Summary Report of Benefit-Risk Assessment

ROZLYTREK HARD CAPSULE 100MG AND 200MG

NEW DRUG APPLICATION

Active Ingredient(s)	Entrectinib
Product Registrant	Roche Singapore Pte Ltd
Product Registration Number	SIN16086P, SIN16087P
Application Route	Abridged evaluation
Date of Approval	27 January 2021

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A INTRODUCTION

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 solid tumours without a known acquired resistance mutation, that are locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have progressed following prior therapies or have no satisfactory alternative treatments.

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

The active substance, entrectinib, is an oral tropomyosin receptor kinase (TRK) inhibitor, which binds to and inhibits TRK family of proteins inclusive of TRKA, TRKB and TRKC that are encoded by NTRK1, NTRK2 and NTRK3 genes, respectively, and inhibits proliferation of tumour cells.

Rozlytrek is available as hard capsules containing 100 mg and 200 mg of Entrectinib. Other ingredients in the capsule are lactose, microcrystalline cellulose, tartaric acid, hypromellose, crospovidone, magnesium stearate and colloidal silicon dioxide. The capsule shell is composed of hypromellose, titanium dioxide (E171, CI77891) and either yellow iron oxide (E172, CI77492) for the 100 mg strength yellow capsule or FD&C Yellow #6 (E110, CI15985) for the 200 mg strength orange capsule. Commercially available printing ink that consists of shellac, propylene glycol, strong ammonia solution and FD&C Blue #2 Aluminium Lake E132 is used.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, Entrectinib, is manufactured at Carbogen AMCIS AG, Bubendorf, Switzerland. The drug product, Rozlytrek, is manufactured at Mayne Pharma Inc, Greenville, USA.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented were adequate to support the approved storage condition and retest period. The packaging is a colourless low-density polyethylene bag. The drug substance is approved for storage at 25oC with a re-test period of 24 months.

Drug product:
The capsule is manufactured using a dry granulation approach, followed by encapsulation. The process is considered to be a standard process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted were adequate to support the approved shelf-life of 24 months when stored at or below 30 ºC. The container closure system is a white high-density polyethylene bottle with a polypropylene/polyethylene child-resistant, tamper-evident screw cap. The screw cap is integrated with desiccant. The approved pack sizes are 30 capsules/ bottle for the 100 mg product and 90 capsules/ bottle for the 200 mg product.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of entrectinib in the treatment of solid tumours with NTRK gene fusion was based primarily on the pooled efficacy analysis of three ongoing studies, Study ALKA-372-001, Study RXDX-101-01 and Study RXDX-101-02, and one ongoing Phase I/Ib paediatric study, Study RXDX-101-03.

Study ALKA-372-001 was a Phase 1, open-label, single-arm, dose-escalation ongoing study in adult patients (≥18 years of age) with advanced solid tumour (with or without NTRK gene fusion) to determine the safety, dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and recommended phase II dose (R2PD) of entrectinib. As of the data cut-off date (31 May 2018), 57 patients were enrolled and treated, which included 46 (80.7%) patients who do not harbour NTRK gene fusion, and 11 (19.3%) patients who harboured NTRK gene fusion.

Study RXDX-101-01 was a Phase 1, ongoing, open-label, single-arm dose-escalation and dose-expansion study in adult patients (≥18 years of age). There were two segments to this study. The dose-escalation segment was to determine the first cycle DLT, MTD, and a biologically effective and RP2D of entrectinib administered orally in patients who need not harbour a NTRK1, NTRK2, NTRK3, ROS1 or ALK molecular alteration. The dose-expansion segment was to assess objective response rate (ORR) in patients enrolled with a NTRK1, NTRK2, NTRK3, ROS1 or ALK molecular alteration. As of the data cut-off date (31 May 2018), 76 patients were enrolled in the dose-escalation segment of the study and treated, which included 53 (69.7%) patients who do not harbour NTRK gene fusion, and 23 (30.3%) patients who harboured NTRK gene fusion. No subjects were enrolled into the dose-expansion segment as of the data cut-off date.

Study RXDX-101-02 was a Phase 2, ongoing, open-label, single-arm, basket-design study to determine the efficacy and safety of entrectinib in adult patients aged ≥18 years with advanced solid tumour cancer harbouring a NTRK1, NTRK2, NTRK3, ROS1 or ALK gene rearrangement. Patients were administered entrectinib at 600mg once daily based on 28-day cycle until disease progression or unacceptable toxicity. The study comprised 7 sub-baskets of patients with different gene aberrations: ALK-positive NSCLC CNS progression postcrizotinib, ALK-positive non-NSCLC solid tumours, Japan RP2D safety and tolerability substudy, NTRK-fusion positive solid tumours, ROS1-positive NSCLC, ROS1-positive NSCLC CNS progression post-crizotinib and ROS1-positive Non-NSCLC solid tumours. Patients must have received prior standard therapy appropriate for their tumour type and stage of disease or would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy in the opinion of the investigator. As of the data cut-off date (31 May 2018), 63 patients harbouring NTRK gene fusion were enrolled and treated.

Pooled Data Analysis – NTRK gene fusion

The interim pooled NTRK Efficacy Evaluable Analysis Set comprised data from 54 adult patients enrolled in the three ongoing clinical studies who had a positive NTRK gene fusion status, as confirmed by a nucleic acid-based diagnostic method at local testing facilities, and had progressed following systemic therapy for their disease, if available, or would have required surgery causing significant morbidity for locally advanced disease .

The primary efficacy endpoint for the NTRK efficacy evaluable analysis set is overall response rate (ORR) determined by blinded independent central review (BICR). Key secondary efficacy endpoints included duration of response (DOR), progression-free survival (PFS) and overall survival (OS) and time to CNS progression.

The NTRK Efficacy Evaluable Analysis Set population was of age ranged 21 years to 83 years old. Majority of the tumour histologies were sarcomas (24.1%), NSCLC (18.5%), salivary gland tumours (MASC) (13.0%), and breast cancer (11.1%), which collectively accounted for approximately half of patients in the integrated analysis. Remaining were cholangiocarcinoma (2%), gynaecological (4%), pancreatic (6%), neuroendocrine (6%), CRC (7%) and thyroid (9%). 57.4% of patients had NTRK3 fusions, 40.7 % had NTRK1 fusions while 1.9% had NTRK2 fusions. 88.9% of patients had received previous cancer therapy. 74% of patients had received prior systemic therapy for metastatic disease. 66.7% of patients had received any previous radiotherapy and 79.6% have had previous cancer surgery.

Treatment with entrectinib achieved an ORR of 57.4% (95% CI: 43%, 71%) in the NTRK efficacy evaluable analysis population. Of the 31 patients who responded to treatment, 4 (7.4%) had a complete response, while 27 (50%) had a partial response. 49% of responders had responses which lasted 12 months or longer, while the median duration of response was 10.4 months.

In terms of PFS, the disease progression rate was 54% and the median PFS was 11.2 months, while the PFS rates at 6 months and 12 months were 75% and 46%, respectively. The OS data were immature – 16 deaths (29.6%) were reported and the median duration of OS was 20.9 months. The proportion of patients alive at 12 months was 77% (95% CI: 64%, 90%).

Summary of key efficacy results from pooled analysis (cut-off date 31 May 2018)

	NTRK Efficacy Evaluable Analysis Set (N=54) 31 May 2018
Overall response rate (ORR)[b], n (%)	31 (57.4)
95% CI	43, 71
Complete response (CR), n (%)	4 (7.4)
Partial response (PR), n (%)	27 (50.0)
Stable disease (SD), n (%)	9 (16.7)
Progressive disease, n (%)	4 (7.4)
Non-CR/PD [a], n (%)	3 (5.6)
Not evaluable, n (%)	7 (13.0)
Duration of response (months), median	10.4
95% CI	7.1, NE
Min, Max	1.9, 20.3
≥ 6 months, % (95% CI)	69 (51, 86)
≥12 months, % (95% CI)	49 (29, 70)
PFS, median (months)	11.2
95% CI	8.0, 14.9
Min, Max	0.6, 23.3
PFS at 6 months, % (95% CI)	75 (63, 87)
PFS at 12 months, % (95% CI)	46 (30, 62)
Duration of OS, median (months)	20.9
95% CI	14.9, NE
Min, Max	0.6, 24.7
Alive at 12 months, % (95% CI)	77 (64, 90)

Six adult patients with primary CNS tumours were assessed using the RANO criteria. All 6 patients had received prior cancer and radiation therapies. 4 had undergone prior surgical therapies. 1 patient had a response with a DOR of 2.79 months and PFS of 6.34 months. The remaining patients were non-evaluable at the time of data cut-off.

Further subgroup analyses were performed by tumour histology type based on small sizes in each tumour type. The ORRs observed across most tumour types were considered high (range 66.7% to 100%) and clinically meaningful. Neuroendocrine tumours, thyroid tumours and CRC had lower but reasonably good response rates, compared to the current standard of care treatments. There were tumour subtypes that did not see a response while on entrectinib, such as ovarian cancer, squamous cell carcinoma, papillary thyroid cancer, etc. There were too few subjects in these tumour types to draw any meaningful conclusion on the efficacy of entrectinib.

Overall response rate (ORR) by tumour type (data cut-off date 30 May 2018)

Tumour type	**Patients (N=54)**	**ORR**	
		N, %	**95% CI**

Breast, All Non-secretory Secretory	6 2 4	5 (83.3) 1 (50.0) 4 (100.0)	35.9, 99.6 1.3, 98.7 39.8, 100.0
Cholangiocarcinoma	1	1 (100.0)	2.5, 100.0
CRC	4	1 (25.0)	0.6, 80.6
Gynaecological, All Endometroid Ovarian	2 1 1	1 (50.0) 1 (100.0) 0 (0.0)	1.3, 98.7 2.5, 100.0 0.0, 97.5
Neuroendocrine	3	1 (33.3)	0.8, 90.6
NSCLC, All Adenocarcinoma NSCLC (NOS) Squamous cell carcinoma	10 7 1 2	7 (70.0) 7 (100.0) 0 (0.0) 0 (0.0)	34.8, 93.3 59.0, 100.0 0.0, 97.5 0.0, 84.2
Pancreatic	3	2 (66.7)	9.4, 99.2
Salivary (MASC)	7	6 (85.7)	42.1, 99.6
Sarcoma, All Cervical adenocarcinoma Dedifferentiated chondrosarcoma Endometrial stromal sarcoma Follicular dendritic cell sarcoma Gastrointestinal Stromal Tumour (GIST) Malignant Peripheral Nerve Sheath Tumour (MPNST) Sarcoma (NOS)	13 1 1 1 1 1 1 7	6 (46.2) 1 (100.0) 0 (0.0) 1 (100.0) 0 (0.0) 1 (100.0) 0 (0.0) 3 (42.9)	19.2, 74.9 2.5, 100.0 0.0, 97.5 2.5, 100.0 0.0, 97.5 2.5, 100.0 0.0, 97.5 9.9, 81.6
Thyroid, All Papillary thyroid Thyroid, others	5 3 2	1 (20.0) 0 (0.0) 1 (50.0)	0.5, 71.6 0.0, 70.8 1.3, 98.7

Eleven patients with BICR confirmed CNS metastatic disease at baseline were further analysed to investigate the intracranial (IC) efficacy of entrectinib. 7 of the patients had measurable lesion, of which 4 had not receive radiation therapy to the brain within 2 months of study entry. The IC-ORRs for all patients with BICR-confirmed CNS disease at baseline and patients with measurable lesion were consistent with the ORR for the overall population. ICPFS in patients with BICR-confirmed CNS disease at baseline were longer than the PFS for the overall population.

Intracranial Efficacy in patients with BICR-confirmed CNS disease at baseline

	All patients (N=11)	**Patients with measurable lesion (N=7)**
Objective response Responders, n ORR, % (95% CI)	 6 54.5 (23.4, 83.3)	 4 57.1 (18.4 90.1)

Best overall response		
CR, n (%)	3 (27.3)	1 (14.3)
PR, n (%)	3 (27.3)	3 (42.9)
SD, n (%)	1 (9.1)	1 (14.3)
PD, n (%)	1 (9.1)	1 (14.3)
Non-CR/PD, n (%)	2 (18.2)	0
Missing/NE, n (%)	1 (9.1)	1 (14.3)
Duration of IC response		
Patients with event, n (%)	2 (33.3)	1 (25.0)
Median, months (95% CI)	NE (5.0, NE)	NE (5.0, NE)
Progression-free Survival		
Patients with event, n (%)	5 (45.5)	3 (42.9)
Median, months (95% CI)	14.3 (5.1, NE)	NE (2.8, NE)

Study RXDX-101-03 was initially designed as a Phase 1/1b, 5-part (Parts A to E), open-label, single-arm study to determine the efficacy and safety of entrectinib in children, adolescents and young adult patients below 22 years old with advanced solid tumour cancer harbouring a NTRK1, NTRK2, NTRK3, ROS1 or ALK gene rearrangement. Patients must be at least 2 years old and younger than 22 years old, and must have received prior standard therapy appropriate for their tumour type and stage of disease and either relapsed or failed to respond, or would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy in the opinion of the investigator. The study design was subsequently updated, in two protocol amendments, to a Phase 1/2 study in patients 18 years and below, with Parts B and D restricted to patients with advanced solid tumour cancer harbouring only a NTRK1, NTRK2, NTRK3 or ROS1 gene arrangement.

The dosing regimen for paediatric patients was established primarily based on population PK (popPK) analyses and physiologically based PK modelling (PBPK), with supportive information from STARTRK-NG. PopPK analysis demonstrated that a BSA-adjusted dose of 300 mg/m^2 administered to adolescent patients attained comparable entrectinib exposures as adults who were given a dose of 600mg once daily. Simulations from two PBPK models, GastroPlus and Simcyp, were used to derive the dose for children 4 years and below.

As of the data cut-off date (31 May 2018), only data from Part A was available. Part A was a dose-escalation phase where patients received oral entrectinib once daily across four dose levels, 250 mg/m^2, 400 mg/m^2, 550 mg/m^2 and 750 mg/m^2. 1 patient harbouring NTRK gene fusion was enrolled and treated. Additional data-cuts with updated efficacy information were provided over the course of evaluation.

Based on the data-cut (01 May 2019), responses were achieved in 7 out of 7 paediatric patients enrolled into Study RXDX-101-03. The table below reflects the data for all 7 patients from the 1 May 2019 data-cut. Best overall response was assessed by retrospective blinded independent central review (BICR).

Age/gender	**Tumor type**	**NTRK gene fusion**	**Assigned dose level (mg/m^2)**	**Best Overall**	**DOR (months)**

				Response (Retrospective BICR)	
[redacted]	High grade glioma	TPR-NTRK-1	400	PR	14.29
[redacted]	Infantile Fibrosarcoma	EML4-NTRK3	750	PR	13.63
[redacted]	Metastatic melanoma	EVT6-NTRK3	400	PR	12.91
[redacted]	Epithelioid glioblastoma	EVT6-NTRK3	550	CR	9.69
[redacted]	Infantile Fibrosarcoma	EVT6-NTRK3	400	PR	6.47
[redacted]	Anaplastic ganglioglioma	EML1-NTRK2	550	CR	5.52
[redacted]	CNS primary ganglioneuroblastoma	KANK1-NTRK2	550	PR	3.68

Efficacy data from paediatric patients treated with entrectinib via compassionate access were also provided as supportive information. Based on the data-cut (31 May 2018), partial response was achieved in 2 of 2 compassionate use patients.

Age/gender	**Tumor type**	**NTRK gene fusion**	**Assigned dose level (mg/m^2)**	**Best Overall Response**	**DOR (months)**
[redacted]	Infantile Fibrosarcoma	EVT6-NTRK3	400	PR	2.2
[redacted]	High grade astrocytoma	BEND4-NTRK2	400	PR	NA

The clinical response to entrectinib was shown to be comparable between paediatric and adult populations, given the similar time to response to entrectinib and comparable, if not superior response rates in the paediatric population. The structure and signalling effects of NTRK 1/2/3 fusions observed between paediatric and adult tumours were generally expected to be similar. TRKA/B/C fusion proteins retain an intact NTRK1/2/3 kinase domain thereby retaining the pathway signalling effects, and this activity is not expected to behave differently between paediatrics or adults. Given that entrectinib is meant to target the intact kinase domain, the effect at cellular level is also not expected to differ between the two populations.

Overall, the clinically meaningful ORR and durable response observed in the interim results of the pooled analysis provided preliminary evidence supporting the efficacy of entrectinib for patients with tumour types harbouring NTRK gene fusion who had progressed on prior

treatments and had no satisfactory alternative treatment options. The clinical data in paediatric patients aged 12 years and older was based on a very small sample size. The efficacy in this patient population was riding on the data in adult patients with NTRK fusion positive solid tumours and extrapolated based on exposure data from popPK analyses.

Pooled Data Analysis – ROS1 NSCLC

The interim pooled ROS1 NSCLC Efficacy Evaluable Analysis Set comprised data from the first 53 adult patients enrolled in the three ongoing clinical studies who had a positive ROS1 status, as confirmed by a nucleic acid-based diagnostic method at local testing facilities.

The primary efficacy endpoint for the ROS1 NSCLC Efficacy Evaluable Analysis Set is overall response rate (ORR) determined by blinded independent central review (BICR). Key secondary efficacy endpoints included duration of response (DOR), progression-free survival (PFS) and overall survival (OS) and time to CNS progression.

The ROS1 NSCLC Efficacy Evaluable Analysis Set population were of age range 27 years to 73 years old, with 79.2% who were younger than 65 years old. Majority were White (58.5%) or Asian (35.8%), and female (64.2%). 39.6% had CD74-ROS1 fusion, 9.4% had EZR-ROS1 fusion, 11.3% had SDC4-ROS1 fusion, 13.2% had SLC34A2-ROS1 fusion, 3.8% had TPM3ROS1 fusion while remaining 22.6% had unknown gene fusion partners. 86.8% of patients had received previous cancer therapy, 45.3% of patients had received any previous radiotherapy and 50.9% have had previous surgery.

Treatment with entrectinib achieved an ORR of 77.4% (95% CI: 64%, 88%) in the ROS1 NSCLC Efficacy Evaluable Analysis Set population. Of the 41 patients who responded to treatment, 3 (5.7%) had a complete response, while 38 (71.7%) had a partial response. 65% of responders had responses which lasted 12 months or longer, while the median duration of response was 24.6 months.

In terms of PFS, the disease progression rate was 47% and the median PFS was 19 months, while the PFS rates at 6 months and 12 months were 80% and 65%, respectively. The OS data were immature 9deaths (17%) were reported and the median duration of OS was not reached. The proportion of patients alive at 12 months was 85% (95% CI: 74%, 95%).

Summary of key efficacy results from pooled analysis (cut-off date 31 May 2018)

	ROS1 NSCLC Efficacy Evaluable Analysis Set (N=53) 31 May 2018
Overall response rate (ORR)[b], n (%)	41 (77.4)
95% CI	63.8, 87.7
Complete response (CR), n (%)	3 (5.7)
Partial response (PR), n (%)	38 (71.7)
Stable disease (SD), n (%)	1 (1.9)
Progressive disease, n (%)	4 (7.5)
Non-CR/PD [a], n (%)	3 (5.7)
Not evaluable, n (%)	4 (7.5)

Duration of response (months), median	24.6
95% CI	11,4, 34.8
Min, Max	1.8, 34.8
≥ 6 months	82 (70, 94)
≥12 months	65 (49, 81)
PFS, median (months)	19.0
95% CI	12.2, 36.6
Min, Max	0.0, 36.6
PFS at 6 months, % (95% CI)	80 (68, 91)
PFS at 12 months, % (95% CI)	65 (51, 78)
Duration of OS, median (months)	NE
95% CI	NE
Min, Max	0.8, 43.1
Alive at 12 months, % (95% CI)	85 (74, 95)

Further subgroup analyses were performed by baseline CNS metastatic disease. 20 patients with BICR confirmed CNS metastatic disease at baseline were further analysed to investigate the intracranial (IC) efficacy of entrectinib. 12 of the patients had measurable lesion. The ICORR, DOR and PFS for all patients with BICR-confirmed CNS disease at baseline were lower than that for the overall population. However, IC-ORR and PFS for patients with measurable lesions were high and consistent with the ORR for the overall population.

Intracranial Efficacy in patients with BICR-confirmed CNS disease at baseline

	All patients (N=20)	**Patients with measurable lesion (N=12)**
Objective response		
Responders, n	11	9
ORR, % (95% CI)	55.0 (31.5, 76.9)	75.0 (42.8, 94.5)
Best overall response		
CR, n (%)	4 (20.0)	2 (16.7)
PR, n (%)	7 (35.0) 0	7 (58.3)
SD, n (%)	(0.0)	0(0.0)
PD, n (%)	3 (15.0)	2 (16.7)
Non-CR/PD, n (%)	4 (20.0)	0 (0.0)
Missing/NE, n (%)	2 (10.0)	1 (8.3)
Duration of IC response		
Patients with event, n (%)	5 (45.5)	4 (44.4)
Median, months (95% CI)	12.9 (5.6, NE)	12.9 (4.6, NE)
Progression-free Survival		
Patients with event, n (%)	13 (65.0)	6 (50.0)
Median, months (95% CI)	7.7 (3.8, 19.3)	19.3 (3.8, 19.3)

Overall, the robust ORR and durable response observed in the interim results of the pooled analysis provided clear evidence supporting the efficacy of entrectinib for ROS1 positive NSCLC adult patients.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of entrectinib was based primarily on safety data derived from the four studies and comprised a total of 504 patients who received at least one dose of entrectinib. Of these, 113 patients (22%) were NTRK fusion positive, 210 patients (42%) were ROS1 positive and 29 patients were paediatrics. The median duration of exposure was longer in the adult patients (7.9 months) compared to paediatric patients (5.5 months).

Overview of safety profile (n=504)

AE	Integrated Safety Population, n (%)
Any AE	499 (99.0)
AE related to entrectinib	458 (90.9)
SAE	201 (39.9)
SAE related to entrectinib	49 (9.7)
≥ Grade 3 AE	308 (61.1)
≥ Grade 3 AE related to entrectinib	162 (31.1)
Discontinuations due to AE	46 (9.1)
Discontinuations due to AE related to entrectinib	23 (4.6)
Deaths due to AE	24 (4.8)

The majority of the treatment-related adverse events were of Grade 1 or 2 in severity. The most common (>20%) adverse events considered to be related to entrectinib were dysgeusia (39.7%), fatigue (31.5%), dizziness (27.2%), constipation (24.0%), diarrhoea (22.8%), weight gain (20.6%). Few patients had adverse events which led to discontinuation of study treatment (9.1%).

Types of adverse events were generally consistent in adult and paediatric patients. Hyperuricemia (9.0%), congestive heart failure (3.4%), eye disorders (27.3%) and cognitive impairment (27.0%) were reported more frequently in adults as compared to paediatrics. However, skeletal fractures (6.1%), haematological toxicity (38.0%) (e.g. neutropenia, thrombocytopenia and lymphopenia), elevated ALT (38.4%) and AST (43.3%) and weight gain (65.6%) were more frequently reported in paediatrics than adults.

As of data cut-off, skeletal fractures were reported to be approximately four-folds higher in paediatrics (20.7% (6/29) in paediatrics vs 5.3% (25/475) in adults). The median time to a fracture event was 3.38 months in paediatrics and 3.42 months in adults. Fracture events occurred spontaneously or with little trauma in paediatric patients younger than 12 years old. Grade 3 fracture events were reported in 3 paediatric patients, of which 1 patient had a femur head fracture. While the precise relationship between entrectinib and risk of skeletal fractures remains to be elucidated, there may potentially be a detrimental effect of entrectinib on the growing skeleton as compared to the mature skeleton.

Within the paediatric population, adverse events that tend to occur at a higher incidence in children younger than 12 years old were related to diarrhea, vomiting, reduced white blood cell count, reduced appetite, dehydration, hypophosphatemia, hypoalbuminaemia, urinary tract infection, pollakiuria, proteinuria, pruritus, somnolence, urinary incontinence and skeletal fractures.

Overall, entrectinib appeared to be reasonably well-tolerated in adult patients with ROS1 positive NSCLC or NTRK fusion cancer with advanced disease. However, the long-term safety and toxicity, in particular the effect on the skeletal developmental in paediatric patients, particularly 12 years of age and below, have not been fully characterised.

E ASSESSMENT OF BENEFIT-RISK PROFILE

For patients with advanced NTRK fusion cancer who progressed after standard treatments (surgical resection, radiotherapy, chemotherapy), the treatment options are limited. Salvage therapy with existing alternatives is often not beneficial due to treatment toxicities or patient co-morbidities that may eventually further deteriorate patients' quality of life.

Overall, favourable clinical benefits of entrectinib were demonstrated in terms of high overall response rate and durable responses in limited number of patients with tumour types that were mainly rare and had progressed on treatment or had no satisfactory alternative treatments. The overall response rate (57.4%) observed in the pooled population based on the data cutoff date 31 May 2018 was considered high and clinically relevant, and the median PFS of 11.2 months was considered reasonably durable. The adverse events observed with entrectinib were mild in majority of the cases, although certain adverse events that occurred in the paediatric population, especially children below 12 years of age, were more serious.

Notwithstanding the small sample size of the integrated analyses, and that the tumour types investigated in the clinical studies were limited and does not exhaustively cover common tumour types noted to have rare NTRK gene fusion and tumour types with NTRK2 gene fusion, current available data demonstrated preliminary favourable results with respect to the high response rate and reasonably long PFS. Taking into consideration the acceptable safety profile of the treatment and the unmet medical need in advanced solid tumours with rare NTRK gene fusion molecular aberration, the benefit-risk balance of entrectinib is considered positive in adult and paediatric patients 12 years of age and older with tumour types harbouring NTRK gene fusion who had progressed on prior treatments and had no satisfactory alternative treatment options. Further safety data in children younger than 12 years old is required to confirm the clinical safety of entrectinib for the proposed tissue agnostic indication.

For patients with ROS-1 positive, locally advanced or metastatic NSCLC, entrectinib demonstrated favourable clinical benefits with a relevant overall response rate and reasonably durable responses. The overall response rate (77.4%) observed in the pooled population based on the data cut-off date 31 May 2018 was considered high and clinically relevant, with a durable median PFS of 19.0 months. The intracranial responses observed suggested activity of entrectinib in the CNS, which is beneficial as CNS metastases are commonly seen in NSCLC patients. The adverse events observed with entrectinib were consistent with that observed in patients with NTRK fusion positive solid tumours and not expected to have divergence.

While there were limitations to the dataset, in particular the small sample size and the lack of a comparator arm which does not allow a firm conclusion on time-to-event endpoints such as

PFS and OS; the high ORR demonstrated with entrectinib was promising and observed to be comparable to a currently registered ALK-inhibitor which is the only currently approved treatment for ROS-1-positive NSCLC.

Considering the high ORR and the acceptable safety profile, and the medical need for better therapies with improved efficacy in patients with CNS metastases, the benefit-risk balance of entrectinib is positive in adult patients with ROS1 positive NSCLC.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the preliminary benefit-risk balance of Rozlytrek was deemed favourable and approval was granted on 27 January 2021 for use in:

- adult and paediatric patients 12 years of age and older with tumour types harbouring NTRK gene fusion who had progressed on prior treatments and had no satisfactory alternative treatment options was deemed favourable. The approval is subject to the submission of the updated interim, final pooled analysis and final study reports of ongoing clinical studies to confirm the efficacy and safety of entrectinib.
- adult patients with ROS-1 positive, locally advanced or metastatic NSCLC.

APPROVED PACKAGE INSERT AT REGISTRATION

Rozlytrek®

Entrectinib

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Antineoplastic agent, Tyrosine Kinase inhibitor

ATC Code: L01XE56

1.2 TYPE OF DOSAGE FORM

Hard Capsule

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

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

1.3 ROUTE OF ADMINISTRATION

Oral

1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: entrectinib
Each 100 mg hard capsule contains 100 mg entrectinib.
Each 200 mg hard capsule contains 200 mg entrectinib.

Excipients
Capsule content: tartaric acid, lactose, hypromellose, crospovidone, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate.

Capsule shell: hypromellose, titanium dioxide (E171), yellow iron oxide (E172, for yellow opaque capsule shell – 100 mg hard capsule), FD&C yellow #6 (E110, for orange opaque capsule shell – 200 mg hard capsule).

Printing ink: shellac, propylene glycol, strong ammonia solution, FD&C blue #2 aluminium lake (E132).

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Solid tumors
Rozlytrek is indicated for the treatment of adult and pediatric patients 12 years of age and older, with neurotrophic tyrosine receptor kinase (*NTRK)* fusion-positive solid tumors without a known acquired resistance mutation, that are locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have progressed following prior therapies or have no satisfactory alternative treatments.

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

2.2 DOSAGE AND ADMINISTRATION

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

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

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

Adults
The recommended dose of Rozlytrek for adults is 600 mg given orally, once daily (see section *3.2 Pharmacokinetic Properties*).

Pediatric patients 12 years and older
The recommended dose of Rozlytrek for pediatric patients, 12 years and older, who have the ability to swallow capsules is 300 mg/m^2 orally, once daily (see Table 1). (See section *3.2 Pharmacokinetic Properties*).

Table 1: **Recommended dosing for Pediatric patients 12 years and older**

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

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

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

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

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

Table 2: Dose Reduction Schedule for Adult patients

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

Pediatric Patients
Table 3 provides specific dose reduction advice for pediatric patients. For pediatric patients, the dose of Rozlytrek may be reduced up to 2 times, based on tolerability.
For some patients an intermittent dosing schedule is required to achieve the recommended reduced total weekly pediatric dose. Rozlytrek treatment should be permanently discontinued if patients are unable to tolerate the lowest reduced dose.

Table 3: Dose Reduction Schedule for pediatric patients 12 years and older

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 pediatric patients for specific adverse reactions are provided in Table 4. (See section *2.4.1 Warnings and Precautions* and section *2.6 Undesirable Effects)*.

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

Adverse Drug Reaction	Severity *	Dose modification
Anemia or Neutropenia	Grade 3 or Grade 4	• Withhold Rozlytrek until recovery to ≤ Grade 2 or to baseline, then resume treatment at same dose level or reduced dose, as clinically needed.
Cognitive Disorders	Grade ≥ 2	• Withhold Rozlytrek until recovery to ≤ Grade 1 or to baseline, then resume treatment at reduced dose. • If event recurs, further reduce dose. • For prolonged, severe, or intolerable events, discontinue as clinically appropriate.
Transaminase Elevations	Grade 3	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline. • Resume at same dose if resolution occurs within 4 weeks. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks.
	Grade 4	• Withhold Rozlytrek until recovery to less than or equal to Grade 1 or to baseline. • Resume at reduced dose if resolution occurs within 4 weeks. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Permanently discontinue for recurrent Grade 4 events.
	ALT or AST elevation greater than 3 times ULN with total bilirubin elevation greater than 1.5 times ULN in the absence of cholestasis or hemolysis	• Permanently discontinue Rozlytrek.
Hyperuricemia	Symptomatic or Grade 4	• Initiate urate-lowering medication • Withhold Rozlytrek until improvement of signs or symptoms • Resume Rozlytrek at same or reduced dose
Congestive Heart Failure	Grade 2 or 3	• Withhold Rozlytrek until recovered to less than or equal to Grade 1 • Resume at reduced dose
	Grade 4	• Withhold Rozlytrek until recovered to less than or equal to Grade 1 • Resume at reduced dose or discontinue as clinically appropriate
QT Interval Prolongation	QTc 481 to 500 ms	• Withhold Rozlytrek until recovered to baseline • Resume treatment at same dose
	QTc greater than 500 ms	• Withhold Rozlytrek until QTc interval recovers to baseline • Resume at same dose if factors that cause QT prolongation are identified and corrected • Resume at reduced dose if other factors that cause QT prolongation are not identified
	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	• Permanently discontinue Rozlytrek
Other clinically relevant adverse reactions	Grade 3 or 4	• Withhold Rozlytrek until adverse reaction resolves or improvement to Grade 1 or baseline • Resume at the same or reduced dose, if resolution occurs within 4 weeks • Consider permanent discontinuation if adverse reaction does not resolve within 4 weeks • Permanently discontinue for recurrent Grade 4 events
Vision Disorders	Grade 2 or above	• Withhold Rozlytrek until improvement or stabilization. • Resume at same dose or reduced dose, as clinically appropriate.

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

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

After discontinuation of the concomitant strong or moderate CYP3A inhibitors, Rozlytrek dose that was taken prior to initiating the strong or moderate CYP3A inhibitor can be resumed. A wash out period may be required for CYP3A4 inhibitors with long half-life. (See section *2.8 Interactions with Other Medicinal Products and other forms of Interaction).*

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

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

2.2.1 Special Dosage Instructions
Pediatric use
Pediatric patients must have the ability to swallow whole Rozlytrek capsules. Dosage for patients 12 years and older is based on body surface area (mg/m^2) with a maximum daily dose of 600 mg (see Table 1 for pediatric dosing). The safety and efficacy of Rozlytrek in children below 12 years of age have not been established.

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

Renal Impairment
No dose adjustment is required in patients with mild or moderate renal impairment. The safety and efficacy of Rozlytrek have not been studied in patients with severe renal impairment. *(*See sections *2.5 Use in Special Populations* and section *3.2.5 Pharmacokinetics in Special Populations)*.

Hepatic Impairment
The safety and efficacy of Rozlytrek have not been studied in patients with hepatic impairment. *(*See section *2.5 Use in Special Populations* and section *3.2.5 Pharmacokinetics in Special Populations)*.

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

2.3 CONTRAINDICATIONS

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

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General
Congestive Heart Failure
Congestive heart failure (CHF) has been reported across clinical trials with Rozlytrek (see Table 5 in section *2.6.1 Undesirable Effects*). These reactions were observed in patients with or without a history of cardiac disease and resolved upon treatment with diuretics and/or dose reduction/interruption of Rozlytrek.

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

Based on the severity of CHF, Rozlytrek treatment should be modified as described in Table 4 in section *2.2 Dosage and Administration*.

Cognitive Disorders
Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with

Rozlytrek, (see section *2.6.1 Undesirable Effects* for description of events). Patients should be monitored for signs of cognitive changes.

Based on the severity of the cognitive disorder, Rozlytrek treatment should be modified as described in Table 4 in section *2.2 Dosage and Administration*.

Patients should be counseled on the potential for cognitive changes with Rozlytrek treatment. Patients should be instructed not to drive or use machines until symptoms resolve, if they experience symptoms of cognitive disorders. (See section *2.4.3 Ability to drive and use 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 adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in pediatric patients fractures occurred in patients with minimal or no trauma. There are no data on the effects of Rozlytrek on healing of known fractures and the risk of occurrence of future fractures. In the majority of pediatric patients treatment was continued with Rozlytrek and the fracture healed.

QTc Interval Prolongation
QT interval prolongation has been observed in patients treated with Rozlytrek in clinical trials (see section *2.6.1 Undesirable Effects)*.

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

Based on the severity of QTc prolongation, Rozlytrek treatment should be modified as described in Table 4 in section *2.2 Dosage and Administration.*

Embryo-fetal toxicity
Based on the findings in animal studies, Rozlytrek may cause fetal harm when administered to a pregnant woman. When administrated to pregnant rats, Rozlytrek caused maternal toxicity and developmental toxicities at exposures 2.3-fold the human exposure by AUC at the recommended dose. (See section *3.3.4 Reproductive toxicity)*.

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

Hepatotoxicity
Among the 504 patients who received Rozlytrek, increased AST of any grade occurred in 43.3% of patients and increased ALT of any grade occurred in 38.4%. Grade 3 – 4 increased AST or ALT occurred in 3.3% and 3.1% of patients, respectively. Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue Rozlytrek based on the severity. If withheld, resume Rozlytrek at the same or reduced dose [see section *2.2 Dosage and Administration*].

Hyperuricemia
Hyperuricemia has been observed in patients treated with Rozlytrek in clinical trials (see section *2.6.1 Undesirable Effects*). Assess serum uric acid levels prior to initiating Rozlytrek and periodically during treatment. Monitor for signs and symptoms of hyperuricemia. Initiate treatment with urate-lowering medications as clinically indicated and withhold Rozlytrek treatment for signs and symptoms of hyperuricemia. Based on the severity of hyperuricemia, resume Rozlytrek at same or reduced dose upon improvement in signs and symptoms (see Table 4 in Section *2.2 Dosage and Administration*).

Eye disorders
Visual disorders, including blurred vison, photophobia, diplopia and dry eyes, were reported in clinical trials with Rozlytrek (see section *2.6.1 Undesirable Effects* for description of events). Patients should be counselled on the potential for visual changes with Rozlytrek treatment. If patients experience symptoms of vision disorders, they should be instructed not to drive or use machines until symptoms resolve. For patients with new visual changes, consider an ophthalmological evaluation. Based on the severity of visual changes, withhold Rozlytrek or modify treatment dosage as described in Table 4 in section *2.2. Dosage and Administration*.

2.4.2 Drug Abuse and Dependence
Not applicable.

2.4.3 Ability to Drive and Use Machines
Rozlytrek may influence the ability to drive and use machines. Patients should be instructed not to drive or use machines until the symptoms resolve, if they experience cognitive adverse reactions, syncope, blurred vision, or dizziness, during treatment with Rozlytrek. (See section *2.4 Warnings and Precautions* and section *2.6 Undesirable effects*).

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

Fertility
See section *3.3.3 Impairment of fertility*.

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

Contraception
Female patients of reproductive potential, must use highly effective contraceptive methods during treatment and for 5 weeks following the last dose of Rozlytrek.

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

2.5.2 Pregnancy
Female patients of reproductive potential must be advised to avoid pregnancy while receiving Rozlytrek (see section *2.4 Warnings and Precautions*). There is no available data on the use of Rozlytrek in pregnant women. Based on animal studies with entrectinib (see section *3.3 Nonclinical Safety*) and its mechanism of action, Rozlytrek may cause fetal harm when administered to a pregnant woman. Patients receiving Rozlytrek should be advised of the potential harm to the fetus. Female patients should be advised to contact the doctor, should pregnancy occur.

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

2.5.3 Lactation
It is not known whether entrectinib or its metabolites are excreted in human breast milk. No studies have been conducted to assess the effects of Rozlytrek on milk production or its presence in breast milk. As the potential for harm to the nursing infant is unknown, mothers should be advised to discontinue breast-feeding during treatment with Rozlytrek and for 14 days after the final dose.

2.5.4 Pediatric Use
The safety and efficacy of Rozlytrek have been studied in pediatric patients. See section *2.4.1 Warnings and Precautions*, 2.6.1 *Undesirable Effects, Clinical Trials* and section *3.1.2 Clinical/Efficacy Studies*. In addition, use of Rozlytrek in pediatric patients 12 years and older is supported by extrapolation of evidence from clinical trials in adults, based on population pharmacokinetic data demonstrating similar drug exposure in adults and pediatric patients 12 years and older. See section *2.2.1 Special Dosage Instructions*, section *3.1.2 Clinical/Efficacy Studies*, and section *3.2.5 Pharmacokinetics, Special Populations.*

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

2.5.5 Geriatric Use
No differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients. No dose adjustment is required in patients ≥ 65 years of age. See section *2.2.1 Special Dosage Instructions* and section *3.2.5 Pharmacokinetics, Special Populations.*

2.5.6 Renal Impairment
No dose adjustment is required in patients with mild or moderate renal impairment based on population pharmacokinetic analysis. The safety and efficacy of Rozlytrek in patients with severe renal impairment have not been studied. See section *2.2.1 Special Dosage Instructions, Renal Impairment* and section *3.2.5 Pharmacokinetics, Special Populations.*

2.5.7 Hepatic Impairment
The safety and efficacy of Rozlytrek in patients with hepatic impairment have not been studied. See section *2.2.1 Special Dosage Instructions* and section *3.2.5 Pharmacokinetics, Special Populations.*

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

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

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

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

Serious adverse reactions occurred in 39.9% of patients. The most frequent serious adverse reactions (≥ 2%) were pneumonia (4.0%), dyspnea (4.6%), pleural effusion (3.0%), pulmonary embolism (2.0%). Grade 3 or 4 adverse reactions occurred in 60.1% of patients; the most common (≥ 2%) were increased weight (7.3%), lung infection (6.0%), dyspnea (5.8%), fatigue/asthenia (5%), cognitive disorders (4.4%), hypoxia (2.4%), syncope (3%), pulmonary embolism (2.8%), pleural effusion (2.8%), diarrhoea (2.6%), urinary tract infection (2.6%), hypotension (2.4%), fractures (2.4%), and congestive heart failure (2.2%).

Tabulated summary of adverse drug reactions from clinical trials
Table 5 summarizes the adverse drug reactions (ADRs) occurring in adult and pediatric patients treated with Rozlytrek. Adverse drug reactions from clinical trials are listed by MedDRA system organ class. The following categories of frequency have been used: very common ≥1/10, common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to < 1/1000), very rare (<1/10,000).

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

System Organ Class Adverse Reaction	Rozlytrek N=504		Frequency Category (All Grades)
	All Grades (%)	Grade ≥3 (%)	
General Disorders and Administration Site Conditions			
Fatigue[14]	45.0	5.0	very common
Edema[6]	37.3	1.4	very common
Pain[7]	24.4	1.6	very common
Pyrexia	20.0	0.8	very common
Gastrointestinal Disorders			
Constipation	42.9	0.4	very common
Diarrhea	33.5	2.6	very common
Nausea	32.1	0.8	very common
Vomiting	23.2	1.2	very common
Abdominal pain	11.1	0.6	very common
Dysphagia	10.1	0.4	very common
Nervous System Disorders			
Dysgeusia	42.3	0.4	very common
Dizziness[5]	39.7	1.2	very common
Dysasthesia[3]	29.0	0.2	very common
Cognitive Disorders[1]	24.2	4.4	very common
Headache	17.5	1.0	very common
Peripheral Sensory Neuropathy[2]	15.7	1.0	very common
Ataxia[4]	15.7	0.8	very common
Sleep disturbances[16]	13.5	0.4	very common
Mood disorders[17]	9.1	0.6	common
Syncope	4.6	3.0	common
Respiratory Disorders			
Dyspnea	27.0	5.8*	very common
Cough	21.4	0.6	very common
Blood Disorders			
Anemia	28.2	9.7	very common
Neutropenia[10]	11.3	4.4	very common
Metabolism and Nutritional Disorders			
Weight increased	26.4	7.3	very common
Decreased appetite	11.9	0.2	very common
Hyperuricemia	9.1	1.8	common
Dehydration	7.9	1.0	common
Tumor lysis syndrome	0.2	0.2*	uncommon
Renal and urinary disorders			
Blood creatinine increased	25.4	0.6	very common
Musculoskeletal Disorders			
Myalgia	19.6	0.6	very common
Arthralgia	19.0	0.6	very common
Muscular weakness	12.3	1.2	very common
Fractures[11]	6.2	2.4	common
Hepatobiliary Disorders			
AST increased	17.5	3.6	very common
ALT increased	16.1	3.4	very common
Infections and Infestations			
Lung infection[8]	13.1	6.0*	very common
Urinary tract infection	12.7	2.6	very common
Eye Disorders			
Vision Blurred[13]	11.9	0.4	very common
Skin and Subcutaneous Tissue Disorders			
Rash[12]	11.5	1.4	very common
Vascular Disorders			
Hypotension[15]	16.5	2.4	very common
Cardiac Disorders			
Congestive Heart Failure[9]	3.0	2.2	common
Electrocardiogram QT prolonged	2.0	0.6	common

ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
* Grades 3 to 5, inclusive of fatal adverse reactions (including 2 reactions of pneumonia, 2 reactions of dyspnea, and 1 reaction of tumour lysis syndrome)
[1] Includes preferred terms: cognitive disorder, confusional state, disturbance in attention, memory impairment, amnesia, mental status changes, hallucination, delirium, 'hallucination visual' and mental disorder.
[2] Includes the preferred terms: neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy
[3] Includes the preferred terms: paresthesia, hyperesthesia, hypoesthesia, dysesthesia
[4] Includes the preferred terms: ataxia, balance disorder, gait disturbances
[5] Includes the preferred terms: dizziness, vertigo, dizziness postural
[6] Includes the preferred terms: face edema, fluid retention, generalized edema, localized edema, edema, edema peripheral, peripheral swelling
[7] Includes the preferred terms: back pain, neck pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity
[8] Includes the preferred terms: bronchitis, lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, upper respiratory tract infection
[9] Includes the preferred terms: acute right ventricular failure, cardiac failure, cardiac failure congestive, chronic right ventricular failure, ejection fraction decreased, pulmonary edema
[10] Includes the preferred terms: neutropenia, neutrophil count decreased
[11] Includes the preferred terms: humerus fracture, foot fracture, ankle fracture, femoral neck fracture, stress fracture, fibula fracture, fracture, rib fracture, spinal fracture, wrist fracture, femur fracture, pathological fracture
[12] Includes the preferred terms: rash, rash maculopapular, rash pruritic, rash erythematous, rash papular
[13] Includes the preferred terms: diplopia, vision blurred, visual impairment
[14] Includes the preferred terms: fatigue, asthenia
[15] Includes the preferred terms: hypotension, orthostatic hypotension
[16] Includes the preferred terms: hypersomnia, insomnia, sleep disorder, somnolence
[17] Includes the preferred terms: anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation

Description of selected adverse drug reactions
Cognitive disorders
A variety of cognitive symptoms were reported across clinical trials (see section *2.4.1 General (Warnings and Precautions)*]. These included events reported as cognitive disorders (6.3%), confusional state (7.3%), disturbance in attention (3.8%), memory impairment (4.2%), amnesia (2.8%), mental status changes (1.2%), hallucination (1.0%), delirium (0.8%), hallucination visual (0.4%) and mental disorder (0.2%). Grade 3 events were reported in 4.4% of patients. In the pediatric population, 3.4% (1/29) pediatric patients experienced disturbance in attention of Grade 1 severity. Patients who had brain metastases at baseline had a higher frequency of these events (29.7%) compared to those without brain metastases (23.1%).

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

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

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

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

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

QTc interval prolongation
Among the 504 patients who received entrectinib across clinical trials, 17 (4.0%) patients with at least one post-baseline ECG assessment

experienced QTcF interval prolongation of > 60 ms after starting entrectinib, and 12 (2.8%) patients had a QTcF interval of ≥ 500 ms.

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

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

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

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

Laboratory Test Abnormality[1]	Rozlytrek NCI-CTCAE Grade N= 504[2]	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or 4 (%)[3]
Chemistry		
Increased Blood Creatinine	94.8	3.1
Hyperuricemia	50.8	6.8
Increased AST	43.3	3.3
Increased ALT	38.4	3.1
Hematology		
Decreased Neutrophils	27.8	6.3
Decreased Hemoglobin	65.7	9.2

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase
[1] Based on number of patients with available baseline and at least one on-treatment test value
[2] N=480 for Blood Creatinine; N=478 for AST; N=479 for ALT; N=382 for Hyperuricemia; N=457 for Neutrophils; N=487 for Hemoglobin
[3] Patients with change from baseline values of Grade of 0−2 to a post−baseline value of Grade 3 or Grade 4 at any time

Hyperuricemia
Amongst the 504 patients who received Rozlytrek across clinical trials, 9.1% of patients experienced hyperuricemia as an adverse event. Grade 4 events were reported in 1.4% of patients, including one patient who died of tumour lysis syndrome. In all 46 patients with an adverse event of hyperuricemia, 6.5% required dose reduction, and 10.9% required dose interruption of Rozlytrek.

2.6.2 Postmarketing Experience
Not applicable

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

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Effects of entrectinib on other drugs
CYP substrates
Based on the *in vitro* studies in human liver microsomes, entrectinib exhibits inhibitory potential toward CYP3A.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Co-administration of strong and moderate CYP3A inhibitors (including, but not limited to, anti-fungal agents, anti-retroviral agents) with Rozlytrek should be avoided or limited to 14 days. If concurrent use is unavoidable, dose adjustment of Rozlytrek is required as described in section *2.2 Dosage and Administration*.

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

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

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

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

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

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

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

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

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

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

The efficacy evaluable analyses set comprised a total of 54 adult patients with confirmed *NTRK* fusion-positive solid tumors treated with Rozlytrek, not previously treated with a TRK inhibitor, presenting with measurable disease at baseline as assessed by investigator, and with ≥ 6 months of follow up. *NTRK* fusion-positive status was determined by a validated nucleic acid-based test performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently accredited laboratory, prior to enrollment in the study.

The baseline demographic and disease characteristics of the efficacy evaluable population were: 40.7% males, median age of 57 years (range: 21 to 83 years), 79.6% white Caucasian, 13.0% Asian, 7.5% Hispanic or Latino and 56.6 % never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (42.6%), 1 (46.3%), or 2 (11.1%). Most patients (96.3%) had metastatic disease [most common sites being lung (61.1%), lymph nodes (55.6%) and brain (22.2%)], 3.7% patients had locally advanced disease, and 25.9% patients had no prior systemic therapies. The overall median duration of follow-up was 13 months.

Efficacy results from patients with *NTRK*-fusion positive solid tumors are summarized in Table7.

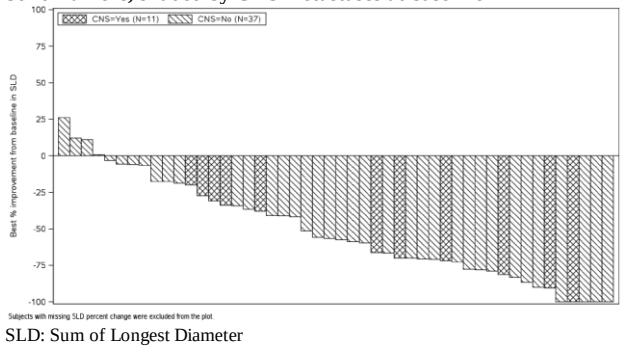
Table 7: Overall efficacy by BICR in Adults with *NTRK*-fusion positive Solid Tumors

Efficacy Endpoints	Rozlytrek N=54
Primary endpoints *(BICR-assessed, RECIST 1.1)*	
ORR	
Number of CR+PR	31/54
ORR% (95% CI)	57.4% (43.2, 70.8)
Complete Response, n (%)	4 (7.4%)
Partial Response, n (%)	27 (50.0%)
Stable Disease, n (%)	9 (16.7%)
Progressive Disease, n (%)	4 (7.4%)
DOR *	
Number (%) of patients with events	16/31 (51.6%)
Median, months (95% CI)	10.4 (7.1, NE)
6-month durable response % (95% CI)	0.69 (0.5, 0.9)
9-month durable response % (95% CI)	0.59 (0.4, 0.8)
12-month durable response % (95% CI)	0.49 (0.3, 0.7)
Secondary endpoints *(BICR-assessed, RECIST 1.1)*	
CBR	
Number of CR+PR+SD 6 months / Number of patients	36/54
CBR% (95% CI)	64.8% (50.62, 77.32)
PFS *	
Number (%) of patients with events/Number of patients	29/54 (53.7)
Median, months (95% CI)	11.2 (8.0, 14.9)
Time to CNS Progression	
Number (%) of patients with events	17/54 (31.5%)
Median, months (95% CI)	17.0 (14.3, NE)
Overall Survival	
Number (%) of patients with events	16/54 (29.6%)
Median, months (95% CI)	20.9 (14.9, NE)

CR: complete response; PR: partial response; NE: not estimable.
Confidence Intervals (CI) calculated using the Clopper-Pearson method.
*Median and percentiles based on Kaplan-Meier estimates

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

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



SLD: Sum of Longest Diameter

Of the 54 adult patients with *NTRK*-fusion positive solid tumors in the efficacy evaluable analysis set, 12 patients were identified by the Investigator to have CNS metastases at baseline. Efficacy results by BICR according to RECIST v 1.1 in this subgroup of patients with CNS metastases at baseline are summarized in Table 8.

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

Secondary Endpoint *(BICR-assessed, RECIST 1.1)*	CNS Metastases at Baseline (by Investigator)-	
	Yes N=12	No N=42
ORR		
Number of CR+PR	6	25
ORR% (95% CI)	50.0% (21.09, 78.91)	59.5% (43.28, 74.37)
Complete Response, n (%)	0	4 (9.5%)
Partial Response, n (%)	6 (50.0%)	21 (50.0%)
Stable Disease, n (%)	4 (33.3%)	5 (11.9%)
Progressive Disease, n (%)	0	4 (9.5%)
DOR		
Number of patients with events	3 (50.0%)	13 (52.0%)
Median, months (95% CI)	NE (4.2, NE)	12.9 (7.1, NE)
PFS		
Number of patients with events	6 (50.0%)	23 (54.8%)
Median, months (95% CI)	7.7 (4.7, NE)	12.0 (8.7, 15.7)

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

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

Table 9: Objective Response Rate (BICR Assessment) by Tumor Type in Adults with NTRK-fusion positive Solid Tumors

Tumor Type	N	Responders n (%)	95% CI
All	54	31 (57.4%)	(43.2, 70.8)
Breast cancer	6	5 (83.3%)	(35.9, 99.6)

Cholangiocarcinoma	1	1 (100%)	(2.5, 100)
Colorectal cancer	4	1 (25.0%)	(0.6, 80.6)
Gynecological cancers	2	1 (50.0%)	(1.3, 98.7)
Neuroendocrine cancers	3	1 (33.3%)	(0.8, 90.6)
Non-small cell lung cancer	10	7 (70.0%)	(34.7, 93.3)
Pancreatic cancer	3	2 (66.7%)	(9.4, 99.2)
Salivary (MASC)	7	6 (85.7%)	(42.1, 99.6)
Sarcoma	13	6 (46.2%)	(19.2, 74.9)
Thyroid cancer	5	1 (20.0%)	(0.5, 71.6)

MASC: mammary analogue secretory carcinoma
Confidence Intervals (CI) are calculated using the Clopper-Pearson method.

Intracranial Response
Of the 54 adult patients with *NTRK*-fusion positive solid tumors in the efficacy evaluable analysis set, 11 patients had CNS metastases at baseline as assessed by BICR, including 7 patients with measurable CNS lesions. Intracranial ORR, DOR, and PFS assessed by BICR according to RECIST version 1.1 in this subgroup of patients with measurable CNS lesions at baseline are summarized in Table 10.

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

Secondary Endpoint *(BICR-assessed, RECIST 1.1)*	**CNS Metastases at Baseline (by BICR)**	
	Measurable disease N=7	**All patients N=11**
IC-ORR		
Responders	4	6
IC-ORR% (95% CI)	57.1% (18.41, 90.10)	54.5% (23.4, 83.3)
Complete Response n (%)	1 (14.3%)	3 (27.3%)
Partial Response n (%)	3 (42.9%)	3 (27.3%)
IC-DOR		
Number of patients with events (%)	1 (25.0%)	2 (33.3%)
Median, months (95%)	NE (5.0, NE)	NE (5.0, NE)
IC-PFS		
Number of patients with events (%)	3 (42.9%)	5 (45.5%)
Median,months (95% CI)	NE (2.8, NE)	14.3 (5.1, NE)

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

Primary CNS tumors
Across the 3 trials, six adult patients with CNS primary tumors were treated with Rozlytrek with a minimum of 6 months of follow-up. IC-ORR, DOR and PFS were assessed by BICR according to Response Assessment in Neuro-Oncology Criteria (RANO). One patient had an objective response with a DOR of 2.79 months and PFS of 6.34 months.

Patient Reported Outcomes
Study STARTRK-2 evaluated patient-reported outcomes of the treatment impact on symptoms, functioning and health-related quality of life (HRQoL) based on the EORTC Core Quality of Life Questionnaire (QLQ-C30), the EORTC Quality of Life Questionnaire lung cancer module (QLQ-LC13), and the EORTC Quality of Life Questionnaire colorectal cancer module (QLQ-CR29).

At baseline, patients with *NTRK*-fusion positive solid tumors reported moderate-to-high HRQoL and functioning scores on the EORTC QLQ-C30 (global health status/HRQoL [mean score=69.79], role functioning [mean score=67.01], physical functioning [mean score=74.17], and cognitive functioning [mean score=84.72]). While receiving Rozlytrek, patients largely maintained or improved on high baseline HRQoL (best mean change score of 9.72 at Cycle 20 on the global health status/HRQoL scale). For functioning, patients continued to report moderate-to-high physical functioning and role functioning scores at most study visits, with clinically meaningful improvements (based on a ≥10-point change from baseline) observed at numerous timepoints, including as early as Cycle 10 (mean change score of 16.67) for role functioning and Cycle 12 (mean change score of 12.50) for physical functioning. The exception was the cognitive functioning scale, for which scores were maintained at their high baseline value, with a trend towards some worsening over time (worst mean change score of -11.11 at Cycle 20).

According to the EORTC QLQ-LC13, *NTRK*-fusion positive NSCLC patients reported low symptom burden at baseline (chest pain [mean score=3.7], coughing [mean score=29.63], and dyspnea [mean score=16.05]) and at most study visits throughout the study.

According to the EORTC QLQ-CR29, *NTRK*-fusion positive mCRC patients reported low symptom burden at baseline (abdominal pain [mean score=22.22], bloating [mean score=33.33], and stool frequency [mean score=16.67]) and at most study visits throughout the study.

Efficacy in Pediatric patients
The efficacy of Rozlytrek in pediatric patients with *NTRK* fusion-positive solid tumors was evaluated in study STARTRK-NG (ST-NG). This study is a multi-center Phase I/II, open-label dose-escalation and expansion study in pediatric patients with relapsed or refractory solid tumors, including primary CNS tumors, with or without *NTRK*, ROS1 or ALK molecular alterations. Patients received 250mg/m^2 to 750mg/m^2 once daily of Rozlytrek in 4-week cycles. The range of survival follow up was 6.5 months to 12.1 months.

Table 11 summarizes the efficacy of Rozlytrek in 5 pediatric patients (less than 18 years of age) with *NTRK* fusion-positive solid tumors as assessed by the Investigator according to RECIST version 1.1 for extra-cranial tumors and according to RANO for CNS primary tumors. Efficacy data in pediatric patients with *NTRK* fusion-positive solid tumors is further supported by extrapolation from results in the respective adult populations.

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

Tumor Type	**Best Overall Response**	**Duration of Response (months)**
Infantile fibrosarcoma	PR	9.10[a]
Infantile fibrosarcoma	SD	-
Epitheloid glioblastoma	CR[b]	3.94[a]
High grade glioma	PR[b]	6.47[a]
Metastatic melanoma	PR	6.47[a]

CR: complete response; PR: partial response; SD: stable disease
[a] Response ongoing at time of clinical cutoff date (31 October 2018)
[b] Response assessment was by RANO criteria

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 53 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 from the time of first response. ROS1-positive status was determined by a validated nucleic acid-based test performed at a CLIA-certified or equivalently accredited laboratory, prior to enrollment in the study.

The baseline demographic and disease characteristics of the efficacy evaluable population were: 35.8% males, median age of 53.5 years (range: 27 to 73 years), 79.2% patients <65 years of age, 58.5% white Caucasian, 35.8% Asian, 5.7% Black, 4.5% Hispanic or Latino and 58.5% never smokers. The ECOG (Eastern Cooperative Oncology Group) performance status at baseline was 0 (37.7%), 1 (50.9%), or 2 (11.3%). Most patients (94.3%) had metastatic disease with 43.4% having brain metastases [other common sites were lung (71.7%) and lymph nodes (77.7%)], 3.8% patients had locally advanced disease, and 26.4% patients had no prior systemic therapies. The overall median duration of follow-up was 16.6 months.

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

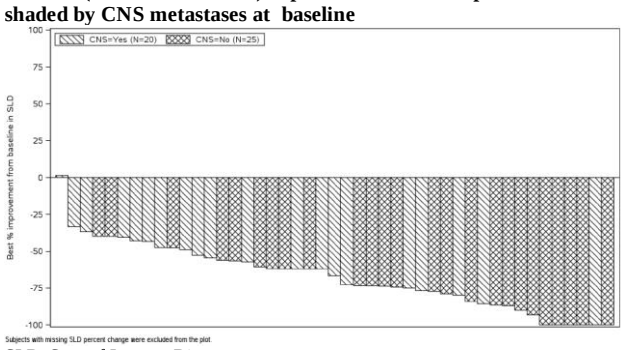
Table 12: Overall Efficacy by BICR in patients with ROS1-positive NSCLC

Efficacy Endpoint	**Rozlytrek N= 53**
Primary endpoints *(BICR-assessed, RECIST 1.1)*	
ORR	
Number of CR+PR	41/53
ORR% (95% CI)	77.4 (63.8, 87.7)
Complete Response, n (%)	3 (5.7)
Partial Response, n (%)	38 (71.7)
Stable Disease, n (%)	1 (1.9)
Progressive Disease, n (%)	4 (7.5)
DOR *	
Number (%) of patients with events	19/41 (46.3%)
Median, months (95% CI)	24.6 (11.4, 34.8)
6-month durable response % (95% CI)	0.82 (0.7, 0.9)
9-month durable response % (95% CI)	0.77 (0.6, 0.9)
12-month durable response % (95% CI)	0.65 (0.5, 0.8)
Secondary endpoints *(BICR-assessed, RECIST 1.1)*	
CBR	
Number of CR+PR+SD 6 months	41/53
CBR% (95% CI)	77.4% (63.8. 87.7)
PFS*	
Number (%) of patients with events	25/53 (47.2)
Median, months (95% CI)	19.0 (12.2, 36.6)
Time to CNS Progression	
Number (%) of patients with events	18/53 (34.0%)
Median, months (95% CI)	NE (15.1, NE)
Overall Survival	
Number (%) of patients with events	9/53 (17%)
Median, months (95% CI)	NE (NE)

CR: complete response; PR: partial response; NE: not estimable.
Confidence Intervals (CI) calculated using the Clopper-Pearson method.
*Median and percentiles based on Kaplan-Meier estimates

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

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



SLD: Sum of Longest Diameter

Of the 53 patients with ROS1-positive NSCLC in the efficacy evaluable analysis set, 23 patients were identified by the Investigator to have CNS metastases at baseline. Efficacy results by BICR according to RECIST v 1.1 in this subgroup of patients with CNS metastases at baseline are summarized in Table 13.

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

Secondary Endpoints *(BICR-assessed, RECIST 1.1)*	**CNS Metastases at Baseline (by Investigator)**	
	Yes N=23	**No N=30**
ORR		
Number of CR+PR	17/23	24/30
ORR% (95% CI)	73.9% (51.6, 89.8)	80.0% (61.4, 92.3)
Complete Response, n (%)	0	3 (10.0)
Partial Response, n (%)	17 (73.9)	21 (70.0)
Stable Disease, n (%)	0	1 (3.3)
Progressive Disease, n (%)	4 (17.4)	0
DOR		
Number of patients with events	6/17 (35.3%)	13/24 (54.2%)
Median, months (95% CI)	12.6 (6.5, NE)	24.6 (11.4, 34.8)
PFS		
Number of patients with events	11/23 (47.8%)	14/30 (46.7%)
Median, months (95% CI)	13.6 (4.5, NE)	26.3 (15.7, 36.6)

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

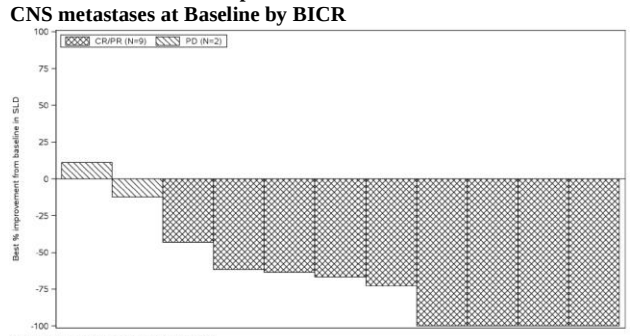
Intracranial Response
Of the 53 patients with ROS-1 positive NSCLC in the efficacy evaluable analysis set, 20 patients had CNS metastases at baseline as assessed by BICR, including 12 patients with measurable CNS lesions. Intracranial ORR, DOR, and PFS assessed by BICR according to RECIST version 1.1 in this subgroup of patients with measurable CNS lesions at baseline are summarized in Table 14 and Figure 3 below.

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

Secondary Endpoint *(BICR-assessed, RECIST 1.1)*	**CNS Metastases at Baseline (by BICR)**	
	Measurable disease N=12	**All patients N=20**
IC-ORR		
Responders	9	11
IC-ORR% (95% CI)	75.0% (42.8, 94.5)	55.0% (31.5, 76.9)
Complete Response n (%)	2 (16.7%)	4 (20.0%)
Partial Response n (%)	7 (58.3%)	7 (35.0%)
IC-DOR		
Number of patients with events (%)	4 (44.4%)	5 (45.5%)
Median, months (95%)	12.9 (4.6, NE)	12.9 (5.6, NE)
IC-PFS		
Number of patients with events (%)	6 (50.0%)	13 (65.5%)
Median, months (95% CI)	19.3 (3.8, 19.3)	7.7 (3.8, 19.3)

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

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



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

Previous treatment with Crizotinib
Efficacy of Rozlytrek in ROS1 positive NSCLC patients who have progressed on prior crizotinib is not well established. In an exploratory analysis conducted in 27 patients with ROS1 positive NSCLC previously treated with crizotinib, ORR was 10.5% and 12.5% in patients who had CNS-only progression and systemic progression while on crizotinib, respectively.

Patient Reported Outcomes
STARTRK-2 evaluated patient-reported outcomes of the treatment impact on symptoms, functioning and health-related quality of life (HRQoL) based on the EORTC Core Quality of Life Questionnaire (QLQ-C30) and the EORTC Quality of Life Questionnaire lung cancer module (QLQ-LC13). Scale scores on these questionnaire range from 0 to 100, with higher scores (i.e. closer to 100) reflecting better HRQoL and functioning but worse symptomology.

At baseline, patients with ROS1 positive NSCLC reported moderate-to-high HRQoL and functioning scores on the EORTC QLQ-C30 (global health status/HRQoL [mean score=57.84], physical functioning [mean score=68.87], role functioning [mean score= 60.29], and cognitive functioning [mean score=81.86]). While receiving Rozlytrek, patients largely maintained or improved on high baseline HRQoL (best mean change score of 11.74 at Cycle 8 on the global health status/HRQoL scale). For functioning, patients continued to report moderate-to-high physical functioning and role functioning scores at most study visits, with a trend towards improvement, including clinically meaningful improvements (based on a ≥10-point change from baseline) observed as early as Cycle 7 (mean change score of 11.11) for role functioning. The exception was the cognitive functioning scale, for which scores were maintained at their high baseline value, with a trend towards some worsening at specific timepoints (worst mean change score of -41.76 at Cycle 22).

According to the EORTC QLQ-LC13, patients reported moderate symptom burden at baseline (chest pain [mean score=17.17], dyspnea [mean score=38.05]) with trends towards immediate improvement. On average, patients reported severe cough at baseline (mean score=44.44), followed by immediate improvement (mean change from baseline score of -17.86 at Cycle 2).

In addition, most patients, indicated that the symptoms commonly associated with Rozlytrek treatment (i.e. lack of appetite, nausea, diarrhea and vomiting) were of low severity, if present.

3.1.3 Immunogenicity
Not applicable.

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

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

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

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

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

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

3.2.2 Distribution

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

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

3.2.3 Metabolism

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

3.2.4 Elimination

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

Entrectinib and M5 account for approximately 73% of radioactivity in systemic circulation at 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,

3.2.5 Pharmacokinetics in Special Populations

Pediatric Population

Data obtained from population pharmacokinetic analyses show that in pediatric patients 12 years and older, a dose of 300 mg Rozlytrek once daily for BSA range 0.81 m^2 to 1.10 m^2, a dose of 400 mg Rozlytrek once daily for BSA range 1.11 m^2 to 1.50 m^2, and a dose of 600 mg Rozlytrek once daily for BSA range ≥1.51 m^2 resulted in a similar systemic exposure attained in adults treated with 600 mg of Rozlytrek once daily.

Geriatric Population

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

Renal impairment

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

Hepatic impairment

As elimination of entrectinib is predominantly through metabolism in the liver, hepatic impairment may increase the plasma concentration of entrectinib and/or its major active metabolite M5. Limited clinical data is available in patients with hepatic impairment and a dedicated pharmacokinetic study in patients with hepatic impairment has not been conducted. Based on population pharmacokinetic analysis, entrectinib and M5 exposures were similar in patients with mild, moderate or severe hepatic impairment and normal hepatic function.

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/ethinicity (Asian, Japanese, white and other ethnicities). No dose adjustment is required for patients of different race/ethnicities. See section *2.2.1 Special Dosage Instructions*.

3.3 NONCLINICAL SAFETY

3.3.1 Carcinogenicity

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

3.3.2 Genotoxicity

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

3.3.3 Impairment of Fertility

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

3.3.4 Reproductive toxicity

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

3.3.5 Other

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

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Storage

Do not store above 30°C (86°F).

Shelf life

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

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Disposal of unused/expired medicines

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

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

4.3 PACKS

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.

Medicine: keep out of reach of children

Current at Nov 2020

F. Hoffmann-La Roche Ltd Basel, Switzerland