3 sleep disturbances occurred in 0.6% of patients. Among the 51 patients who experienced sleep disturbances, 6% required a dose reduction and no patients discontinued Rozlytrek due to sleep disturbances.

The incidence of CNS adverse reactions was similar in patients with and without CNS metastases; however, the incidence of dizziness (38% vs 31%), headache (21% vs 13%), paraesthesia (20% vs 6%), balance disorder (13% vs 4%), and confusional state (11% vs 2%) appeared to be increased in patients with CNS metastases who had received prior CNS irradiation (N = 90) compared to those who did not (N = 48). Patients who had brain metastases at baseline had a higher frequency of these events (39%) compared to those without brain metastases (25%).

See also section 4.4 *Special Warnings and Precautions for Use*.

Skeletal fractures

In an expanded safety population that included 762 adult patients and 91 paediatric patients who received Rozlytrek across clinical trials, 9.1% of adult patients and 29.7% of paediatric patients experienced fractures. In adult and paediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area; in paediatric patients some fractures occurred with no trauma. 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 adult patients. In both adult and paediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). In two paediatric patients, bilateral femoral neck fractures occurred. A total of 52 fracture events were reported in 27 paediatric patients, with 14 patients who experienced more than one occurrence of fracture. Among the 27 paediatric patients who experienced fractures, 24 patients were less than 12 years of age. Fractures resolved in 85.2% (23/27) of paediatric patients. The median time to fracture was 8.11 months (range 0.26 to 45.3 months) in adults and 4.3 months (range: 2.0 months to 28.7 months) in paediatric patients. Rozlytrek was interrupted in 26.1% of adults and 18.5% of paediatric patients who experienced fractures. Six paediatric patients discontinued treatment and one patient reduced the dose of Rozlytrek due to

fractures. Twelve paediatric patients experienced Grade 2 fractures and 10 patients experienced Grade 3 fractures. Two adult patients discontinued treatment and 2 patients reduced the dose due to fractures. Thirty-six adult patients experienced Grade 2 fractures and nineteen adult patients experienced Grade 3 fractures. See also section 4.4 *Special Warnings and Precautions for Use*.

Hepatotoxicity
Among the 355 patients who received Rozlytrek, increased AST of any grade occurred in 42% of patients and increased ALT of any grade occurred in 36%. Grade 3 – 4 increased AST or ALT occurred in 2.5% and 2.8% of patients, respectively; the incidence may be underestimated as 4.5% of patients had no post-treatment liver function tests (see Table 5). The median time to onset of increased AST was 2 weeks (range: 1 day to 29.5 months). The median time to onset of increased ALT was 2 weeks (range: 1 day to 9.2 months). Increased AST or ALT leading to dose interruptions or reductions occurred in 0.8% and 0.8% of patients, respectively. Rozlytrek was discontinued due to increased AST or ALT in 0.8% patients. See also section 4.4 *Special Warnings and Precautions for Use*.

Hyperuricaemia
Among 355 patients who received Rozlytrek across clinical trials, 32 patients (9%) experienced hyperuricaemia reported as adverse reactions with symptoms, as well as elevated uric acid levels. Grade 4 hyperuricaemia occurred in 1.7% of patients, including one patient who died due to tumour lysis syndrome. Among the 32 patients with hyperuricaemic adverse reactions, 34% required urate-lowering medication to reduce uric acid levels, 6% required dose reduction and 6% required dose interruption. Hyperuricaemia resolved in 73% of patients following initiation of urate-lowering medication without interruption or dose reduction of Rozlytrek. No patients discontinued Rozlytrek due to hyperuricaemia. See also section 4.4 *Special Warnings and Precautions for Use*.

QT interval prolongation
Among the 355 patients who received Rozlytrek across the clinical trials, 3.1% of patients with at least one post-baseline ECG assessment experienced QTcF interval prolongation of >60 ms after starting Rozlytrek and 0.6% had a QTcF interval >500 ms (see sections 4.4 *Special Warnings and Precautions for Use* and 5.1 *Pharmacodynamic Properties*).

Vision disorders
Among the 355 patients who received Rozlytrek across clinical trials, vision changes occurred in 21% of patients, including Grade 1 (82%), Grade 2 (14%) and Grade 3 (0.8%). Vision disorders occurring in ≥1% included blurred vision (8.7%), photophobia (5.1%), diplopia (3.1%), visual impairment (2%), photopsia (1.3%), cataract (1.1%), and vitreous floaters (1.1%). See also section 4.4 *Special Warnings and Precautions for Use*.

Weight gain
Increased weight was reported by around a quarter of adult patients, 7% at grade 3 severity (an increase of more than 20% from baseline). Fluid retention or oedema was co-reported for a number of cases and may have contributed to weight gain. Among 30 paediatric patients treated with entrectinib for various NTRK-positive cancers, six (20%) reported grade 3 weight increase.

Safety in Paediatric Patients
Serious adverse reactions occurred in 49.5% of paediatric patients who received Rozlytrek. Serious adverse reactions in > 2% of patients included skeletal fractures (13.2%), pyrexia (7.7%), pneumonia (5.5%), hydrocephalus (5.5%), device related infection (3.3%), hypoxia (3.3%), gait disturbance (2.2%), pain (2.2%), upper respiratory infection (2.2%), dyspnoea (2.2%), headache (2.2%), fall (2.2%), vomiting (2.2%), sepsis (2%) and infection (2%).

Permanent discontinuation of Rozlytrek due to an adverse reaction occurred in 12.1% of paediatric patients. Adverse reactions which resulted in permanent discontinuation of Rozlytrek in > 2% of patients included skeletal fracture. Dosage interruptions of Rozlytrek due to an adverse reaction occurred in 41.8% of patients. Adverse reactions which required dosage interruption in > 2% of patients included pneumonia, COVID-19 and urinary tract infection.

Dose reductions of Rozlytrek due to an adverse reaction occurred in 26.4% of patients. Adverse reactions which required dose reductions in > 2% of patients included increased weight and increased blood creatinine.

Table 5 summarises the adverse reactions in STARTRK-NG (n=68), TAPISTRY (n=21) and STARTRK-2 (n=2).

Table 5. Adverse reactions (≥20%) in Paediatric patients who received Rozlytrek in STARTRK-NG, TAPISTRY and STARTRK-2

Adverse Reaction	Rozlytrek (n=91)	
	All Grades (%)	Grade 3 or 4 (%)
General Disorders		
Pyrexia	50.5	2.2
Fatigue[1]	28.6	2.2
Gastrointestinal Disorders		
Vomiting	40.7	1.1
Diarrhoea	39.6	2.2
Constipation	37.4	1.1
Nausea	28.6	0
Investigations		
Increased Weight	38.5	18.7
Respiratory, Thoracic And Mediastinal Disorders		
Cough	37.4	1.1
Musculoskeletal And Connective Tissue Disorders		
Skeletal Fracture[2]	29.7	11.0
Pain in Extremity	23.1	2.2
Metabolism And Nutrition Disorders		
Decreased Appetite	23.1	1.1
Nervous System Disorders		
Headache	20.9	2.2
Infections		
Upper Respiratory Tract Infection	30.8	2.2
Skin and Subcutaneous Tissue		
Rash[3]	22.0	0

[1]Includes fatigue, asthenia
[2]Includes clavicle fracture, tibia fracture, femur fracture, fibula fracture, foot fracture, fracture, pathological fracture, limb fracture, lower limb fracture, pelvic fracture, spinal compression fracture, stress fracture, ulna fracture
[3] Include rash, rash maculopapular, rash pruritic, rash erythematous, rash papular

Clinically relevant adverse reactions in <20% of paediatric patients who received Rozlytrek included pruritus, urinary incontinence, eye pain, photophobia, abdominal pain, urinary tract infection and nasal congestion.

Laboratory abnormalities
Table 6 summarises the laboratory abnormalities that most commonly worsened from baseline in adult and paediatric patients treated with Rozlytrek.

Table 6: Laboratory abnormalities (≥ 20%) worsening from baseline in patients receiving Rozlytrek in ALKA, STARTRK-1, STARTRK-2, STARTRK-NG and TAPISTRY

Laboratory Abnormality	Rozlytrek NCI CTCAE Grade	
	All Grades (%)[1]	Grade 3 or 4 (%)[1]
Haematology		
Anaemia	64.8	11.9
Lymphopenia	39.1	2.3
Neutropenia	34.2	8.3
Chemistry		
Increased creatinine[2]	78.8	8.5
Hyperuricemia	57.2	19.9
Increased AST	51	2.5
Increased ALT	47.5	2.4
Hypernatremia	38.9	0.6
Hypocalcemia	34.1	3.8
Hypophosphatemia	31.4	6.3
Increased lipase	31.4	9.9
Hypoalbuminemia	30.4	7.2
Increased amylase	25.6	5.0
Hyperkalemia	26.4	2.3
Increased alkaline phosphatase	27.2	0.5
Hyperglycemia[3]	NE[3]	NE[3]

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 121 to 827 patients.

[2] Based on NCI CTCAE v5.0

[3] NE = Not evaluable. Per NCI CTCAE v5.0, the criteria for grading is not numerical and therefore grade could not be determined.

Table 7 summarises the laboratory abnormalities in STARTRK-NG (n=68), TAPISTRY (n=6) and STARTRK-2 (n=2) in paediatric patients treated with Rozlytrek.

Table 7. Laboratory abnormalities (≥20%) worsening from baseline in Paediatric patients receiving Rozlytrek in STARTRK-NG, TAPISTRY and STARTRK-2

Laboratory Abnormality	Rozlytrek[1]	
	All Grades (%)	Grade 3 or 4 (%)
Haematology		
Decreased Haemoglobin	57.3	7.9
Decreased Neutrophils	57.0	23.3
Decreased Leukocytes	47.8	2.3
Increased Lymphocytes	33.8	3.8
Chemistry		
Increased Creatinine	82.8	9.2
Increased AST	59.6	3.4
Increased ALT	53.3	2.2
Increased Sodium	36.4	1.1
Increased Magnesium	31.8	4.5
Increased Alkaline Phosphatase	30	0
Decreased Glucose	30.7	0
Increased Potassium	25.8	4.5
Decreased Albumin	25.8	7.2
Increased Calcium	25.6	7.8
Increased Bilirubin	17.8	6.7

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase
[1] The denominator used to calculate the rate varied from 75 to 90 based on the number of patients with a baseline value and at least one post-treatment value. All values based on NCI CTCAE v5.0

Other clinically relevant laboratory abnormalities in patients who received Rozlytrek included decreased phosphorous**.**

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 agent, tyrosine kinase inhibitor, ATC code: L01EX14.

Mechanism of Action
Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB and TRKC (encoded by the neurotrophic tyrosine receptor kinase [*NTRK*] genes *NTRK1*, *NTRK2* and *NTRK3*, respectively), proto-oncogene tyrosine-protein kinase ROS1 (ROS1; encoded by the gene *ROS1*), and anaplastic lymphoma kinase (ALK; encoded by the gene *ALK*) with IC_{50} values of 0.1 to 2 nM. Entrectinib also inhibits JAK2 and TNK2 with IC50 values > 5 nM. The major active metabolite of entrectinib, M5, showed similar *in vitro* activity against TRK, ROS1 and ALK.

Fusion proteins that include TRK, ROS1 or ALK kinase domains can drive tumourigenic potential through hyperactivation of downstream signalling pathways leading to unconstrained cell proliferation. Entrectinib inhibits the TRK kinases, ROS1 and ALK, leading to inhibition of downstream signalling pathways, cell proliferation and induction of tumour cell apoptosis. Entrectinib demonstrated *in vitro* and *in vivo* inhibition of cancer cell lines derived from multiple tumour types harbouring NTRK, ROS1 and ALK fusion genes.

Entrectinib demonstrated steady-state brain-to-plasma concentration ratios of 0.4 - 2.2 in multiple animal species (mice, rats and dogs) and demonstrated *in vivo* anti-tumour activity in mice with intracranial implantation of TRKA- and ALK-driven tumour cell lines.

Cardiac electrophysiology
Across clinical trials, 355 patients who received Rozlytrek (at doses ranging from 100 mg to 2600 mg daily under fasting or fed conditions; 75% received 600 mg orally once daily) had at least one post-baseline ECG assessment. Amongst this group, 3.1% experienced QTcF prolongation of more than 60 ms past their baseline after starting Rozlytrek, and 0.6% had a post-baseline QTc interval longer than 500 ms (see section 4.4 *Warnings and Special Precautions for Use*).

Clinical trials
ROS1-positive NSCLC
The efficacy of Rozlytrek was evaluated in a pooled subgroup of patients with ROS1-positive metastatic NSCLC who received Rozlytrek at various doses and schedules (90% received Rozlytrek 600 mg orally once daily) and were enrolled in one of three multicentre, single-arm, open-label clinical trials: ALKA, STARTRK-1 and STARTRK-2. To be included in this pooled subgroup, patients were required to have histologically confirmed, recurrent or metastatic, ROS1-positive NSCLC, ECOG performance status ≤2, measurable disease per RECIST v1.1, ≥18 months of follow-up from first post-treatment tumour assessment, and no prior therapy with a ROS1 inhibitor. Identification of ROS1 gene fusion in tumour specimens was prospectively determined in local laboratories using either a fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), or polymerase chain reaction (PCR) laboratory-developed tests. All patients were assessed for CNS lesions at baseline. The primary efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) according to RECIST v1.1 as assessed by blinded independent central review (BICR). Intracranial response according to RECIST v1.1 was assessed by BICR. Tumour assessments with imaging were performed every 8 weeks.

Efficacy was assessed in 92 patients with ROS1-positive NSCLC. The median age was 53 years (range: 27 to 86); female (65%); White (48%), Asian (45%), Black (5%); and Hispanic or Latino (2.4%); never smoked (59%); and ECOG performance status 0 or 1 (88%). Ninety-nine percent of patients had metastatic disease, including 42% with CNS metastases; 96% had adenocarcinoma; 65% received prior platinum-based chemotherapy for metastatic or recurrent disease or had progressed in less than 6 months following platinum-based adjuvant or neoadjuvant therapy. ROS1 positivity was determined by NGS in 79%, FISH in 16%, and PCR in 4%. Twenty-five percent had central laboratory confirmation of ROS1 positivity using an analytically validated RNA-based NGS test.

Efficacy results from patients with ROS1-positive NSCLC are summarised in Table 8.

Table 8. Efficacy results for patients with ROS1-positive NSCLC per BICR assessment.

Efficacy Parameters	Rozlytrek
Objective response rate (ORR)	**n = 92**
ORR (95% CI)	74% (64, 83)
CR, n (%)	14 (15%)
PR, n (%)	54 (59%)
Duration of response (DOR)*	**n = 68**
Range (months)	2.4, 55.2+
% with duration ≥ 9 months	75%
% with duration ≥ 12 months	57%
% with duration ≥ 18 months	38%

CR = complete response; PR = partial response;
Confidence Intervals (CI) calculated using the Clopper-Pearson method.
*Observed DOR
+ denotes ongoing response

Of the 92 patients with ROS1-positive NSCLC in the efficacy evaluable analysis set, 10 had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 7 of these 10 patients.

NTRK fusion-positive solid tumours

Efficacy in adult patients

The efficacy of Rozlytrek was evaluated in a pooled subgroup of adult patients with unresectable or metastatic solid tumours with a NTRK gene fusion enrolled in one of three multicentre, single-arm, open-label clinical trials: ALKA, STARTRK-1 and STARTRK-2. To be included in this pooled subgroup, patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery causing significant morbidity for locally advanced disease; measurable disease per RECIST v1.1; at least 2 years of follow-up from first post-treatment tumour assessment of Rozlytrek; and no prior therapy with a TRK inhibitor. Patients received Rozlytrek at various doses and schedules (94% received Rozlytrek 600 mg orally once daily) until unacceptable toxicity or disease progression. Identification of positive NTRK gene fusion status was prospectively determined in local laboratories or a central laboratory using various nucleic acid-based tests. The major efficacy outcome measures were ORR and DOR, as determined by a BICR according to RECIST v1.1. Intracranial response according to RECIST v1.1 as evaluated by BICR. Tumour assessments with imaging were performed every 8 weeks.

Efficacy was assessed in the first 54 adult patients with solid tumours with an NTRK gene fusion enrolled into these trials. The median age was 58 years (range: 21 to 83); female (59%); White (80%), Asian (13%) and Hispanic or Latino (7%); and ECOG performance status 0 (43%) or 1 (46%). Ninety-six percent of patients had metastatic disease, including 22% with CNS metastases, and 4% had locally advanced, unresectable disease. All patients had received prior treatment for their cancer including surgery (n=43), radiotherapy (n=36), or systemic therapy (n=48). Forty patients (74%) received prior systemic therapy for metastatic disease with a median of 1 prior systemic regimen and 17% (n=9) received 3 or more prior systemic regimens. The most common cancers were sarcoma (24%), lung cancer (19%), salivary gland tumours (13%), breast cancer (11%), thyroid cancer (9%), and colorectal cancer (7%). A total of 52 (96%) patients had an NTRK gene fusion detected by NGS and 2 (4%) had an NTRK gene fusion detected by

other nucleic acid-based tests. Eighty-three percent of patients had central laboratory confirmation of NTRK gene fusion using an analytically validated RNA-based NGS test.

Efficacy results from patients with NTRK-positive solid tumours are summarised in Table 9.

Table 9. Efficacy results for patients with solid tumours harbouring an NTRK gene fusion

Efficacy Parameter	**Rozlytrek**
Objective response rate (ORR)	**n=54**
ORR (95% CI)	59% (45, 72)
CR, n (%)	7 (13%)
PR, n (%)	25 (46%)
Duration of response (DOR)*	**n=32**
Range, (months)	2.8, 47.8+
% with duration ≥ 6 months	72%
% with duration ≥ 9 months	66%
% with duration ≥ 12 months	56%

CR = complete response; PR = partial response.
Confidence Intervals (CI) calculated using the Clopper-Pearson method.
* Observed DOR
+ denotes ongoing response

Table 10: Efficacy against NTRK fusion-positive tumours, by tumour histology

Tumor Type	**Patients N = 54**	**ORR**		**DOR**
		%	**95% CI**	**Range (months)**
Sarcoma	13	46%	19%, 75%	2.8, 33.6+
Non-small cell lung cancer	10	60%	26%, 88%	3.7, 47.8+
Salivary (MASC)	7	86%	42%, 100%	2.8, 38.5+
Breast cancer	6	83%	36%, 100%	4.2, 42.3+
Thyroid cancer	5	60%	NA	7.9, 31.5+
Colorectal cancer	4	25%	NA	15.1
Neuroendocrine cancers	3	CR	NA	32.9+
Pancreatic cancer	3	PR, PR	NA	7.1, 12.9
Gynecological cancers	2	PR	NA	38.2
Cholangiocarcinoma	1	PR	NA	9.3

+ denotes ongoing response
MASC: mammary analogue secretory carcinoma; NA = not applicable; PR = partial response.

Table 11. Efficacy against *NTRK* fusion-positive tumours, by fusion gene partner

***NTRK* Partner**	**Patients N = 54**	**ORR**		**DOR**
		%	**95% CI**	**Range (months)**
ETV6 – NTRK3	25	72%	51%, 88%	2.8, 47.8+
TPM3 – NTRK1	4	50%	7%, 93%	2.8, 15.1
TPR – NTRK1	4	100%	40%, 100%	5.6, 33.6+
LMNA – NTRK1	2	PR, PD	NA	4.2
SQSTM1 – NTRK1	2	PR, PD	NA	18.8+
PEAR1 – NTRK1	2	SD, NE	NA	NA
EML4 – NTRK3	2	PR, NE	NA	13.2
CD74 – NTRK1	1	PR	NA	10.4
PLEKHA6 – NTRK1	1	PR	NA	9.3
CDC42BPA – NTRK1	1	PR	NA	29.4
EPS15L1 – NTRK1	1	PR	NA	3.7
RBPMS – NTRK3	1	PR	NA	4.6

ERC1 – NTRK1	1	SD	NA	NA
PDIA3 – NTRK1	1	SD	NA	NA
TRIM33 – NTRK1	1	SD	NA	NA
AKAP13 – NTRK3	1	SD	NA	NA
KIF7 – NTRK3	1	SD	NA	NA
FAM19A2 – NTRK3	1	PD	NA	NA
CGN – NTRK1	1	NE	NA	NA
SQSTM1 – NTRK2	1	NE	NA	NA

+ denotes ongoing response
PR = partial response; PD = progressive disease; SD = stable disease; NA = not applicable; NE = not evaluable.

Among the subset of patients who received prior systemic therapy for metastatic disease, the ORR was 53%, similar to that seen in the overall population.

Among the 54 adult patients, 4 had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months of study entry. Responses in intracranial lesions were observed in 3 of these 4 patients.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of entrectinib and its pharmacologically active major circulating metabolite (M5) were characterised in adult patients with *ROS1*-positive NSCLC, *NTRK* gene fusion-positive solid tumours and, and healthy subjects. The pharmacokinetics of entrectinib and M5 are linear and are not dose-dependent or time-dependent. Steady state is achieved within one week for entrectinib and two weeks for M5 following daily administration of Rozlytrek. The pharmacokinetic parameters for entrectinib and M5 are described in Table 12.

Table 12. Pharmacokinetic parameters for entrectinib and metabolite M5

Parameter	Entrectinib Mean* (% CV)	M5 Mean* (% CV)
AUC_{D1} (nM*h)	31800 (48%)	10200 (82%)
AUC_{ss} (nM*h)	48000 (77%)	24000 (97%)
C_{maxD1} (nM)	2250 (58%)	622 (79%)
C_{maxss} (nM)	3130 (80%)	1250 (90%)
$R_{acc(AUC)}$	1.55 (49%)	2.84 (93%)

* Geometric mean

Absorption

The maximum entrectinib plasma concentration was reached 4 to 6 hours after oral administration of a 600 mg dose.

Effect of food

A high-fat (approximately 50% of total caloric content), high-calorie (approximately 800 to 1000 calories) meal did not have a significant effect on entrectinib exposure.

Distribution

Entrectinib and its major active metabolite M5 are both >99% bound to human plasma proteins *in vitro*.

The estimated volume of distribution (V/F) of 551 L and 81.1 L for entrectinib and M5, respectively.

Metabolism

Entrectinib is metabolised 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) is the only major active circulating metabolite identified. M5 has similar pharmacological potency to entrectinib in vitro and circulating M5 exposures at steady-state in patients were 40% of the corresponding entrectinib exposure.

Excretion
Following administration of a single oral dose of [^{14}C]-labelled entrectinib, 83% of radioactivity was excreted in faeces (36% of the dose as unchanged entrectinib and 22% as M5) with minimal excretion in urine (3%).

The estimated apparent clearance (CL/F) was 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
No clinically significant differences in the pharmacokinetics of entrectinib were observed based on age (12 years to 86 years), sex, race (White, Asian and Black), body weight (32 to 130 kg), mild to moderate renal impairment (CLcr 30 to <90 mL/min) and hepatic impairment (see section 4.4 *Special Warnings and Precautions for Use*).

Paediatric population (12 years and older)
In paediatric patients 12 years and older, the predicted systemic exposures for body surface area-based doses of 600 mg (BSA >1.50 m^2), 500 mg (BSA of 1.11 to 1.50 m^2) and 400 mg (BSA of 0.91 to 1.10 m^2) are comparable to the exposure in adults at the 600 mg dose.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Entrectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay; however, an in vitro assay in cultured human peripheral blood lymphocytes did demonstrate a potential for abnormal chromosome segregation (aneugenicity). Entrectinib was not clastogenic or aneugenic in the in vivo micronucleus assay in rats and did not induce DNA damage in a comet assay in rats.

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

Juvenile animal toxicity
In a 13-week juvenile rat toxicology study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to 16 years of age in humans). Entrectinib resulted in:

- decreased body weight gain and delayed sexual maturation at doses ≥4 mg/kg/day (approximately 0.06 times the human exposure (AUC) at the 600 mg dose),
- deficits in neurobehavioral assessments including functional observational battery and learning and memory (at doses ≥8 mg/kg/day, approximately 0.14 times the human exposure at the 600 mg dose), and
- decreased femur length at doses ≥16 mg/kg/day (approximately 0.18 times the human exposure at the 600 mg dose).

See also section 4.4 *Special Warnings and Precautions for Use – Paediatric use*.

6. PHARMACEUTICAL PARTICULARS

6.1 STORAGE

Storage:

Do not store above 30°C. Keep capsules in the original bottle. Keep the bottle tightly closed to protect from moisture.

Shelf life:

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

6.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Packs

Described as per local requirements.

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.

Medicine: keep out of reach of children

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