NEW ZEALAND DATA SHEET

1. PRODUCT NAME
Rozlytrek (entrectinib) 100 mg and 200 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 100 mg hard capsule contains 100 mg entrectinib.

Each 200 mg hard capsule contains 200 mg entrectinib.

Excipients with known effect
Each 100 mg hard capsule contains 65 mg lactose. Each 200 mg hard capsule contains 130 mg lactose.

For the full list of excipients, see section *6.1 List of excipients*.

3. PHARMACEUTICAL FORM
Hard capsule.

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Solid tumours
Rozlytrek is indicated for the treatment of adult and paediatric patients 12 years of age and older, with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive locally advanced or metastatic solid tumours, who have progressed following prior therapies, or as initial therapy when there are no acceptable standard therapies.
This indication was approved based on objective response rate and response duration in single-arm trials. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.

Non-small cell lung cancer (NSCLC)
Rozlytrek is indicated for the treatment of adult patients with ROS1-positive, locally advanced or metastatic NSCLC.

4.2 Dose and method of administration

General

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.

Dose

Adult patients
The recommended dose of Rozlytrek for adult patients is 600 mg given orally, once daily (see section *5.2 Pharmacokinetic properties*).

Paediatric patients
The recommended dose of Rozlytrek for paediatric patients 12 years of age and older, who have the ability to swallow capsules is 300 mg/m^2 orally, once daily (see Table 1) (see section *5.2 Pharmacokinetic properties*).

Table 1. Recommended dosing for paediatric patients

Body surface area (BSA)	Once daily dose
0.81 - 1.10 m^2	300 mg
1.11 - 1.50 m^2	400 mg
≥ 1.51 m^2	600 mg

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

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

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

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

Table 2. Dose reduction schedule for adult patients

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

Paediatric patients
Table 3 provides specific dose reduction advice for paediatric patients 12 years and older. For paediatric patients 12 years and older, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability.

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

Table 3. Dose reduction schedule for paediatric patients

Starting Dose once daily	First dose reduction	Second dose reduction
300 mg	200 mg once daily	100 mg once daily
400 mg	300 mg once daily	200 mg, once/day for 5 days each week*
600 mg	400 mg once daily	200 mg once daily

*5 days each week: Monday, Wednesday, Friday, Saturday, and Sunday

Dose modifications for specific adverse reactions
Recommendations for Rozlytrek dose modifications for adults and paediatric patients for specific adverse reactions are provided in Table 4 (see sections 4.*4 Special warnings and precautions for use* and *4.8 Undesirable effects*).

Table 4. Recommended dose modifications for specified adverse drug reactions for adult and paediatric patients

Adverse Drug Reaction	Severity *	Dose modification
Anaemia 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 reduce 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.

Adverse Drug Reaction	Severity *	Dose modification
	ALT or AST elevation greater than 3 times ULN with total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or haemolysis	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 ≤ Grade 1. Resume treatment at reduced dose.
	Grade 4	Withhold Rozlytrek until recovered to ≤ Grade 1. Resume treatment 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 treatment 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)

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

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, the 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 a long half-life (see section *4.5 Interactions with other medicines and other forms of interactions*).

Paediatric patients
The concomitant use of strong or moderate CYP3A inhibitors in paediatric patients should be avoided (see section *4.5 Interactions with other medicines and other forms of interactions*).

Concomitant CYP3A inducers
Co-administration of Rozlytrek with CYP3A inducers in adult and paediatric patients should be avoided (See section *4.5 Interactions with other medicines and other forms of interactions*).

Special populations

Elderly
No dose adjustment of Rozlytrek is required in patients ≥ 65 years of age (see section *5.2 Pharmacokinetic properties*).

Paediatric populations
The dosage for patients is based on body surface area (mg/m^2) with a maximum daily dose of 600 mg (see Table 1 for paediatric dosing).

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. The safety and efficacy of Rozlytrek have not been studied in patients with severe renal impairment. However, since entrectinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment (see sections *4.4 Special warnings and precautions for use* and *5.2 Pharmacokinetic properties*).

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 sections *4.4 Special warnings and precautions for use* and *5.2 Pharmacokinetic properties*).

Ethnicity
No dose adjustment is necessary for patients of different ethnicities (see section *5.2 Pharmacokinetic properties*).

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

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

4.4 Special warnings and precautions for use

Congestive heart failure
Congestive heart failure (CHF) has been reported across clinical trials with Rozlytrek (see Table 5 in section *4.8 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 oedema, should be evaluated and treated as clinically appropriate.

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

Cognitive disorders

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

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

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

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 both adult and paediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area,. There are no data on the effects of Rozlytrek on healing of known fractures and the risk of occurrence of future fractures. In the majority of paediatric patients treatment was continued with Rozlytrek and the fracture healed.

QTc interval prolongation

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

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

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

Use in the elderly

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 sections *4.2 Dose and method of administration* and *5.2 Pharmacokinetic properties*).

Paediatric use

The safety and efficacy of Rozlytrek have been established in paediatric patients.

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 Undesirable effects*).

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 sections *4.2 Dose and method of administration* and *5.2 Pharmacokinetic properties*).

Hepatic impairment
A study has been conducted investigating the effect of impaired hepatic function on the pharmacokinetics of entrectinib and its active metabolite M5. No dose adjustment is required in patients with underlying mild, moderate or severe hepatic impairment. While there was a trend to increased systemic exposure with increasing hepatic impairment, the variability in systemic exposure was high and observed exposures overlapped across all the study groups. Patients should be carefully monitored for adverse reactions with dose adjustments made as necessary (see sections *4.2 Dose and method of administration* and *5.2 Pharmacokinetic properties*).

4.5 Interactions with other medicines and other forms of interactions

Effects of entrectinib on others drugs

CYP substrates
Based on *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 in healthy adult subjects, co-administration of multiple doses of entrectinib and midazolam (a sensitive CYP3A substrate) increased the systemic exposure of midazolam by approximately 50%, indicating a weak inhibitory effect of entrectinib on the metabolism of midazolam (Geometric mean ratio [GMR] with/without entrectinib for AUC_{inf} was 150% [90% CI: 129%, 173%]).

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

P-glycoprotein (P-gp) substrates
In vitro data suggest that entrectinib has inhibitory potential towards P-gp.

In a clinical study in healthy adult subjects, co-administration of a single oral dose of entrectinib with a sensitive P-gp substrate, digoxin, increased the digoxin C_{max} by approximately 28% and overall exposure by approximately 18% (GMR with/without entrectinib for C_{max} was 128% [90% CI: 98.2%, 167%] and AUC_{inf} was 118% [90% CI: 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.

Breast cancer resistance protein (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 contraceptives
Physiologically-based pharmacokinetic simulation of the effects of co-administration of multiple oral doses of entrectinib with ethinyl estradiol, an oral contraceptive, predicted no drug-drug interaction. GMR with/without entrectinib for AUC_{inf} of 112% (90% CI: 111%, 113%) and C_{max} was 112% (90% CI: 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
In healthy adult subjects, co-administration of multiple oral doses of rifampin, a strong CYP3A inducer, with a single oral dose of entrectinib, reduced the systemic exposure of entrectinib by 77%. GMR with/without rifampin for AUC_{inf} was 23.3% (90% CI: 18.4%, 29.5%) and C_{max} was 44.4% (90% CI: 35.3%, 55.9%).

Co-administration of Rozlytrek with CYP3A inducers should be avoided (see section *4.2 Dose and method of administration*).

CYP3A inhibitors
In healthy adult subjects, co-administration of a single oral dose of entrectinib with multiple oral doses of itraconazole, a strong CYP3A4 inhibitor, increased the systemic exposure of entrectinib by 500%. GMR with/without itraconazole for AUC_{inf} was 604% (90% CI: 454%, 804%) and C_{max} was 173% (90% CI: 137%, 218%).

Co-administration of strong and moderate CYP3A inhibitors (including, but not limited to, anti-fungal agents and 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 *4.2 Dose and method of 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 AUC_{inf} was 74.5% (90% CI: 64.7%, 85.9%) and C_{max} was 76.5% (90% CI: 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.

4.6 Fertility, pregnancy and lactation

Pregnancy - Category D
Based on the findings in animal studies and its mechanism of action, Rozlytrek may cause foetal harm when administered to a pregnant woman.

Female patients receiving Rozlytrek should be advised of the potential harm to the foetus.

Female patients of child-bearing potential must be advised to avoid pregnancy while receiving Rozlytrek.

Female patients should be advised to contact the doctor, should pregnancy occur.

There are no available data on the use of Rozlytrek in pregnant women. In an embryofoetal developmental study in rats, maternal toxicity (decreased body weight gain and food consumption) and foetal 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 foetal weights and reduced skeletal ossification were observed at exposures equivalent to 0.7 times the human exposure by AUC at the recommended dose.

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

<u>Contraception in male and female patients</u>
Female patients of child-bearing potential should have medically supervised pregnancy testing prior to initiating Rozlytrek therapy.

Female patients of child-bearing 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.

Patients receiving Rozlytrek should be advised of the potential harm to the foetus.

Breast-feeding
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.

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.

4.7 Effects on ability to drive and use machines

Rozlytrek may influence the ability to drive and use machines. Patients should be instructed to not drive or use machines until the symptoms resolve, if they experience cognitive adverse reactions, syncope, blurred vision, or dizziness, during treatment with Rozlytrek (see sections *4.4 Special warnings and precautions* and *4.8 Undesirable effects*).

4.8 Undesirable effects

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 paediatric 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.

Paediatric patients

The integrated safety population includes 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. The overall safety profile observed was generally similar between paediatric patients and adults. Rozlytrek was associated with a higher incidence of skeletal fractures in paediatric 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 paediatric patients (n=91) compared to adult patients (n=762) were neutropenia (19.8% vs 4.5%), weight increased (18.7% vs 9.6%), 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 paediatric 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 anaemia (8.8%).

Tabulated summary of adverse drug reactions from clinical trials

Table 5 summarises the adverse drug reactions (ADRs) occurring in adult and paediatric patients treated with Rozlytrek. ADRs 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 Drug Reaction	Rozlytrek n = 853		Frequency Category (All Grades)
	All Grades (%)	Grade ≥3 (%)	
General Disorders and Administration Site Conditions			
Fatigue[14]	43.5	5.0	very common
Oedema[6]	34.3	1.8	very common
Pain[7]	25.6	1.5	very common
Pyrexia	23.8	0.9	very common
Gastrointestinal Disorders			
Constipation	42.3	0.4	very common
Diarrhoea	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
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
Respiratory, Thoracic and Mediastinal Disorders			
Dyspnoea	23.8	4.9*	very common
Cough	21.1	0.4	very common
Blood and Lymphatic System Disorders			
Anaemia	33.4	9.7	very common
Neutropenia[10]	15.8	6.1	very common
Metabolism and Nutritional Disorders			
Weight increased	34.1	10.6	very common
Hyperuricaemia	16.4	2.3	very common
Decreased appetite	13.0	0.7	very common
Dehydration	6.6	1.1	common
Tumour lysis syndrome	0.2	0.2*	uncommon
Renal and urinary disorders			
Blood creatinine increased	31.5	1.2	very common
Musculoskeletal Disorders			
Arthralgia	21.0	0.7	very common
Myalgia	19.7	0.8	very common

System Organ Class/ Adverse Drug Reaction	Rozlytrek n = 853		Frequency Category (All Grades)
	All Grades (%)	Grade ≥3 (%)	
Fractures[11]	11.3	3.4	very common
Muscular weakness	10.4	1.3	very common
Hepatobiliary Disorders			
AST increased	21.1	2.9	very common
ALT increased	20.2	3.2	very common
Infections and Infestations			
Urinary tract infection	15.7	2.7	very common
Lung infection[8]	14.4	6.1*	very common
Eye Disorders			
Vision blurred[13]	11.7	0.2	very common
Skin and Subcutaneous Tissue Disorders			
Rash[12]	13.4	1.2	very common
Vascular Disorders			
Hypotension[15]	15.9	2.3	very common
Cardiac Disorders			
Congestive heart failure[9]	5.4	2.5*	common
Electrocardiogram QT prolonged	3.6	0.9	common

ALT = alanine aminotransferase; AST = aspartate aminotransferase

* Grades 3 to 5, inclusive of fatal adverse reactions (including 4 reactions of pneumonia, 3 reactions of dyspnoea, 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 impairment and mental disorder

[2] Includes the preferred terms: neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy

[3] Includes the preferred terms: paraesthesia, 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 oedema, fluid retention, generalised oedema, localised oedema, oedema, oedema 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 oedema

[10] Includes the preferred terms: neutropenia, neutrophil count decreased

[11] Includes the preferred terms: acetabulum fracture, ankle fracture, avulsion fracture, bursitis, cartilage injury, clavicle 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, osteoporotic 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 *4.4 Special warnings and precautions for use*). 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 paediatric 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 paediatric patients. In general, there was inadequate assessment for tumour involvement at the site of fracture; however, radiologic abnormalities possibly indicative of tumour involvement were reported in some adult patients. In both adult and paediatric 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 45.34 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 paediatric patients, with 14 patients who experienced more than one occurrence of fracture. In paediatric patients, fractures mostly occurred in patients less than 12 years of age. Fractures resolved in 85.2% (23/27) of paediatric patients. The median time to fracture was 4.3 months (range: 2.0 months to 28.7 months) in paediatric patients. Rozlytrek was interrupted in 18.5% (5/27) of paediatric patients who experienced fractures. Six paediatric patients discontinued Rozlytrek due to fractures. Rozlytrek dose was reduced for one paediatric 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 ≥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 41.0 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. Treatment-emergent shifts from baseline in key laboratory abnormalities

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
Hyperuricaemia	57.2	19.9
Increased AST	51.0	2.5
Increased ALT	47.5	2.4
Haematology		
Decreased neutrophils	34.2	8.3
Decreased haemoglobin	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 hyperuricaemia; n = 769 for neutrophils; n = 792 for haemoglobin

[3] Patients with change from baseline values of Grade of 0 - 2 to a post-baseline value of Grade 3 or Grade 4 at any time

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

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.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agent, tyrosine kinase inhibitor, ATC code: L01EX14.

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

Fusion proteins that include TRK, ROS1 or ALK kinase domains drive tumourigenic potential through hyperactivation of downstream signalling pathways leading to unconstrained cell proliferation. Entrectinib potently inhibits the TRK kinases, ROS1 and ALK, leading to inhibition of downstream signalling pathways, cell proliferation and induction of tumour cell apoptosis. Entrectinib demonstrates potent inhibition of cancer cell lines harbouring NTRK, ROS1 or ALK fusion genes, irrespective of tumour type. Entrectinib has anti-tumour potency in NTRK and ROS1 fusion-driven tumour models, leading to tumour regressions across multiple tumour types, including sarcomas, head and neck carcinoma, non-small cell lung carcinoma (NSCLC), colorectal cancer (CRC), acute myeloid leukemia (AML), and gliomas.

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

Clinical trials

NTRK fusion-positive solid tumours

Efficacy in adult patients
The efficacy of Rozlytrek in the treatment of NTRK fusion-positive solid tumours in adult patients was evaluated by combining the results from 3 single-arm, open label clinical trials (ALKA, STARTRK-1 and STARTRK-2) 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 tumours with NTRK1/2/3, ROS1, or ALK molecular alterations to determine the maximum tolerated dose. Study STARTRK-1 was a Phase I multicentre single arm, open label study in patients ≥ 18 years of age with solid tumours with NTRK1/2/3, ROS1, or ALK molecular alterations. The study included a dose escalation segment and a dose expansion segment. In the dose expansion segment, patients received 600 mg daily doses in repeated 4-week cycles and the primary objective was to evaluate the recommended Phase 2 dose. Study STARTRK-2 was a multicentre, international Phase II single-arm basket study in patients with solid tumours with NTRK1/2/3, ROS1, or ALK gene rearrangements. Patients received 600 mg Rozlytrek once daily doses in 4-week cycles. The TAPISTRY study is a multi-centre Phase II, open label study in adult and paediatric patients to evaluate the safety and efficacy of targeted therapies or immunotherapy in patients with unresectable, locally advanced or metastatic solid tumours with specific oncogenic genomic alterations, including NTRK fusion-positive or ROS1 fusion-positive tumours. 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 Tumours (RECIST) v1.1. The secondary efficacy outcome measures included clinical benefit rate (CBR), progression-free survival (PFS), time to 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 tumours treated with Rozlytrek, not previously treated with a TRK inhibitor, presenting with measurable disease at baseline 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 enrolment 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% 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 tumours are summarised in Table 7.

Table 7. Overall efficacy by BICR in adults with NTRK fusion-positive solid tumours

Efficacy Endpoints	**Rozlytrek n = 242**
Primary endpoints *(BICR-assessed, RECIST v1.1)*	
Objective response rate	
Number of responders	152/242
ORR% (95% CI***)	62.8% (56.4, 68.9)
CR, n (%)	41 (16.9%)
PR, n (%)	111 (45.9%)

Efficacy Endpoints	Rozlytrek n = 242
Duration of response*	
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 v1.1)*	
Clinical benefit rate**	
Number of patients with clinical benefit	169/242
CBR% (95% CI***)	69.8% (63.6, 75.6)
Progression-free survival*	
Number (%) of patients with events	155/242 (64.0%)
Median, months (95% CI)	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

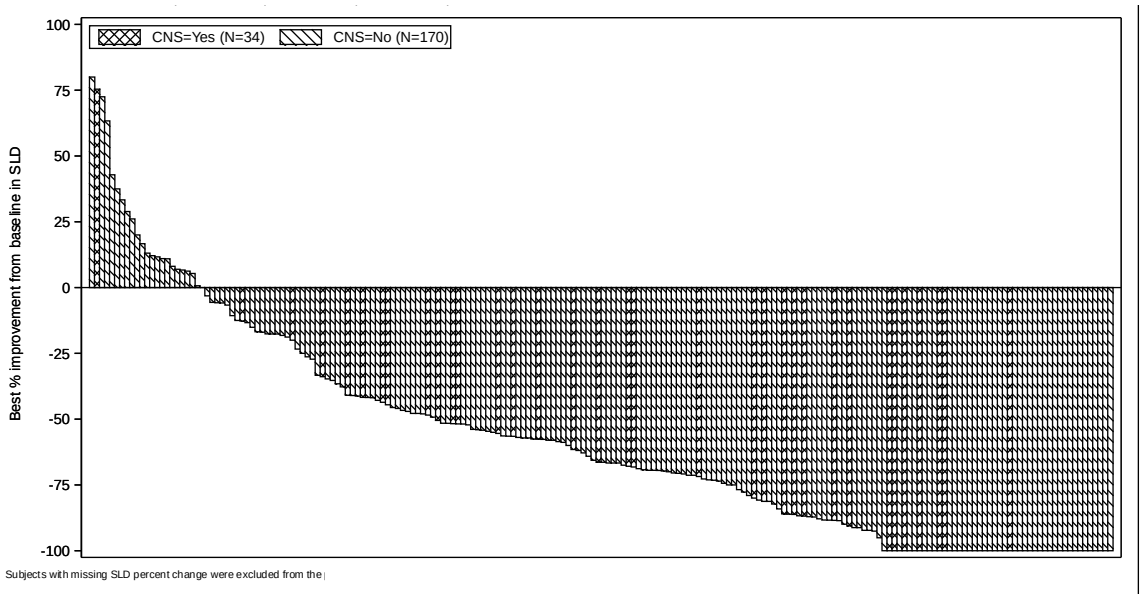
*Median and event-free rates based on Kaplan-Meier estimates

**Clinical benefit rate: proportion of patients with complete response, partial response, stable disease, or non CR/no 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 tumours experienced tumour shrinkage, as assessed by BICR according to RECIST v1.1.

Figure 1. Best percentage change in the sum of target lesions from baseline (BICR Assessment) in adults with NTRK fusion-positive solid tumours, shaded by CNS metastases at baseline



Of the 242 adult patients with NTRK fusion-positive solid tumours 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 v1.1 in this subgroup of patients with CNS metastases at baseline are summarised in Table 8.

Table 8. Efficacy in adults with NTRK fusion-positive solid tumours with CNS metastases at baseline

Secondary Endpoint *(BICR-assessed, RECIST v1.1)*	**CNS Metastases at Baseline (by Investigator)** **Yes** **n = 41**	**No** **n = 201**
Objective response rate		
Number of responders	27	125
ORR% (95% CI*)	65.9% (49.41, 79.92)	62.2% (55.10, 68.92)
CR, n (%)	4 (9.8%)	37 (18.4%)
PR, n (%)	23 (56.1%)	88 (43.8%)
Duration of response		
Number of patients with events	22 (81.5%)	64 (51.2%)
Median, months (95% CI)	16.6 (12.9, 29.4)	27.1 (16.7, 47.8)
Progression-free survival		
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 tumour type in all efficacy evaluable adult patients with NTRK fusion-positive solid tumours is presented in Table 9.

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

Tumour type	Patients (N=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 origin	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
Prostrate 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 tumours 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 v1.1, in this subgroup of patients with measurable CNS lesions at baseline are summarised in Table 10.

Table 10. Intracranial efficacy in adults with NTRK fusion-positive solid tumours with CNS metastases at baseline by BICR

Secondary Endpoint *(BICR-assessed, RECIST v1.1)*	**CNS Metastases at Baseline (by BICR)**	
	Measurable disease n = 20	**All patients n = 36**
Intracranial objective response rate		
Responders	14	19
IC-ORR% (95% CI*)	70.0% (45.7, 88.1)	52.8% (35.5, 69.6)
CR, n (%)	7 (35%)	12 (33.3%)
PR, n (%)	7 (35%)	7 (19.4%)

Intracranial duration of response		
Number of patients with events (%)	11 (78.6%)	144 (73.7%)
Median, months (95% CI)	19.7 (7.4, 26.6)	17.2 (7.4, 26.6)
Intracranial progression-free survival		
Number of patients with events (%)	14 (70%)	27 (75%)
Median, months (95% CI)	17.9 (6.4, 26.7)	12.3 (7, 20)

IC-ORR derived using RECIST v1.1 criteria applied only to CNS lesions.
*Confidence Intervals (CI) calculated using the Clopper-Pearson method.

Primary CNS tumours

In the three trials conducted, a total of 16 adult patients with CNS primary tumours 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, diarrhoea 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 am 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 tumours, and this was maintained while receiving Rozlytrek, as measured by the EORTC QLQ-C30.

Efficacy in paediatric patients

The efficacy of Rozlytrek in paediatric patients with NTRK fusion-positive solid tumours was evaluated in studies STARTRK-NG and TAPISTRY. Study STARTRK-NG is a multicentre Phase I/II, open-label dose-escalation and expansion study in paediatric patients with relapsed or refractory solid tumours, including primary CNS tumours, with or without NTRK, ROS1 or ALK molecular alterations. Patients received 250mg/m^2 to 750mg/m^2 once daily doses of Rozlytrek in 4-week cycles. See section 5.1 *Clinical Trials – NTRK fusion-positive solid tumours – Efficacy in adult patients* for TAPISTRY study details. 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 tumours and according to RANO for primary CNS tumours. 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 paediatric patients (less than 18 years of age) with confirmed NTRK fusion-positive solid tumours 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 enrolment in the study.

Of the 44 paediatric 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 m^2 (range: 0.2-1.9m^2). 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 (3 patients). 45.5% of patients had primary CNS tumours. The overall median duration of follow-up was 24.2 months.

Efficacy results from paediatric patients with NTRK fusion-positive solid tumours are summarised in Table 11.

Table 11. Overall efficacy in paediatric patients with NTRK fusion-positive solid tumours assessed by the BICR

Efficacy Endpoints	Rozlytrek **n=44**
Primary endpoints*	
ORR Number of responders ORR% (95% CI****) Complete Response, n (%) Partial Response, n (%)	 32/44 72.7% (57.21, 85.04) 20 (45.5%) 12 (27.3%)
Secondary endpoints*	
DOR* Number (%) of patients with events Median, months (95% CI) 6-month durable response % (95% CI) 9-month durable response % (95% CI) 12-month durable response % (95% CI)	 6/32 (18.8%) NE (25.4, NE) 97 (90, 100) 97 (90, 100) 84 (70, 99)
Time to first objective response Median, months [range]	 1.86 [1.1, 5.5]
CBR*** Number of patients with clinical benefit CBR% (95% CI****)	 38/44 86.4% (72.65, 94.83)
PFS* Number (%) of patients with events Median, months (95% CI)	 11/44 (25.0%) 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 tumours (24 patients) and by RANO criteria for primary CNS tumours (20patients)

***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 tumour type in paediatric patients with NTRK-fusion positive solid tumours is presented in Table 12.

Table 12. Efficacy by tumour type, in paediatric patients with NTRK fusion-positive solid tumours

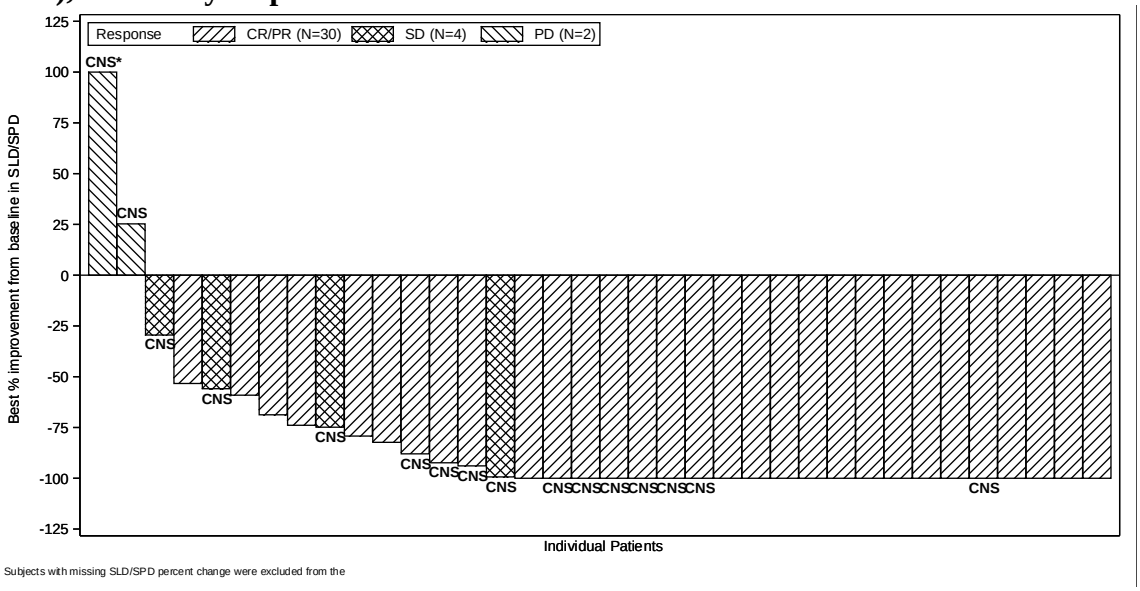
Tumour Type	Patients (n=44)	ORR		DOR
		n (%)	95% CI	Range (months)
All	44	32 (72.7)	(57.21, 85.04)	3.7*, 42.4*
Primary CNS**	20	10 (50.0)	(27.2, 72.8)	5.5, 42.3*
Infantile fibrosarcoma	11	10 (90.9)	(58.72, 99.77)	5.7*, 24.0*
Spindle Cell	8	8 (100.0)	(63, 100)	5.4*, 23.0*
Sarcoma (other)	2	1 (50.0)	(1.26, 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 tumours 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;

Figure 2. Best percentage change from baseline in tumour size (BICR assessment) in paediatric patients with *NTRK*-fusion positive solid tumours (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 enrolment in the study.

The baseline demographics and disease characteristics of the efficacy evaluable population were: 36.2% males, median age of 53.0 years (range: 27 to 86 years), 79.8% patients < 65 years of age, 48.9% Caucasian, 43.6% Asian, 5.3% Black, 2.4% Hispanic or Latino and 59.6% never smokers. The Eastern Cooperative Oncology Group (ECOG) 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 summarised in Table 13.

Table 13. Overall efficacy by BICR in patients with ROS1-positive NSCLC

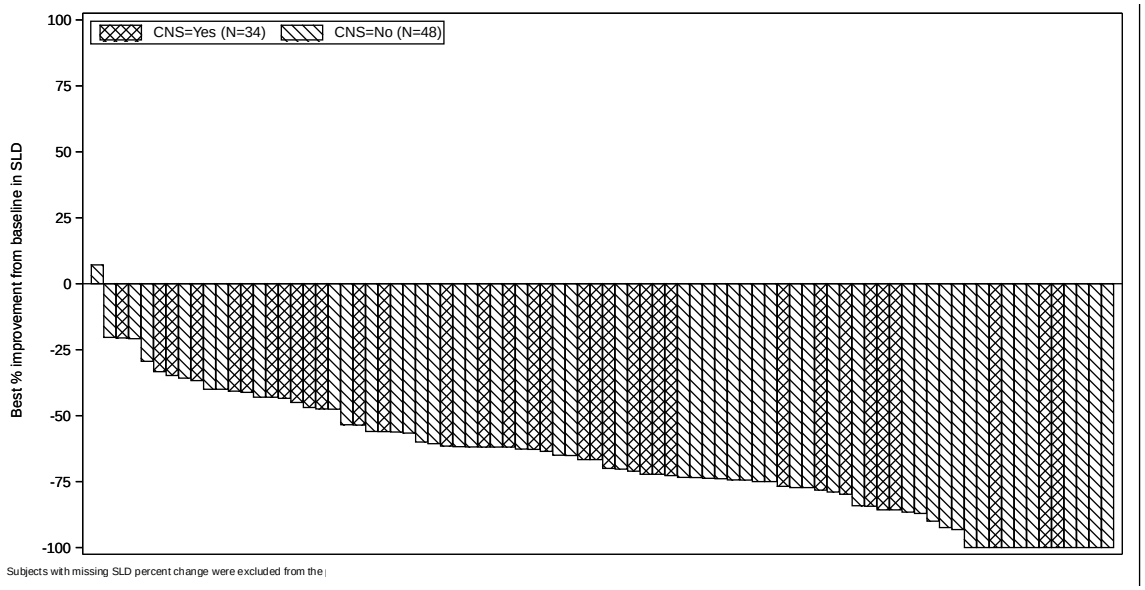
Efficacy Endpoint	Rozlytrek n = 94
Primary endpoints *(BICR-assessed, RECIST v1.1)*	
Objective response rate	
Number of responders	69/94
ORR% (95% CI****)	73.4 (63.3, 82.0)
CR, n (%)	11 (11.7%)
PR, n (%)	58 (61.7%)
Duration of response*	
Number (%) of patients with events	36/69 (52.2%)
Median, months (95% CI)	16.5 (14.6, 28.6)**
6-month durable response % (95% CI)	0.82 (0.72, 0.91)
9-month durable response % (95% CI)	0.79 (0.69, 0.89)
12-month durable response % (95% CI)	0.66 (0.54, 0.78)
Secondary endpoints *(BICR-assessed, RECIST v1.1)*	
Clinical benefit rate* **	
Number of patients with clinical benefit	70/94
CBR% (95% CI****)	74.5% (64.4, 82.9)
Progression-free survival*	
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 tumour shrinkage of their defined target lesions, as assessed by BICR according to RECIST v1.1 (see Figure 3).

Figure 3. 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 v1.1 in this subgroup of patients with CNS metastases at baseline are summarised in Table 14.

Table 14. Efficacy in ROS1-positive NSCLC patients with CNS metastases at baseline

Secondary Endpoints *(BICR-assessed, RECIST v1.1)*	**CNS Metastases at Baseline (by Investigator)** **Yes** **n = 40**	**No** **n = 54**
Objective response rate		
Number of CR + PR	27/40	42/54
ORR% (95% CI*)	67.5% (50.9, 81.4)	77.8% (64.4, 88.0)

CR, n (%)	4 (10.0)	7 (13.0)
PR, n (%)	23 (57.5)	35 (64.8)
Duration of response		
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)
Progression-free survival		
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

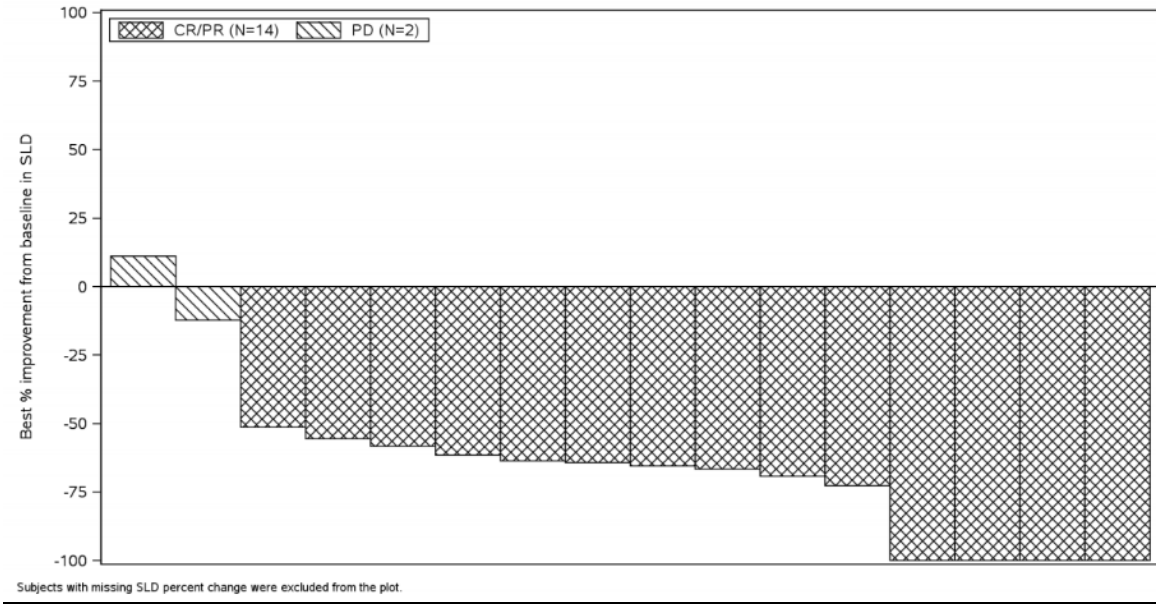
Of the 94 patients with ROS1-positive NSCLC in the efficacy evaluable analysis set, 34 patients had CNS metastases at baseline as assessed by BICR, including 18 patients with measurable CNS lesions. Intracranial ORR, DOR, and PFS assessed by BICR according to RECIST v1.1 in this subgroup of patients with measurable CNS lesions at baseline are summarised in Table 15 and Figure 4 below.

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

Secondary Endpoint *(BICR-assessed, RECIST v1.1)*	**CNS Metastases at Baseline (by BICR)**	
	Measurable disease n = 18	**All patients n = 34**
Intracranial objective response rate		
Responders	14	17
IC-ORR% (95% CI*)	77.8% (52.4, 93.6)	50% (32.4, 67.6)
CR, n (%)	2 (11.1%)	5 (14.7%)
PR, n (%)	12 (66.7%)	12 (35.3%)
Intracranial duration of response		
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)
Intracranial progression-free survival		
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)

CR = complete response; PR = partial response; NE = not estimable.
IC-ORR derived using RECIST v1.1 criteria applied only to CNS lesions.
*Confidence Intervals (CI) calculated using the Clopper-Pearson method.

Figure 4. Intracranial Activity - Best percent change from baseline in tumour sum in ROS1-positive NSCLC patients with measurable CNS metastases at baseline by BICR



SLD: Sum of Longest Diameter
Patients without measurable CNS disease at baseline or without post-baseline measurements were excluded from the plot

Patient Reported Outcomes
Patients with ROS1-positive NSCLC reported rapid and durable clinically meaningful improvement (change from baseline of ≥10 points on a 0 - 100 scale) in lung-cancer symptoms (cough, dyspnoea, 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.

5.2 Pharmacokinetic properties

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

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

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

Absorption

Following a single 600 mg oral administration of Rozlytrek to patients with NTRK fusion-positive and ROS1-positive NSCLC under fed conditions, entrectinib was rapidly absorbed

reaching time-to-maximum plasma concentration (T_{max}) after approximately 4 - 6 hours. Based on population pharmacokinetic analysis, steady-state was achieved within 5 days for entrectinib with 600 mg once daily dosing.

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

No clinically significant effect of food on entrectinib bioavailability was observed. Following a single 600 mg oral administration of Rozlytrek to healthy subjects under fasting conditions and following a high fat, high calorie meal, the GMR under fed/fasted condition for AUC_{inf} was 115% (90% CI: 107, 124) and for C_{max} was 106% (90% CI: 98.9, 115). Entrectinib can be administered with or without food (see section *4.2 Dose and method of administration*).

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.

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) and the direct N-glucuronide conjugate, M11 (formed by UGT1A4), are the two major circulating metabolites identified.

Excretion

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

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

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

Pharmacokinetics in Special Populations

<u>Paediatric population</u>

The pharmacokinetics of entrectinib have been evaluated in 65 paediatric patients >1 year of age receiving 300 mg/m^2 (based on their BSA category). Non-compartmental analysis and population PK modeling approaches demonstrated that systemic exposure of the sum of entrectinib and M5 in paediatric patients receiving 300 mg/m^2 of Rozlytrek once daily were within the range of the adults treated with 600 mg of Rozlytrek once daily. The available efficacy and safety data also confirm the adequacy of the recommended doses.

<u>Elderly population</u>

No differences in entrectinib exposure were noted in patients older than 65 years and adult patients younger than 65 years 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 pharmacokinetics 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 38 subjects enrolled into the following groups based on Child-Pugh criteria: 8 subjects with normal hepatic function, 7 with mild hepatic impairment, 12 with moderate hepatic impairment, and 11 with severe hepatic impairment. Following administration of a single oral dose of 100 mg entrectinib in healthy volunteers, 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, it was also observed that the variability in systemic exposure was high and observed exposures overlapped across all the study groups.

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, Caucasian and other ethnicities). No dose adjustment is required for patients of different race/ethnicities (see section *4.2 Dose and method of administration*).

5.3 Preclinical safety data

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

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

Other
In a 13-week juvenile rat toxicology study from post-natal day 7 to day 97 (approximately equivalent to neonate to 16 years of age in humans), effects on growth and development were

observed in the dosing and recovery phases including decreased body weight gain and delayed sexual maturation (at ≥ 4 mg/kg/day, approximately 0.1 times the human exposure by AUC at the recommended dose), deficits in neurobehavioral assessments including functional observational battery and learning and memory (at ≥ 8 mg/kg/day, approximately 0.2 times the human exposure by AUC at the recommended dose) and decreased femur length (at 16 mg/kg/day, approximately 0.3 times the human exposure by AUC at the recommended dose).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Lactose
Microcrystalline cellulose
Tartaric acid
Hypromellose
Crospovidone
Magnesium stearate
Silicon dioxide

Capsule shell
Hypromellose
Titanium dioxide
Iron oxide yellow (100 mg capsule only)
Sunset yellow FCF (200 mg capsule only)

Printing ink
Shellac
Propylene glycol
Strong ammonia solution
Indigo carmine aluminium lake

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months.

6.4 Special precautions for storage
Store below 30°C. Keep capsules in the original bottle. Keep the bottle tightly closed to protect from moisture.

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

6.5 Nature and contents of container

Rozlytrek hard capsules are packaged in white high-density polyethylene bottles with desiccant and a child-resistant screw cap.

100 mg hard capsules are supplied in bottles of 30 capsules.

200 mg hard capsules are supplied in bottles of 90 capsules.

6.6 Special precautions for disposal

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

9. DATE OF FIRST APPROVAL

11 June 2020

10. DATE OF REVISION OF THE TEXT

12 November 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of changes
5.1	Correction to Figures 1, 2 and 3.