Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Entrectinib

Proprietary Product Name: Rozlytrek

Sponsor: Roche Products Pty Ltd

December 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the Therapeutic Goods Act 1989 (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ADME	Absorption, distribution, metabolism and excretion
Adv/met	Advanced or metastatic
AE	Adverse event
AESI	Adverse event of special interest
AIHW	Australia Institute of Health and Welfare
AKAP13	A-kinase anchoring protein 13
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
AST	Aspartate aminotransferase
AUC	Area under the serum concentration time curve
AUC_0	Area under the serum concentration time curve at time = 0
AUC_{0-24}	Area under the plasma concentration time curve during 24 hours
AUC_{inf}	AUC curve to infinite time
AUC_{ss}	Area under the serum concentration time curve at steady state
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutical Classification System
BDNF	Brain-derived growth factor
BICR	Blinded independent central review
BLA	Biologics License Application (United States Food and Drug Administration)
BSA	Body surface area
CBR	Clinical benefit rate
CDC42BPA	CDC42 binding protein kinase alpha

Abbreviation	Meaning
CDRH	Center for Devices and Radiologic Health (United States Food and Drug Administration)
CGN	Cingulin
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency)
CI	Confidence interval
C_{max}	Maximum serum concentration
CMI	Consumer Medicine Information
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CrCL	Creatinine clearance
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP2D6	Cytochrome P450 2D6
CYP3A	Cytochrome P450 3A
CYP3A4_fm	Fraction metabolised by CYP3A4
CYP	Cytochrome P450
DLT	Dose limiting toxicities
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EML4	Echinoderm microtubule associated protein like 4

Abbreviation	Meaning
EPS15L1	Epidermal growth factor receptor pathway substrate 15 like 1
ERC1	ELKS/RAB6-interacting/CAST family member 1
ESMO	European Society for Medical Oncology
ETV6	Erythroblast transformation specific variant transcription factor 6
EU	European Union
F01-F07	Different development formulations of entrectinib
FAM19A2	TAFA chemokine like family member 2
FDA	Food and Drug Administration (United States)
FISH	Fluorescence *in situ* hybridisation
GMR	Geometric mean ratio
HDPE	High density polyethylene
IC-DOR	Intracranial duration of response
IC-ORR	Intracranial objective response rate
IHC	Immunohistochemistry
IV	Intravenous
JAK 2	Janus kinase 2
K+	Potassium ion
KIF7	Kinesin family member 7
KRAS	Kirsten rat sarcoma
LMNA	Lamin A/C
LV	Left ventricular
M5	Entrectinib metabolite 5 (4'-hydroxy-5-carboxylumiracoxib)
MATE 1	Multidrug and toxin extrusion protein 1
Max	Maximum
Min	Minimum

Abbreviation	Meaning
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NDA	New drug application
NGF	Nerve growth factor
NONMEM	Non-linear mixed effects modelling
NR	Not reported
NSCLC	Non-small cell lung cancer
NSG	Next generation sequencing
NT3	Neurotrophin-3
NT4/NTF5	Eurotrophin-4
NTRK	Neurotrophic tropomyosin receptor kinase
OATP1B1	Organic anion transporter family member 1B1
OATP1B3	Organic anion transporter family member 1B3
ORR	Objective response rate
OS	Overall survival
PBPK	Physiologically-based pharmacokinetics
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PD-L1	Programmed death-ligand 1
PDIA3	Protein disulfide isomerase family A member 3
PEAR1	Platelet endothelial aggregation receptor 1
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetic(s)

Abbreviation	Meaning
pKa	Acid dissociation constant
PLEKHA6	Pleckstrin homology domain containing A6
PMA	Premarket approval application
PMC	Post-marketing commitment
PMR	Post marketing requirement
PPI	Proton pump inhibitor
PPK	Population pharmacokinetics
PPK WG	Population pharmacokinetics working group
PROs	Patient reported outcomes
QT	Time interval from start of the Q wave to the end of the T wave in a heartbeat
QTc	Corrected QT interval
RANO	Response Assessment in Neuro-Oncology (Criteria)
RBPMS	RNA binding protein, mRNA processing factor
RECIST	Response evaluation criteria in solid tumours
RMP	Risk management plan
RNA	Ribonucleic acid
ROS1	Proto-oncogene tyrosine-protein kinase ROS
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small cell lung cancer
SGF_{sp}	Simulated gastric fluid sine pepsin
SOC	System Organ Class
SQSTM1	Sequestosome 1
TGA	Therapeutic Goods Administration

Abbreviation	Meaning
T_{max}	Time of maximum concentration
TPM3	Tropomyosin 3
TPR	Translocated promoter region, nuclear basket protein
TRIM33	Tripartite motif containing 33
TRK	Tropomyosin receptor kinase
TTR	Time to response
UGT1A4	Uridine 5'-diphospho-glucuronosyltransferase 1-4
US(A)	United States (of America)
W&P	Warnings and precautions

I. Introduction to product submission

Submission details

Submission PM-2019-01808-1-4 (non-small cell lung cancer indication)

Type of submission:	New chemical entity
Product name:	Rozlytrek
Active ingredient:	Entrectinib
Decision:	Approved
Date of decision:	14 May 2020
Date of entry onto ARTG:	15 May 2020
ARTG numbers:	318002, 318003
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia, or for the entire period of provisional registration, whichever is longer.
Sponsor's name and address:	Roche Products Pty Ltd Level 8, 30-34 Hickson Road, Sydney, NSW 2000
Dose form:	Hard capsule
Strengths:	100 mg, 200 mg
Container:	Bottle
Pack sizes:	100 mg hard capsules: 30 capsules per bottle 200 mg hard capsules: 90 capsules per bottle
Approved therapeutic use:	*Non-small cell lung cancer (NSCLC)* *Rozlytrek is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours are ROS1-positive.*
Route of administration:	Oral
Dosage:	A validated assay is required for the selection of patients with ROS1-positive locally advanced or metastatic NSCLC.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

ROS1-positive status should be established prior to initiation of Rozlytrek therapy.

Dosage

The recommended dose of Rozlytrek for adults is 600 mg given orally, once daily.

For further information regarding dosage, refer to the Product Information (PI).

Pregnancy category: D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Submission PM-2019-01809-1-4 (solid tumour indication)

Type of submission:	Extension of indications
Product name:	Rozlytrek
Active ingredient:	Entrectinib
Decision:	Approved for provisional registration
Date of decision:	15 May 2020
Date of entry onto ARTG:	19 May 2020
ARTG numbers:	318002, 318003
, *Black Triangle Scheme*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia, or for the entire period of provisional registration, whichever is longer.
Sponsor's name and address:	Roche Products Pty Ltd Level 8, 30-34 Hickson Road, Sydney, NSW 2000
Dose form:	Hard capsule
Strengths:	100 mg, 200 mg
Container:	Bottle

Pack sizes:	100 mg hard capsules: 30 capsules per bottle 200 mg hard capsules: 90 capsules per bottle
Approved therapeutic use:	*Solid tumours* *Rozlytrek is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours that:* • *have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation,* • *are metastatic or where surgical resection is likely to result in severe morbidity, and* • *have either progressed following treatment or have no satisfactory alternative therapy.* *This indication was approved via the provisional approval pathway, based on objective response rate and duration of response in single-arm trials. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.*
Route of administration:	Oral
Dosage:	*Dosage* The recommended dose of Rozlytrek for adults is 600 mg given orally, once daily. The recommended dose of Rozlytrek for paediatric patients is based on body surface area (BSA): • BSA greater than 1.50 m^2: 600 mg • BSA 1.11 to 1.50 m^2: 500 mg • BSA 0.91 to 1.10m^2: 400 mg. For further information regarding dosage, refer to the PI.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Roche Products Pty Ltd (the sponsor) to register Rozlytrek (entrectinib) 100 mg and 200 mg, hard capsule for treatment of non-small cell lung cancer (NSCLC) as follows:

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

In a concurrent submission, the sponsor also applied for provisional registration of the following solid tumour indication relating to the same products:

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

Entrectinib is a tyrosine kinase inhibitor with significant inhibitory activity against ROS proto-oncogene 1(ROS1), tropomyosin receptor kinases (TRK) A, B, and C, and anaplastic lymphoma kinase (ALK).

Physiologically, when bound by their respective ligands, receptor tyrosine kinases dimerise, autophosphorylate, and activate downstream signalling pathways involved in cell growth and apoptosis. Mutation of the genes that encode them can drive oncogenic transformation and has been implicated in multiple tumour types.

ROS1 positive non-small cell lung cancer

In the case of *ROS1*-driven tumours, the causative mutation is usually a larger-scale genetic rearrangement, in which a fusion causes a region encoding the ROS1 kinase domain to be juxtaposed to a new genetic partner. Through multiple possible mechanisms (such as loss of autoinhibitory regions or inclusion of novel upstream oligomerisation domains) the result is a novel, constitutively active fusion kinase.

ROS1-positive non-small cell lung cancer (NSCLC) is a rare form of lung cancer, representing 1 to 2% of patients with NSCLC. The physiological function of the *ROS1* gene has not been identified, but chromosomal translocations can result in functional/active rearrangements that are oncogenic. *ROS1*-positive NSCLC has similar histopathology to other adenocarcinoma type small cell lung cancers (SCLC), and therefore requires molecular diagnostic techniques for identification/classification. *ROS1* rearrangements rarely overlap with *ALK* gene rearrangements or with oncogenic epidermal growth factor receptor (*EGFR*) gene mutations or Kirsten rat sarcoma (*KRAS*) gene mutations. Therefore, *ROS1* rearrangements define a unique molecular subset of oncogenic drivers in NSCLC.

Lung cancer tends to present late, at an advanced stage (42% at Stage IV);[2] and when the prognosis is poor.[3] Lung cancer contributes 4.3% of the incident cases of cancer in Australia. The 5 year relative survival is around 20% and the Australia Institute of Health and Welfare (AIHW) estimates that in 2019 lung cancer will be the leading cause of death from cancer in Australia (9,034 deaths, followed by colorectal cancer with 5,597, prostate cancer with 3,306, breast cancer with 3,090 and pancreatic cancer with 3,051.[3] In 2015,

[2] Stage IV lung cancer is the most advanced stage of lung cancer; the original tumour has spread or metastasised from the original lung to both lungs, the pericardium, chest cavity and/or to other distal parts of the body.

[3] Australian Institute of Health and Welfare. Cancer Data in Australia 2019. Available from aihw.gov.au (Accessed on 8 September 2019)

there were 11,788 persons diagnosed with lung cancer in Australia, a rate of 49.4/100,000 population.[3] There were 6,779 (57.5%) males and 5009 (42.5%) females diagnosed with lung cancer in Australia in 2015.[3] From 2010 to 2014, lung cancer was the most common cancer diagnosed for Aboriginal and Torres Strait Islander people.[3]

Based on this information, and 85% of lung cancer being NSCLC, the TGA clinical evaluator estimates 1000 to 2000 patients with *ROS1* positive NSCLC diagnosed in Australia per year, with the majority at an advanced stage.

The previously available treatments include standard chemotherapy, radiotherapy and surgery. Newer treatments included targeted therapy and immunotherapy, including the immune checkpoint inhibitors.

The only therapy that is registered specifically for the targeted treatment of *ROS1*-positive cancer in Australia is crizotinib.[4]

The registration of crizotinib for *ROS1*-positive NSCLC was based on single arm data from a study of 53 patients with *ROS1*-positive NSCLC. In this study, crizotinib caused tumour shrinkage in 72% (95% confidence intervals (CI): 58%, 83%) of patients with a median duration of response of 24.7 (95% CI: 15.2 to 45.3) months.[5] In the setting of this rare disease with a predictable natural history, for example inexorable progression, this evidence was considered sufficient evidence to support a risk-benefit assessment. Crizotinib, however, is subject to P-glycoprotein (P-gp)-mediated efflux and has poor blood-brain barrier penetration. Central nervous system (CNS) progression occurs in around 60% of patients during crizotinib therapy.[6]

Neurotrophic tropomyosin receptor kinase fusion-positive locally advanced or metastatic solid tumours

In addition, entrectinib is also a potent inhibitor of the tropomyosin receptor kinases (TRK) A, B and C, which has been shown to have anti-tumour activity against *NTRK* gene fusion-positive solid tumours.[7]

The sponsor clinical overview states:

> 'The neurotrophic receptor tyrosine kinase family of genes *NTRK1*, *NTRK2*, and *NTRK3* encode the tropomyosin receptor kinases A, B and C (TRKA, TRKB and TRKC), respectively. TRK family members are transmembrane proteins serving as high affinity signal transducing receptors for neurotrophins. They are expressed in neuronal tissue and play an essential physiological role in the development and function of the central and peripheral nervous systems. TRKA binds nerve growth factor (NGF);[8,9,10], TRKB binds brain-derived growth factor (BDNF) and eurotrophin-4 (NT4, also known as NTF5) with high affinity and neurotrophin-3

[4] See the AusPAR for Xalkori crizotinib Pfizer Australia Pty Ltd PM-2016-03535-1-4; published online on 18 October 2018: https://www.tga.gov.au/auspar/auspar-crizotinib-0 1-4 Final 18 October 2018
[5]National Institute for Health and Care Excellence. Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer Technology appraisal guidance Published: 4 July 2018 (Available from nice.org.uk)
[6]Petrelli F, et al. Efficacy of ALK inhibitors on NSCLC brain metastases: A systematic review and pooled analysis of 21 studies*. PLoS ONE*, 2018; 13(7): e0201425.
[7] Doebele, Robert C, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials *The Lancet Oncology*, 2019; 21 (2), 271 – 282.
[8] Kaplan DR, et al. The trk proto-oncogene product: a signal transducing receptor for nerve growth factor. *Science*, 1991; 252(5005):554-558.
[9] Kaplan, D., et al. Tyrosine phosphorylation and tyrosine kinase activity of the trk proto-oncogene product induced by NGF. *Nature*, 1991; 350, 158–160.
[10] Klein R, et al. The trk proto-oncogene encodes a receptor for nerve growth factor. *Cell.* 1991;65(1):189-197.

(NT3) to a lesser extent;[10,11] and TRKC binds NT3.[12] Binding of neurotrophins to their cognate TRK receptors results in homodimerization, receptor autophosphorylation and activation of downstream signal transduction pathways involved in cell proliferation, apoptosis, and survival of neurons and other cell types.

The *NTRK* gene fusion-positive tumour type is not necessarily of neurological origin. Typically, intra-chromosomal or inter-chromosomal rearrangements form hybrid genes in which 3′ sequences of *NTRK1*, *NTRK2* or *NTRK3* that include the kinase domain are juxtaposed to 5′ sequences of a different gene. The product of the fusion is a chimeric oncoprotein characterized by ligand independent constitutive activation of the TRK kinase. Essentially, these proteins become intracellular, unregulated, independently operating growth promoters. The growth promoting mechanism operates in a number of different cell types as it is independent of neurotrophins.'

NTRK fusion-positive solid tumours are rare, and because of differences in testing methodologies, the exact frequency of NTRK fusions in solid tumours remains unclear. The diagnosis has been based on deoxyribonucleic acid (DNA) based next generation sequencing technologies, which can be complemented by targeted ribonucleic acid (RNA) sequencing.[13] These can vary depending upon the primers used. In a profiling of adult and paediatric solid tumour samples there was a prevalence of 0.32%. The prevalence was up to 1% in the sponsor's screening of tumour samples.

Until recently, no targeted therapies for *NTRK*-fusion positive cancer were available. At the time this submission was under consideration, there were currently no therapies registered in Australia specifically for the treatment of tumours which are NTRK-fusion positive.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, entrectinib had been granted approval in United States of America (USA) (approved in August 2019), Japan (approved in June 2019) and Canada (approved on 10 February 2020), and was under consideration in the European Union (EU), as shown in Table 1.

Table 1: International regulatory status of Rozlytrek as of March 2020

Region	Submission date	Status	Approved indications
EU Centralised procedure. Rapporteur: Italy	8 January 2019	Under consideration	Under consideration

[11] Soppet, Dan, et al. The neurotrophic factors brain-derived neurotrophic factor and neurotrophin-3 are ligands for the B tyrosine kinase receptor. *Cell*. 1991, 65(5): 895-903.
[12] Klein, R., et al.The trkB tyrosine protein kinase is a receptor for brain-derived neurotrophic factor and neurotrophin-3. *Cell*, 1991; 66(2), 395–403.
[13] Cocco E, et al. NTRK fusion-positive cancers and TRK inhibitor therapy. Nature Reviews Clinical Oncology,2018; 15, 731–747.

Region	Submission date	Status	Approved indications
Co-Rapporteur: Sweden			
USA	18 December 2018	Approved on 15 August 2019	*Rozlytrek is a kinase inhibitor indicated for the treatment of:* • *Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive.* *Adult and pediatric patients 12 years of age and older with solid tumors that:* • *have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation,* • *are metastatic or where surgical resection is likely to result in severe morbidity, and* • *have progressed following treatment or have no satisfactory alternative therapy.* *This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.*
Japan	18 December 2018	Approved on 18 June 2019	*Neurotrophic tyrosine receptor kinase (NTRK) fusion–positive advanced or recurrent solid tumors*
Japan	15 March 2019	Approved on 21 February 2020	*ROS1 fusion–positive unresectable advanced or recurrent non–small cell lung cancer*
Canada	7 May 2019	Approved on 10 February 2020 (under the Notice of	*Rozlytrek (entrectinib) is indicated for the treatment of adult patients with unresectable locally advanced or metastatic*

Region	Submission date	Status	Approved indications
		Compliance with Conditions (NOC/c) Guidance) ROS-1 submission was under consideration	*extracranial solid tumours, including brain metastases, that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, and with no satisfactory treatment options.* ROS-1 indications was under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-01808-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	1 July 2019
First round evaluation completed	17 March 2020
Sponsor provides responses on questions raised in first round evaluation	17 April 2020
Second round evaluation completed	14 May 2020
Delegate's Overall benefit-risk assessment	3 March 2020
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	14 May 2020
Completion of administrative activities and registration on the ARTG	15 May 2020
Number of working days from submission dossier acceptance to registration decision*	196

*Statutory timeframe for standard applications is 255 working days

Table 3: Timeline for Submission PM-2019-01809-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	1 July 2019
First round evaluation completed	2 December 2019
Sponsor provides responses on questions raised in first round evaluation	24 December 2019
Second round evaluation completed	31 January 2020
Delegate's Overall benefit-risk assessment	3 March 2020
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	18 May 2020
Completion of administrative activities and registration on the ARTG	19 May 2020
Number of working days from submission dossier acceptance to registration decision*	202

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

The following publically available United States (US) Food and Drug Administration (FDA) report;[14] was referenced by the Delegate.

- FDA review: New Drug Applications (NDA) and Biologics License Applications (BLA) multi-disciplinary review and evaluation NDA 212725 and NDA 212726 Rozlytrek (entrectinib).

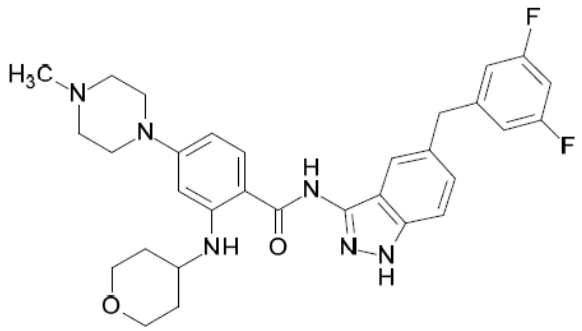
Quality

The quality evaluator has recommended approval with respect to chemistry and manufacturing controls.

The full chemical name of entrectinib is *N*-{5-[(3,5-difluorophenyl)methyl]-1*H*-indazol-3-yl}-4-(4-methylpiperazin-1-yl)-2-[(oxan-4-yl)amino]benzamide, structure shown below.

[14] FDA review: NDA/BLA Multi-disciplinary Review and Evaluation NDA 212725 and NDA 212726 Rozlytrek (entrectinib). August 2019. Available from the FDA website.

Figure 1: Chemical structure of entrectinib



It is a heterocyclic nitrogenous base consisting of 6 rings and containing an amide linkage. It is prepared synthetically and isolated as the crystalline anhydrous free base form.

For adult patients, the proposed entrectinib dosing regimen is 600 mg (for example 200 mg taken 3 times a day) taken orally daily with or without food. For paediatric patients, the daily dosing regimen is based on body surface area, capped at 600 mg and uses 100 mg increments for dose adjustment. Capsules are intended to be swallowed whole. Treatment duration is until disease progression or unacceptable toxicity. The PI includes dose reductions based on tolerability down to 200 mg once daily for adults and to 100 mg once daily for 3 days each week for paediatric patients. Further instructions are included for dose modifications for specific adverse reactions.

Entrectinib is in Biopharmaceutics Classification System (BCS);[15] class IV (low solubility and low permeability).

The proposed Rozlytrek capsules are immediate release, hard capsules containing 200 mg or 100 mg of entrectinib and the fill is directly scaled. The shells are made of hypromellose. The appearance of Rozlytrek capsules is:

- 100 mg: Size 2 hard capsules with yellow body and cap with 'ENT 100' imprinted in blue on the body
- 200 mg: Size 0 hard capsules with orange body and cap with 'ENT 200' imprinted in blue on the body

The proposed capsules are formulated with tartaric acid as an acidulant (pH modifier) in order to address food and proton-pump inhibitor (PPI) effects observed with the initial clinical formulation (F1) which did not contain such an excipient. Bioequivalence between the market (F06) and pivotal (F2A) formulations was demonstrated. The excipients are otherwise conventional.

The capsules are presented in high density polyethylene (HDPE) bottles with child resistant closures and a desiccant in the cap. Different pack sizes are proposed, 30 capsule bottles for the 100 mg strength and 90 capsule bottles for the 200 mg.

Nonclinical

There are no objections on nonclinical grounds to the registration of entrectinib for the proposed indications, provided adequate clinical safety data are available.

Entrectinib has demonstrated inhibition of cancer cell lines harbouring *NTRK* and *ROS1* fusion genes, irrespective of tumour type. Anti-tumour activity has also been shown in

[15] The **Biopharmaceutics Classification System** (**BCS**) is a system to differentiate the drugs on the basis of their solubility and permeability.

NTRK and *ROS1* fusion-driven tumour models, including sarcomas, head and neck carcinoma, NSCLC, colorectal cancer (CRC), acute myeloid leukaemia (AML), and gliomas.[14]

A publicly accessible summary of the nonclinical pharmacology and toxicology studies submitted to the FDA and major findings of each is available on pages 42 to 89 of the FDA multi-disciplinary review document for NDA 212725 (entrectinib).[14] The sponsor has provided reassurances that there are no significant differences between the datasets submitted to Australia and the US.

The TGA nonclinical evaluator's conclusions included the following:

- The primary pharmacology studies lend support for the proposed for the treatment of patients with *ROS1*-positive, locally advanced or metastatic NSCLC/ *NTRK* fusion-positive locally advanced or metastatic solid tumours.
- A secondary pharmacology screening study showed significant activity to about 40 targets at 10 μM (only concentration tested). Further investigation of off-target sites should be conducted as a post-marketing requirement.
- Toxicity findings of clinical relevance include the CNS, skin and cardiovascular (QT interval prolongation);[16] effects. Other target organs are cornea, lymphohaematopoietic tissues and liver. Immune suppression as a result of Janus kinase 2 (*JAK 2*) inhibition by entrectinib is also a clinical risk.
- The nonclinical studies predicted fetal toxicity and teratogenicity at the proposed clinical dose. Pregnancy category D is considered appropriate.[17]
- The juvenile rat was more sensitive than the adult to entrectinib-induced toxicities, with deficits in spatial learning and memory and delayed growth/development (including sexual maturation) as prominent findings.

Clinical

The clinical evaluator has recommended approval. The dossier contained clinical pharmacology, Phase I and Phase II studies. There were no Phase III studies. The studies included patients with *NTRK1*, *NTRK2*, *NTRK3*, *ROS1*, or *ALK* molecular alterations.

[16]The **QT interval** is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes. The recently described congenital short QT syndrome has been found to be associated with an increased risk of paroxysmal atrial and ventricular fibrillation and sudden cardiac death.

[17]**Australian Pregnancy Category D**: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Table 4: Overview of the clinical studies of entrectinib from which pharmacology, efficacy and safety data supporting this submission were obtained

Reference #	Description	Objectives	Dose[A]	Population size			
				PK	Safety	Efficacy (NTRK)[B]	Efficacy (ROS1)
Clinical studies in patients							
ALKA-372-001 (GO40783) 'ALKA'	First in human, dose escalation (3 + 3 design) in adults with NTRK1/2/3, ROS1 or ALK+ advanced or metastatic (adv/met) solid tumours. Formulation: F1	Dose limiting toxicities (DLTs), maximum tolerated dose (MTD)	100 to 1600 mg/day	57	57	1	9
RXDX-101-01 (GO40784) 'STARTRK-1'	Dose escalation (3 + 3 design) in adults with NTRK1/2/3, ROS1 or ALK+ adv/met solid tumours. Formulation: F1 and F2A	DLTs, MTD, recommended Phase II dose (RP2D), objective response rate (ORR)	100 to 800 mg/day	74	76	3 (1 primary CNS)	7
RXDX-101-02 (GO40782) 'STARTRK-2'	Basket trial adults with NTRK1/2/3, ROS1 or ALK+ adv/met solid tumours excluding ALK+NSCLC. Plus: QT substudy. Formulation: F2A (4 patients got F1)	ORR by blinded independent central review (BICR)	600 mg daily	203	206	57 (5 primary CNS, 1 non-measurable)	35

Reference #	Description	Objectives	Dose[A]	Population size			
				PK	Safety	Efficacy (NTRK)[B]	Efficacy (ROS1)
RXDX-101-03 (CO40778) 'STARTRK-NG'	Dose escalation/expansion in paediatric/adolescent patients (aged 2 to 22) with recurrent or refractory solid tumours or primary brain tumours, including NTRK 1/2/3, ROS1 and ALK+. Formulation: F1 (3 patients got F2B)	DLTs, MTD, RP2D, ORR by BICR	BSA based dosing: 250 to 750 mg/m^2	16	16	1	0
RXDX-101-14 (GO40785)	Single and multiple dose PK: effect on midazolam exposure of single and multiple entrectinib doses in adults with NTRK1/2/3, ROS1 or ALK+ adv/met solid tumours, with expanded access afterwards	Pharmacokinetics (PK)/ drug-drug interaction (DDI)	600 mg daily	12	14	(6)[C]	(4)[C]
Clinical pharmacology studies in healthy volunteers							
CA14707 (GP40835)	Single dose PK: effect of formulation (F1, F2, F2A, F2B) with or without food and PPI	PK/ DDI	800 mg	65	72	0	0

Reference #	Description	Objectives	Dose[A]	Population size			
				PK	Safety	Efficacy (NTRK)[B]	Efficacy (ROS1)
	(lansoprazole)						
RXDX-101-04 (GP40836)	Single dose PK (F2A): effect of food and race (Caucasian, Japanese)	PK	400 mg or 600 mg	24	24	0	0
RXDX-101-05 (GP40837)	Single dose PK (powder in capsule): absorption, distribution, metabolism, and excretion (ADME)	PK	600 mg	7	7	0	0
RXDX-101-06 (GP40829)	Single dose PK: effect of food and formulation (F1, F400 granules)	PK	400 mg or 600 mg	16	16	0	0
RXDX-101-07 (GP40830)	Single dose PK: effect of food and formulation (F05, F06, F07, F2A)	PK	600 mg	48	48	0	0
RXDX-101-08 (GP40831)	Single dose PK: effect of formulation (F06A - registration scale manufacture, F06B)	PK	600 mg	24	24	0	0
RXDX-101-09 (GP40832)	Single dose PK (F06): effect of steady state PPI	PK/ DDI	600 mg	19	19	0	0
RXDX-101-12 (GP40833)	Single dose PK (F06): effect of strong	PK/ DDI	100 mg or 600 mg	20	20	0	0

Reference #	Description	Objectives	Dose[A]	Population size			
				PK	Safety	Efficacy (NTRK)[B]	Efficacy (ROS1)
	CYP3A4 inhibitor (itraconazole) or inducer (rifampin)						
RXDX-101-13 (GP40834)	Single dose PK: effect of entrectinib (F2A) on single dose digoxin	PK/ DDI	600 mg	10	10	0	0
RXDX-101-15 (GO40786)	Single dose PK: effect of food (F06) and formulation (F06, F2A)	PK	600 mg	83	83	0	0
GP41048	Single dose PK: F1 versus F06(preliminary report, dated 11 April 2019)	PK	600 mg	14	NR	0	0

F1/F2,F05, F06, F07, F2A, F2B = various entrectinib formulations used in clinical development.

[A] Entrectinib dose (oral)

[B] Noted in brackets are patients excluded from the primary efficacy population.

[C] Six of the patients treated had an NTRK fusion and four patients had a ROS1 fusion, however efficacy was not a per-protocol outcome.

Pharmacology

Pharmacokinetics and clinical pharmacology

Bioavailability

Absolute oral bioavailability of entrectinib has not been determined. The human mass balance study suggested oral bioavailability is more than 50%.

Marketed versus clinical trial formulations: The proposed market formulation is F06, and the formulation predominantly used in the clinical trials was F2A. F06 and F2A were shown to be bioequivalent in Study RXDX-101-15 under fasting conditions with geometric mean ratios (GMR) and 90% confidence interval (CI) within 80% to 125%:

- F06/F2A GMR (90% CI) of maximum concentration (C_{max}) = 0.933 (0.883, 0.986)

- F06/F2A GMR (90% CI) of area under the concentration time curve to infinity (AUC_{inf}) = 0.914 (0.854, 0.979)

Formulations and pH sensitivity: Entrectinib has pH dependent solubility: low gastric pH is necessary for good dissolution and absorption with fasted dosing. In the fed state, small intestinal bile salt solubilisation of entrectinib is increased, and gastric absorption plays a less dominant role in absorption, so changes in gastric pH (including due to PPI use) have less of an effect on overall absorption.

Food effect with F06 (market) formulation: In Study RXDX-101-15, food had no impact on entrectinib exposures when administered as F06: GMR and 90% CI bounds of fasted versus fed (following a high-fat, high-calorie meal) F06 administration were within 80% to 125%:

- Fed/fasted GMR (90% CI) of C_{max} = 1.06 (0.989, 1.15)
- Fed/fasted GMR (90% CI) of AUC_{inf} = 1.15 (1.07, 1.24)

Proton pump inhibitor co-administration with F06 (market) formulation: In Study RXDX-101-09, 600 mg F06 entrectinib was administered to fasted, healthy volunteers with or without lansoprazole (a PPI). The PPI decreased total exposure and maximum serum concentration by about a quarter:

- F06 (fasted):
  - With/without PPI GMR (90% CI) of C_{max} = 0.765 (0.676, 0.866)
  - With/without PPI GMR (90% CI) of AUC_{inf} = 0.745 (0.647, 0.859).

The population pharmacokinetics (PPK) model did not indicate an exposure-efficacy relationship at 600 mg daily dosing (see section '*Population pharmacokinetic and physiologically based pharmacokinetic modelling*', below), so a 25% change in systemic exposure is not considered clinically meaningful.

The effect of PPI administration under fed conditions was not evaluated for F06, but was assessed with the F2A formulation at 800 mg in Study CA14707.

There was no significant change of exposure with versus without PPI administration in the fed dosing state:

- F2A (fed)
  - With/without PPI GMR (90% CI) of C_{max} = 0.884 (0.741, 1.06)
  - With/without PPI GMR (90% CI) of AUC_{inf} = 1.16 (0.901, 1.48).

Absorption

Entrectinib is detectable in plasma 0.5 hours after oral dosing. Median time of maximum concentration in serum T_{max} after oral administration of 600 mg entrectinib is 4 hours (range 4 to 6 hours).

Distribution

The estimated apparent volume of distribution was 551 L for entrectinib and 81 L for M5 (the desmethyl metabolite, which is the only active metabolite, and has similar *in vitro* potency as entrectinib against the TRK A/B/C and ROS kinases).

Plasma protein binding of both entrectinib and M5 is over 99% *in vitro*. The *in vitro* blood-to-plasma ratio was 1.3 for parent entrectinib and 1.0 for M5.

In vitro data indicate that parent entrectinib is not a substrate of P-gp, breast cancer resistance protein (BCRP),organic anion transporter family member 1B1 (OATP1B1), or organic anion transporter family member 1B3 (OATP1B3), although M5 is a substrate of P-gp and BCRP. Broad tissue penetration was demonstrated in animal models. After a

single intravenous (IV) infusion in rats, brain to plasma concentration ratios were around 0.6, and when treated with 400 mg/kg entrectinib daily for 2 weeks, reached over 2. In a month long study in dogs, distribution to brain was approximately equal to plasma. Dose-dependent anti-tumour activity was also demonstrated in an intracranial mouse implantation model, suggesting blood brain barrier penetration and intracranial activity.

Steady state exposure in adult patients: Dose proportional increases were seen in both C_{max} and AUC after repeat dosing across the dose range of 200 mg to 800 mg in the STARTRK-1 trial. Steady state in plasma was reached within a week for entrectinib and by Day 15 for M5. Between-subject variability was moderate to high. Exposure to entrectinib in STARTRK-1 and STARTRK-2 trials is summarised in Table 4 and Table 5, respectively.

Table 5: Steady-state pharmacokinetics in adults with solid tumours in STARTRK-1 trial (at the proposed dosage, using F2A formulation given under fed conditions)

Time	PK parameters	Geometric mean (coefficient of variation (CV)%)	
		Entrectinib	M5
Cycle 1 Day 14 (n = 12)	C_{max} (nM)	3130 (80%)	1250 (90%)
	AUC_{0-24} (nM*h)	48000 (77%)	24000 (97%)
Cycle 1 Day 28 (n = 8)	C_{max} (nM)	2660 (64%)	703 (83%)
	AUC_{0-24} (nM*h)	72800 (42%)	24600 (46%)

AUC_{0-24}: Area under the plasma concentration time curve during 24 hours.

Source: reproduced from the FDA multidisciplinary review.[14]

Table 6: Pharmacokinetics in adults (n = 203) with solid tumours in the STARTRK-2 trial (at the proposed dosage, using predominantly the F2A formulation given under fed conditions)[14]

Time	PK parameters	Geometric mean (CV%)	
		Entrectinib	M5
Day 1	C_{max} (nM)	1590 (50%)	545 (82%)
	AUC_{0-24} (nM*h)	2700 (47%)	9590 (79%)
Steady-state	C_{max} (nM)	2860 (47%)	995 (72%)
	AUC_{0-24} (nM*h)	51700 (48%)	19000 (71%)

Source: reproduced from the FDA multidisciplinary review.[14]

Steady state exposure in paediatric patients

PK data from the STARTRK-NG trial indicates that steady state exposures with a paediatric dose of 400 mg/m^2 (F1 formulation) daily are at the lower end of steady state exposures observed in adults with 600 mg (F2A) daily, and that steady state exposures with a paediatric dose of 550 mg/m^2 (F1) formulation are generally higher than the median exposure observed in adults. Paediatric PK data also indicates large inter-subject variability.

Metabolism

In vitro, the majority (90%) of entrectinib metabolism is mediated by CYP3A4, with a smaller fraction attributable to UDP-glucuronosyltransferase 1-4 (UGT1A4). The main metabolites *in vivo* were formed by oxidation, N-demethylation and N-glucuronidation.

M5 formation and degradation appear to both be mediated by CYP3A4. M5 is clinically relevant with a metabolite-to-parent ratio of 0.41 (by AUC) at steady state in patients: at 24 hours after a (radiolabelled) oral dose, parent entrectinib, M5 and the glucuronide metabolite M11 comprised about 70%, 12% and 19% of the plasma exposure, respectively.

In the Phase II STARTRK-2 trial, at the recommended dose of 600 mg daily, the geometric mean (CV %) accumulation ratio of entrectinib exposure was 1.87 (20%) for entrectinib and 1.97 (21%) for M5.

Excretion

The mean total radiolabelled material excreted during 13 days after a single 600 mg oral enterctinib dose was 86% (range 72% to 91%) of the administered radioactive dose: 3% was urinary and 83% faecal. Parent entrectinib (36%) and M5 (22%) accounted for the largest fractions of radiolabelled excreta.

Blood and plasma radioactivity profiles were consistent with a two compartment model with a rapid redistribution phase. PPK analysis estimated:

- Geometric mean clearance = 19.6 L/hour (entrectinib) and 52.4 L/hour (M5) (for a 70 kg patient)
- Geometric mean (CV %) terminal elimination half-life was approximately 19 hours (17%) for entrectinib and 44 hours (16%) for M5.

Comparability between patients and healthy volunteers

Data from Study RXDX-101-07 and the STARTRK-1 trial (both conducted with F2A and dosed under fed conditions) indicates that the PK of entrectinib and M5 are comparable between patients and healthy volunteers. The variability of exposure parameters (C_{max} and AUC_{0-24} for both entrectinib and M5) was higher for patients than for healthy adults (CV of 48 to 82% and 25 to 29%, respectively).

Drug-drug interactions

Table 7: Findings of dedicated drug-drug interaction studies

Study	Findings	
RXDX-101-12 (itraconazole and rifampin, in healthy volunteers)	Entrectinib exposure (single 600 mg oral dose) was increased by co-administration of a potent CYP3A inhibitor (itraconazole 200 mg orally daily for 10 days): • C_{max} ratio: 1.73 (90% CI: 1.37, 2.18) • AUC_{inf} ratio: 6.04 (90% CI: 4.54, 8.04) M5 exposure was also increased	Entrectinib exposure (single 600 mg oral dose) was decreased by co-administration of a potent CYP3A inducer (rifampin 600 mg orally daily for 16 days): • C_{max} ratio: 0.44 (90% CI: 0.35, 0.56) • AUC_{inf} ratio: 0.23 (90% CI 0.18, 0.30) M5 exposure was also decreased
RXDX-101-13 (digoxin, in healthy volunteers)	*In vitro* transporter studies suggested a potential inhibitory effect of entrectinib and M5 on P-gp, BCRP, OATP1B1, and MATE1.	

Study	Findings
	In healthy volunteers, digoxin exposure (single 0.5 mg oral dose) was increased by co-administration of entrectinib (single 600 mg oral dose): • T_{max} was delayed by around 1 hour • C_{max} ratio: 1.28 (90% CI: 0.98, 1.67) • AUC_{inf} ratio: 1.18 (90% CI: 1.06, 1.32) These data indicate a weak effect of entrectinib and M5 on P-gp, and are reported in the FDA label.
RXDX-101-14 (midazolam, in patients)	*In vitro*, entrectinib and M5 showed the potential to inhibit CYP3A4/5, CYP2D6, and CYP2C8/9 and entrectinib showed the potential to inhibit CYP3A4. In patients with solid tumours: • Multiple daily doses (but not a single dose) of 600 mg entrectinib increased exposure to midazolam by 50%. • Multiple daily doses and a single dose of 600 mg entrectinib decreased C_{max} of midazolam by 21% and 34%, respectively. • Induction of CYP3A4 by entrectinib was not apparent.

Dose selection

In the STARTRK-1 trial, using the F2A formulation, there were no DLT reported at the 100 mg/m^2, 200 mg/m^2 and 400 mg/m^2 dose levels. At the 800 mg dose level, two patients reported DLT: Grade 3 fatigue and Grade 3 disturbance in attention. The MTD was therefore 600 mg entrecinib F2A formulation administered once daily under fed conditions, and this was declared the RP2D. This was the only dose studied in STARTRK-2.

For the STARTRK-NG trial, 250 mg/m^2 was selected as the starting dose for escalation based on being about 60% of the adult RP2D and PBPK modelling.

In the STARTRK-NG trial, four (25.0%) patients reported DLTs: one (14.3%) at the 550 mg/m^2 dose level and three (100%) at the 750 mg/m^2 dose level. The RP2D was therefore determined to be 550 mg/m^2.

Population pharmacokinetic and physiologically based pharmacokinetic modelling

Study 1091319 (population pharmacokinetics): population pharmacokinetics modelling in NONMEM;[18]

Study 1091319 included plasma concentration time data from the STARTRK-1, STARTRK-2 and STARTRK-NG trials.

The modelling software, techniques, selection criteria and validation method were appropriate. Entrectinib conformed to a one-compartment model with first order elimination. Clearance and volume of distribution were allometrically scaled with exponents of 0.75 and 1.0, respectively. No clinically significant covariates were identified, although there was a covariate effect for the F1 formulation on bioavailability.

The effect of hepatic function was not explored and the sample size was limited for many covariates. The model did not include a maturation function (limiting ability to estimate doses in infants and young children) and did not account for ontogeny of CYP3A4.

[18] NONMEM is a software package for population pharmacokinetic modelling.

The M5 component of the model was limited, but suitable for simulating plasma concentration time curves for M5 with the 600 mg dose and deriving secondary exposure parameters.

The exposure response analyses were plausible and did not indicate an exposure response relationship for efficacy at the proposed dosage. The risk of serious and higher Grade (3+) adverse events appears to be correlated with increasing exposure, particularly with patients who received high exposure with daily doses of about 800 mg or higher.

The data was not able to support a concentration QT analysis.

There were limited PK data from Study RXDX-101-03 (conducted in children and adolescents) and these data indicated dose proportionality.

Study 1091111 (physiologically-based pharmacokinetics): physiologically based absorption modelling in GastroPlus

This study included plasma concentration time data from:

- Study RXDX-101-05 for a formulation with acidulant in the fasted state
- Study RXDX-101-08 for a 600 mg dose in the fasted and fed states.
- Study RXDX-101-09 for a 600 mg F06 dose with PPI
- Study CA14707 for 800 mg F2A in the fasted and fed states with and without PPI
- Study CA14707 for the F1 formulation (without acidulant) with PPI, fasted and fed
- Study RXDX-101-12 for itraconazole effect
- Study RXDX-101-03 for paediatric patients aged 4 to 20 years

The recommended paediatric dose regimen based on the simulation in this study was 300 mg/m^2 for children weighing 15 kg or more.

The simulations are plausible and analysis was conducted according to best practice and using all the available data. They therefore represent the best available prediction for dose in patients below 4 years of age. However, the reliance of the simulation on untested assumptions means the predictions alone are not sufficient to support dosing in this population, and require confirmation in a clinical study.

Study 1091399 (physiologically-based pharmacokinetics): physiologically based CYP3A4 modelling in Simcyp and paediatric dose recommendation

The SimCyp model was developed following the GastroPlus analysis (Study 1091111) and utilised *in vitro* data, in addition to data from the following clinical studies:

- Study RXDX-101-12 (itraconazole and rifampin DDI) in healthy volunteers
- Study RXDX-101-14 (midazolam DDI) in solid tumour patients
- Study RXDX-101-04 in healthy volunteers
- Study RXDX-101-01 (open-label Phase I/Ib, F2A formulation part) in patients
- Study RXDX-101-02 (open-label Global Phase II, F2A formulation) in patients
- Study RXDX-101-03 (open-label Phase I/Ib) in children and adolescents with solid tumours

No clinically significant effect of entrectinib on ethinylestradiol is predicted, with a modelled AUC ratio of 1.13 and C_{max} ratio of 1.12. The simulated effect of moderate CYP3A4 inhibitors (erythromycin) on entrectinib is to increase AUC around 3 fold, with a C_{max} ratio of 1.77. The predictions for DDI with moderate CYP3A4 inhibitors and on the oral contraceptive pill are plausible and well supported.

The recommended paediatric dose regimen based on the simulation in this study was 300 mg/m^2 for children aged 6 months to 4 years; 250 mg/m^2 for children aged 1 to 6 months); and 150 mg/ m^2 for children aged from 0 to 1 months. The predictions for dosing for patients below 4 years of age are based on the best available evidence but require clinical trial confirmation with observed data from the age group.

Paediatric dosing and population pharmacokinetics

The TGA population pharmacokinetics working group (PPK-WG) reviewed the PPK and PBPK modelling submitted by the sponsor, as well as the modelling performed by the FDA, as described in the FDA review document.[14]

Sponsor modelling: The sponsor simulated dose regimens for paediatric patients in Study 1091319 (PPK) and Study 1091399 (PBPK), and made dosing recommendations of 300 mg/m^2 based on the former. Further PBPK simulations led the sponsor to develop the fixed dosing strategy outlined in Table 7, which has not been tested in a clinical study. Paediatric patients treated in the STARTRK-NG trial (see section, safety, Study RXDX-101-03/CO40778 (STARTRK-NG trial) description) were treated at initial doses of 250 mg/m^2 (n = 3), 400 mg/m^2 (n = 3), 550 mg/m^2 (n = 7), or 750 mg/m^2 (n = 3).

Table 8: Body surface area based dosing categories proposed by the sponsor

Category	BSA (m2)	Starting dose	1st dose reduction	2nd dose reduction
I	0.43-0.50	100 mg QD	100 mg, once/day for 5 days each week*	100 mg, once/day for 3 days each week**
II	0.51-0.80	200 mg QD	200 mg, once/day for 5 days each week*	**100 mg, once/day for 5 days each week***
III	0.81-1.10	300 mg QD	200 mg QD	100 mg QD
IV	1.11-1.50	400 mg QD	300 mg QD	**200 mg, once/day for 5 days each week***
V	≥1.51	600 mg QD	400 mg QD	200 mg QD

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

The proposed PI contains very similar dosing recommendations, with the second dose reduction for category III amended to match that for category II, and for category IV amended to match category V.

United States Food and Drug Administration modelling: The FDA conducted their own independent PPK modelling, and on the basis of that, recommended:[14]

- For paediatric patients age 12 years and older (adolescents)
  - 600 mg once a day (QD) for patients with BSA > 1.50 m^2
  - 500 mg QD for patients with BSA between 1.11 and 1.50 m^2
  - 400 mg QD for patients with BSA between 0.91 and 1.10 m^2
- For paediatric patients aged under 12 years
  - 'there are insufficient data available to determine a dose with the to-be-marketed formulation that can achieve comparable exposure to adults at the recommended dose of 600 mg QD.'

The FDA report;[14] describes results from two modelling scenarios: one in which the power coefficient of weight effect on clearance was estimated (scenario 1) and a second that used the assumption of allometric scaling, where the power coefficient of weight on clearance was fixed to 0.75 (scenario 2). The model under scenario 2 predicted exposures that were 20% and 30% higher for adolescents with BSAs between 1.11 and 1.50 m^2 or 0.91 and 1.10 m^2, respectively, than the exposures actually observed for adults at those BSAs (see Table 8). Based on this data, they determined that the model based on allometric scaling

assumptions (for example using the fixed power co-efficient of 0.75) was likely to overestimate exposure for those BSA categories.

Table 9: Predicted pharmacokinetic exposure in paediatric patients 12 years and older (population pharmacokinetics)

Simulation Scenario	Exposure [nM]	WT on CL	Adults[1] (>= 18 yrs)	Adolescents[1] (>=12-<18 yrs & BSA>= 1.5 m²)	Adolescents[1] (>=12-<18 yrs & 1.1<=BSA< 1.5 m²)	Adolescents[1] (>=12-<18 yrs & BSA< 1.1 m²)	RD[2]	RD[3]	RD[4]
1	Cavg	0.31	2254	2336.5	2188.9	1959.9	3.7	-2.9	-13
1	Cmax	0.31	2945.1	3087.7	3035	2912	4.8	3.1	-1.1
1	Cmin	0.31	1556.4	1584.1	1357.4	1064.4	1.8	-12.8	-31.6
2	Cavg	0.75	2123.4	2318.9	2621.4	2769.5	9.2	23.5	30.4
2	Cmax	0.75	2759.8	3047.6	3535.9	3933.3	10.4	28.1	42.5
2	Cmin	0.75	1448.3	1552.6	1671	1614	7.2	15.4	11.4

Note1: Geometric mean based on simulated exposure in 300 virtual adolescent and 300 adult patients with 10 replicates.
Adults (N=300, BSA median (range): 1.88 (1.30-3.00));
Adolescents >=12-<18 yrs & BSA>= 1.5 m² (N=226, BSA median (range): 1.73 (1.51-2.70));
Adolescents >=12-<18 yrs & 1.1<=BSA< 1.5 m² (N=67, BSA median (range): 1.40 (1.15-1.50));
Adolescents >=12-<18 yrs & BSA< 1.1 m² (N=7, BSA median (range): 1.08 (1.04-1.10));

Note2: Relative difference in geometric mean between entrectinib exposure in adolescents with BSA of at least 1.5m² compared to adults
Note3: Relative difference in geometric mean between entrectinib exposure in adolescents with BSA between 1.1 and 1.5m² compared to adults
Note4: Relative difference in geometric mean between entrectinib exposure in adolescents with BSA less than 1.1m² compared to adults
Source: Reviewer's Analysis based on "poppk.xpt"

Extracted from FDA report.[14]

Regarding dosing in patients under 12 years old, the FDA notes:

> '…while the assumption of allometric scaling is, in general, reasonable for pediatric patients less than 12 years of age, this assumption is not supported by the observed PK data of entrectinib in adult patients and additional data will be required to determine a reasonably safe and effective dose in these younger pediatric patients.'

TGA PPK working group advice: Allometric scaling using the fixed exponent of 0.75 may not be adequate to determine dosing for young children due to the rapid maturational changes that take place in organ systems affecting drug disposition during childhood. Exponents in neonates based on propofol databases, for example, are between 1 and 2. The other option is to incorporate a maturation function between 0 to 2 years to account for maturation while maintaining allometry in the model.

Given the mechanism of metabolism of entrectinib (predominantly through CYP3A4), it is expected that this compound should follow the rules of allometry quite closely (such as a compound like fentanyl or propofol). That a co-efficient of 0.31 rather than 0.75 reasonably describes the data at hand could indicate a lack of sufficient range of weight and age data to estimate the allometric scale appropriately. Of concern is that estimating the allometric scale, while describing the data well – limits the validity of extrapolation to patients outside the age or weight range of the studied population. Given that there is not sufficient data to discern whether a 0.75 exponent is appropriate, nor to confirm what the appropriate model is, it is necessary to conclude that there is insufficient data in the under 12 years age group to allow a recommendation for dosing.

Dose modelling is supportable for the adolescent age group, as renal capacity and hepatic enzyme expression approach adult levels from around age 12. The BSA based dosing approach as per the FDA approval is preferred to the sponsor's proposed BSA based dosing, as it provides a smoother dose adjustment across BSA categories.

Pharmacology-related conclusions

The main clinical pharmacology-related recommendations supported by the dossier are:

- Bioequivalence in adults was demonstrated between the primary clinical trial formulation (F2A) and the market intended formulation (F06) in Study RXDX-101-15.
- The recommended dosage in adults is 600 mg daily, with or without food.
- Dosing in adolescent patients (between the ages of 12 and 18) is able to be supported, based on PPK modelling. The BSA based dosing approach approved by the FDA is supported by the TGA's PPK working group.
- Because of a paucity of suitable paediatric data and the failure of allometric scaling using a fixed exponent of 0.75 to adequately predict observed exposure in adult and adolescent patients, a safe and effective dose can't be established for paediatric patients under the age of 12.
- No dose adjustment is required in mild hepatic impairment:
    - the effect of moderate or severe hepatic impairment on entrectinib PK is unknown. A post-market requirement of marketing approval for the US sponsor of entrectinib is that a study be conducted to clarify this.
- No dose adjustment is required in mild or moderate renal impairment:
    - the effect of severe renal impairment on entrectinib PK is unknown, but not predicted to be clinically significant as entrectinib shows minimal renal clearance.
- Avoid concomitant use with strong and moderate CYP3A4 inducers.
- If concomitant use with strong or moderate CYP3A4 inhibitors can't be avoided, reduce adult entrectinib dose to 100 mg daily (strong inhibitors) or 200 mg daily (moderate inhibitors), respectively.

Efficacy

Clinical studies that contributed efficacy data

Of the studies described only the ALKA trial, STARTRK-1 trial and STARTRK-2 trial contributed data to the main efficacy analyses for the two submitted indications.

Study ALKA-372-001/GO40783 (ALKA trial)

Table 10: Study ALKA-372-001/GO40783 (ALKA trial) description

Study description	
Population (enrolled = 58)	Phase I, first-in-human, open label, dose escalation (3 + 3 design) in adults with NTRK1/2/3, ROS1 or ALK + adv/met solid tumours. Inclusion criteria (abridged): • Histo/cytologically confirmed diagnosis of solid cancer with TRKA, TRKB, TRKC, ROS1, or ALK genetic alterations, with no acceptable therapeutic options • Tissue for analysis available • Prior therapy was allowed except therapies targeted against the genetic alteration present • CNS involvement ok if controlled/asymptomatic

Study description	
	• ECOG;[19] no worse than 2, life expectancy at least 3 months Exclusion criteria (abridged): • Standard (significant medical/surgical illnesses, inadequate organ function, reproductive status) • Elevated QT risk;[14] • Interstitial lung disease Location: 2 sites in Italy Commenced 2012. Data cut-off for interim report 31 May 2018.
Intervention	Formulation: F1 Dose range: 100 to 1600 mg/day Dose schedules (cycle = 28 days): • Schedule A: 4 days on, 3 days off schedule for 3 weeks, followed by a 7 day rest period in a 4 week cycle; fasted condition; once or twice daily dosing. Starting dose 100 mg/m^2/day • Schedule B: continuous daily dosing in a 4 week cycle; fed condition; once or twice daily dosing. Starting dose 200 mg/m^2/day • Schedule C: 4 days on, 3 days off schedule in a 4 week cycle; fed condition; once or twice daily dosing. Starting dose 400 mg/m^2/day
Endpoints	Primary: • To determine the MTD and DLT Secondary: • To define the safety profile of entrectinib • To evaluate the PK of entrectinib in plasma • To document any antitumour activity of entrectinib (by imaging) • Up to 5 target lesions per patient identified by imaging at start of study and end of last cycle. Analysis populations: • PK (n = 57), Safety (n = 57)

[19] **ECOG Performance Status:** The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work

2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

5 – Dead

Study description	
	• Number of patients included in Primary Analysis Set for the NTRK indication = 1 • Number of patients included in Primary Analysis Set for the ROS1 indication = 9

Study RXDX-101-01/GO40784 (STARTRK-1 trial)

Table 11: Study RXDX-101-01/GO40784 (STARTRK-1 trial) description

Study description	
Population (enrolled = 76)	Phase I, open label, dose escalation (3 + 3 design) and dose expansion study in adults with relapsed or refractory adv/met solid tumours, including tumours with NTRK1/2/3, ROS1 or ALK molecular alteration. The Delegate notes that the submitted report states: 'At least 15 patients were anticipated to enroll into the dose escalation segment of the study. The actual number of patients enrolled was 76. As of the enrollment cutoff of 30 November 2017, no patients were enrolled in the ongoing dose expansion segment. Presumably patients who at the time of STARTRK-1 trial design were envisioned to continue in the dose expansion segment were instead enrolled in STARTRK-2.' Inclusion criteria (abridged): • Histo/cytologically confirmed diagnosis of solid cancer, with no acceptable therapeutic options • NTRK1/2/3, ROS1 or ALK gene rearrangement required (dose expansion segment only; preferred but not required for dose escalation segment), predicted to result in a functional kinase, with no concomitant other driver mutation (for example EGFR or KRAS) • Measurable disease by local assessment per RECIST;[18]v1.1 • Tissue for analysis if clinically feasible (dose expansion only) • Prior therapy was allowed including crizotinib and ceritinib and investigational drugs • CNS involvement ok if controlled/asymptomatic • ECOG no worse than 2, life expectancy at least 3 months Exclusion criteria (abridged): • Prior entrectinib • Standard (significant medical/surgical illnesses, inadequate organ function, reproductive status) • Elevated QT risk • Peripheral neuropathy Grade 2 or higher • Interstitial lung disease • Recruitment for a particular molecular alteration would be stopped if no responses were seen after 6 enrolled patients Location: 11 sites in the US, Spain and South Korea Ongoing. Commenced July 2014. Data cut-off for interim report 31 May 2018.

Study description	
Intervention	Formulations: F1 and F2A Dose range: 100 to 800 mg/day Cycle = 28 days Dose schedule: • Dose escalation segment: commenced at 100 mg/m^2, with dose escalations of 100% until MTD was reached • Dose expansion segment: A flat dose would be chosen derived from the BSA-based RP2D, and this flat dose was administered to a further cohort of patients.
Endpoints	Primary endpoints: • Dose escalation segment: DLT, MTD, R2PD • Dose expansion segment: efficacy (ORR) Secondary endpoints: • Dose escalation segment o Safety and tolerability of entrectinib o PK of entrectinib in plasma o Efficacy: ORR, clinical benefit rate (CBR), duration of response (DOR), progression-free survival (PFS), overall survival (OS). o Pharmacodynamics (PD) • Dose expansion segment o Efficacy: CBR, DOR, PFS, OS o Intracranial response;[20] o PK o PD o Safety Measurement of efficacy: • Assessed using RECIST;**Error! Bookmark not defined.** v1.1 • Thorax, abdomen and brain imaging was done at Baseline, end of cycle 1, then every 2 subsequent cycles • Blinded central review was undertaken Analysis populations: • PK (n = 74), safety (n = 76) • Number of patients included in Primary Analysis Set for the NTRK indication = 3 (1 excluded due to having a CNS primary) • Number of patients included in Primary Analysis Set for the ROS1 indication = 7

[20] By blinded central review, using Radiographic Assessment in Neurooncology (RANO) or Radiographic Assessment in Neuro-oncology-Brain Metastases (RANO-BM), as applicable.

Study RXDX-101-02/GO40782 (STARTRK-2 trial)

Table 12: Study RXDX-101-02/GO40782 (STARTRK-2 trial) description

Study description	
Population (enrolled = 207)	Phase II, open label, basket study in adults with NTRK1/2/3, ROS1 or ALK+ adv/met solid tumours excluding ALK+NSCLC, with a ventricular repolarisation sub-study. Inclusion criteria (abridged): • Histo/cytologically confirmed diagnosis of solid cancer, with NTRK1/2/3, ROS1 or ALK gene rearrangement predicted to result in a functional kinase, and with no concomitant other driver mutation (for example EGFR or KRAS) o Diagnostic testing for enrolment was 'as determined by Ignyta's CAP/CLIA laboratory or by any nucleic acid-based diagnostic testing method performed at a local CLIA-certified or equivalently-accredited diagnostic laboratory' § Where enrolled on local molecular testing, tissue for central confirmation at Igynta's lab was required o In the US only, haematology patients who fulfilled criteria otherwise could be enrolled on single-patient protocols • Measurable disease by local assessment per RECIST;**Error! Bookmark not defined.** v1.1 o If not, could be enrolled for non-efficacy endpoints ('non-evaluable for primary endpoint' cohort) • Prior therapy was allowed, but not targeted inhibitors for that molecular alteration (approved or investigational) o One exception: prior crizotinib was allowed for ALK or ROS1-rearranged tumours, if they presented with CNS only progression and stable extracranial disease. • CNS involvement ok if controlled/asymptomatic • ECOG;19 no worse than 2, life expectancy at least 4 weeks Exclusion criteria (abridged): • Prior entrectinib • Standard (significant medical/surgical illnesses, inadequate organ function, reproductive status) • Elevated QT risk • Peripheral neuropathy Grade 2 or higher • Previous interstitial lung disease other than radiation therapy linked Location: 84 sites in 15 countries (Australia, Belgium, France, Germany, Hong Kong, Italy, Japan, Korea, The Netherlands, Poland, Singapore, Spain, Taiwan, United Kingdom and the USA) Ongoing. Commenced November 2015. Data cut-off for interim report 31 May 2018.
Intervention	Formulation: F2A (4 patients got F1). Dose: 600 mg daily, in continuous cycles of 28 days Dose reductions or interruptions Crossover

Study description	
Endpoints	Primary: • ORR in each basket (defined by molecular alteration), by BICR using RECIST;**Error! Bookmark not defined.** v1.1, confirmed responses only (repeat imaging ≥4 weeks after initially documented) Secondary: • DOR, time to response (TTR), CBR • Intracranial response and CNS PFS in patients with measurable CNS disease at Baseline per RANO or RANO-BM • PFS and OS • To define the safety and tolerability • PK and PK-PD • To evaluate the effect of entrectinib on ventricular repolarisation (ECG/QT substudy) • Patient-reported outcomes (PRO): treatment-related symptoms and general health status Sensitivity analyses included analyses by investigator. The submitted interim clinical study report (CSR) only reports analysis of the primary and secondary objectives for NTRK 1/2/3 and ROS1-positive tumours (not ALK). Analysis populations: • Of the 207 patients enrolled, 206 received at least one dose of entrectinib: 63 in the NTRK basket, 105 in the ROS1 basket, and 38 in the 'other' basket. • PK (n = 203), safety (n = 206) • Number of patients included in Primary Analysis Set for the NTRK indication = 57 (excluded from the primary efficacy analysis were 5 patients with primary CNS tumours, as well as 1 patient with non-measurable disease at Baseline) • Number of patients included in Primary Analysis Set for the ROS1 indication = 35

ROS1 integrated efficacy analysis

Methodology

The integrated efficacy analysis for ROS1 that was submitted by the sponsor included data for the first consecutive 53 patients with ROS1 fusion positive solid tumours who were enrolled in ALKA, STARTRK-1 or STARTRK-2 trials, who had measurable disease by RECIST v1.1 criteria (per investigator);**Error! Bookmark not defined.** v1.1 and who had at least 12 months of follow-up from the time of first tumour response.

In the STARTRK-1 trial and ALKA trial (which contributed 16 patients to the ROS1 cohort), patients could only be enrolled for whom no alternative effective standard therapy was available or for whom standard therapy was considered unsuitable or intolerable.

A previous agreement with the FDA had been that the analysis should only include patients who were ROS1-inhibitor naïve, and two patients who had received prior crizotinib were included in the sponsor's analyses. The FDA removed these two patients from the analysis set, renaming it the 'Primary Analysis Set'. The Primary Analysis Set was further redefined as it was discovered two patients had less than 12 months' follow up from date of response. The final FDA-defined Primary Analysis Set;[14] therefore consisted of the first consecutive 51 patients with ROS1 fusion-positive solid tumours who were

enrolled in ALKA, STARTRK-1 or STARTRK-2 trial, who had measurable disease and at least 12 months of follow-up from the time of post-treatment tumour assessment.

Two further analysis sets were described in the integrated review. These were larger pooled populations, consisting of all patients from ALKA, STARTRK-1 or STARTRK-2 trial who had ROS1 fusion-positive NSCLC, regardless of duration of follow-up and with ECOG performance status of less than 2:

- Efficacy Analysis Set (n = 103):
  - Could have measurable or unmeasurable disease per investigator
  - ROS1 inhibitor-naïve (n = 101) or prior crizotinib (n = 2).
- Measurable Disease Set (n = 94):
  - Measurable disease per investigator
  - ROS1 inhibitor-naïve (n = 92) or prior crizotinib (n = 2).

The TGA assessment of benefit-risk focusses on the ROS1 Primary Analysis Set as defined by the FDA.[14]

Efficacy measures

The following efficacy measures contributed to the TGA risk-benefit analysis:

- Objective Response Rate:
  - The proportion of patients with confirmed complete response (CR) or partial response) per RECIST criteria (version 1 by blinded independent central review (BICR).**Error! Bookmark not defined.**
  - Non-responders included:
    - Response not confirmed
    - Missing baseline or post baseline tumour assessment
    - Discontinued for any reason prior to post-baseline response evaluation
- Duration of Response (DOR, in months) in responders:
  - Date of first objective response to first documentation of radiographic disease progression or death due to any cause, whichever was earlier.
  - If no death or progression: censored at last tumour assessment date prior to cut-off.
- Intracranial ORR (IC-ORR):
  - Confirmed ORR in patients with measurable CNS disease at Baseline, per RECIST version 1 criteria or RANO for primary CNS tumours, by BICR.
  - Reported for measurable and non-measurable disease.
- Intracranial DOR (IC-DOR, months) in intracranial responders
  - Date of first intracranial response to first documentation of radiographic CNS disease progression or date of death due to any cause, whichever was earlier.
  - If no death within 30 days of last dose, and no CNS disease progression censored at the last tumour assessment date prior to any date of subsequent anticancer therapy, including surgery or radiotherapy to the brain.

Descriptive analysis of results in patients with ROS1-positive NSCLC previously treated with crizotinib was also provided.

A number of other endpoints were included in the sponsor's analysis of efficacy (for both indications). Regarding these, the FDA noted:[14]

> 'Clinical Benefit Rate, which includes stable disease, is not an acceptable endpoint in a single arm study; this endpoint was not evaluated in this review.
>
> Time-to-event endpoints such as OS or PFS are not interpretable in a single-arm study; the results of PFS, OS and other time-to-event endpoints, with the exception of DOR and IC-DOR, were not evaluated in this review.
>
> There were very few patients who completed QLQ-CR29;[21] therefore, no results for QLQ-CR29 are presented in this review.
>
> Although the study protocol further defined the improvement or worsening of global QOL functioning domains and symptom domains based on 10-point change, there was no agreement on the clinically meaningful threshold (for example change of ≥ 10 point) for the symptom subscale score between FDA and Genentech.'

These endpoints did not contribute significantly to the risk-benefit analysis for either of the TGA submissions, and are not discussed further in this overview.

Statistical analysis plan

The statistical analysis plan (SAP) specified a final analysis after enrolment of about 50 patients with *ROS1* positive NSCLC, and that responding patients would have at least 12 months of efficacy follow-up. The sample size of 50 was chosen to provide 82% power to exclude 50% from the lower bound of a two-sided 95% CI, based on an assumed true ORR of 70%.

A response rate that excludes 50% or higher was stated to be considered clinically meaningful. Justification of the pre-specified threshold for clinical significance (50%) is not given by the sponsor but was agreed to in discussion with the FDA.

Consecutive enrolment was chosen to minimise selection bias.

Point estimates with 95% 2 sided CIs were reported, but formal significance testing was not performed and p-values not reported. Multiplicity was also not addressed, justified based on the rarity of the population and expectation of significant clinical benefit.

Enrolled ROS1 fusion-positive NSCLC population

Disposition: Death was the most common reason for study discontinuation (36%) and progressive disease was the most common reason for treatment discontinuation (77%), consistent with the studied indication.

Protocol deviations: Protocol deviations within the ROS1 Primary Analysis Set were reviewed, and were not likely to have altered the assessment of safety or efficacy in patients with ROS1-positive NSCLC.

Baseline characteristics: Baseline demographics, disease and treatment characteristics of the 51 patients in the ROS1 Primary Analysis Set are summarised in Table 9.

[21] The 29 question European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Colorectal Cancer (**EORTC QLQ-CR29**) is a patient-reported outcome measure to evaluate health-related quality of life among colorectal cancer patients in research and clinical practice.

Table 13: Baseline demographics and characteristics of the ROS1 Primary Analysis Set

Baseline characteristics	ROS1 Primary Analysis Set (n = 51)	Baseline characteristics	ROS1 Primary Analysis Set (n = 51)
Age, years		**Number of prior systemic therapies for this cancer**	
Median (min, max)	53 (27, 72)	0	7 (13.7%)
Age group, n		1 or 2	20 (39.2%)
≥ 65	10 (19.6%)	≥ 3	24 (47.1%)
< 65	41 (80.4%)	**Prior systemic therapy for metastatic disease**	
Gender, n		None	17 (33.3%)
Female	34 (66.7%)	Platinum-based chemotherapy*	34 (66.7%)
Male	17 (33.3%)	**Extent of disease at start of treatment**	
Race, n		Localised***	1 (2.0%)
Asian	19 (37.3%)	Local advanced	2 (03.9%)
Black or African American	3 (5.9%)	Metastatic disease	48 (94.1%)
White	29 (56.9%)	**Histology**	
Ethnicity		Adenocarcinoma	48 (94.1%)
Hispanic or Latino	2 (3.9%)	Others	3 (5.9%)
Not Hispanic or Latino	38 (74.5%)	**CNS measurable disease at Baseline (BICR)**	
Missing	9 (17.7%)	No	7 (13.7%)
Unknown or Not Reported	2 (3.9%)	Yes	12 (23.5%)
Region, n		**CNS metastases at Baseline (BICR)**	
North America	14 (28.3%)	No	32 (62.8%)
Europe	19 (35.9%)	Yes	19 (37.2%)

Baseline characteristics	ROS1 Primary Analysis Set (n = 51)	Baseline characteristics	ROS1 Primary Analysis Set (n = 51)
Hong Kong, Japan, Korean, Singapore, and Taiwan	18 (35.9%)	**CNS metastases at Baseline (INV)**	
ECOG performance status		No	29 (56.9%)
0	19 (37.2%)	Yes	22 (43.1%)
1	26 (51.0%)	**Any prior radiotherapy of the brain****	
2	6 (11.8%)	No	37 (72.6%)
Smoking status		Yes	14 (27.4%)
Never	29 (56.9%)		
Former/Current	22 (43.1%)		

Derived from FDA multidisciplinary review;[14] for the ROS1 indication.

*One patient started treatment with entrectinib within 6 months of completion of platinum-based neoadjuvant/adjuvant chemotherapy

**One patient who had prior radiotherapy of the brain was missing data for time from end of prior radiotherapy to first dose of entrectinib

*** The ROS1 summary of clinical efficacy in the dossier states that one patient in the Efficacy Evaluable Analysis Set, from the ALKA trial, had extent of disease 'localized'. This must have been referring to status at time of diagnosis, however, as the ALKA trial CSR states that all patients had metastatic (n = 55) or locally advanced (n = 2) disease at time of study entry.

Diagnostic testing in the ROS1-efficacy set

All patients included in the ROS1 Primary Analysis Set for ROS1 had a *ROS1* gene fusion that was predicted to translate into a fusion protein with a functional kinase domain (other mutations or evidence of second drivers such as EGFR alterations were not considered efficacy-evaluable).

ROS1 positivity for initial enrolment of the 51 patients included in the efficacy analysis was determined by:

- Next generation sequencing (NGS)[22] in 72% of patients (n = 36)
  - 53% by RNA-based NGS (n = 27)
  - 14% by DNA-based NGS (n = 7)
  - 4% by DNA and RNA-based NGS (n = 2)
- Fluorescence *in situ* hybridisation (FISH)[23] in 29% of patients (n = 15)

[22] Next generation sequencing (NGS), massively parallel or deep sequencing are related terms that describe a DNA sequencing technology.
[23] Fluorescence in situ hybridization (FISH) is a molecular cytogenetic technique that uses fluorescent probes that bind to only those parts of a nucleic acid sequence with a high degree of sequence complementarity.

ROS1 fusion was confirmed centrally, where possible, by the clinical trial assay (Pharos Trailblaze).[24] Out of the 53 patients in the ROS1 Primary Analysis Set, 30 patients (59%) had a Pharos result available, and overall 39 (76%) had either prospective or central, retrospective laboratory confirmation of *ROS1* positivity using an analytically validated NGS test.

No tissue is available for retesting.

Table 14: Diagnostic testing in the ROS1 primary analysis set

Trial	Patient (n)	Test type	Fusion partner	Concomitant oncodriver assessed (Y/N)	Tissue available for re-testing
ALKA	9	FISH*	UNK	N	N
STARTRK-1	6	FISH	UNK	N	N
	1	NGS	*CD74-ROS1*	N	N
STARTRK-2	18	NGS	*CD74-ROS1*	N in 11 Y in 7	N
	5	NGS	*SDC4-ROS1*	N	N
	2	NGS	*TPM3- ROS1*	N in 1 Y in 1	N
	7	NGS	*SLC34A2-ROS1*	N	N
	3	NGS	*EZR-ROS1*	N	N

* Re-testing with RNA-based NGS identified fusion partners in three of these patients: SDC4-ROS1, CD74-ROS1 and EZR-ROS1.

Results in patient with ROS fusion-positive non-small cell lung cancer

Objective response rate and duration of response: The results of FDA's analyses of ORR and DOR according to blinded independent central review (BICR) for the ROS1 Primary Analysis Set (as defined above) are summarised in Table 11. The cut-off date for final analysis was 31 May 2018 for ORR and 31 October 2018 for DOR, as the latter incorporated updated data sent to FDA by the sponsor during their review.

[24] The Trailblaze Pharos assay for NTRK1/2/3, ROS1, and ALK gene rearrangements is a next-generation sequencing (NGS) based assay for the qualitative detection of fusions in the NTRK1/2/3, ROS1, or ALK genes in the RNA from formalin-fixed paraffin-embedded (FFPE) human solid tumor tissue. The assay is intended to be used as an aid in selecting patients, including those who are treatment-naïve, with solid tumors that harbor a gene rearrangement in NTRK1/2/3, ROS1, or ALK, for whom enrollment in the STARTRK-2 study may be appropriate. A laboratory developed test (LDT) version of the Trailblaze Pharos assay was previously used to identify non-treatment-naïve patients with NTRK1/2/3, ROS1, or ALK gene rearrangements who might be eligible for the STARTRK-2 study.

Table 15: Efficacy analysis in the ROS1 Primary Analysis Set, per RECIST;Error! Bookmark not defined. **v1.1 by blinded independent central review**

Objective Response Rate (ORR)	Entrectinib (n = 51)	
Responders, n	40	
CR	3 (5.9%)	
PR	37 (72.5%)	
ORR (95%CI)	78.4% (64.7%, 88.7%)	
Date of data cut off	*31 May 2018*	*31 October 2018*
Median DOR in months (95% CI)*	15.7 (9.5, 34.8)	15.7 (11.4, 34.8)
DOR ≥ 6 months**, n (%)	30 (75.0)	30 (75.0)
DOR ≥ 9 months**, n (%)	27 (67.5)	28 (70.0)
DOR ≥ 12 months**, n (%)	17 (42.5)	22 (55.0)
DOR ≥ 18 months**, n (%)	7 (17.5)	12 (30.0)

*Kaplan-Meier estimate. Among the 40 responders, 21 events (17 disease progression and 4 deaths) had occurred at the time of data cut-off on 31 October 2018

**Observed DOR

Source: efficacy analysis from the FDA multidisciplinary review.[14]

The FDA conducted sensitivity analyses in the Efficacy Analysis Set and Measurable Disease Set.[14] The results in these populations were consistent with the findings in the Primary Analysis Set for ORR and DOR.

The FDA review;[14] also performed a number of subgroup analyses based on demographics and some other baseline characteristics: ECOG performance status, smoking status, prior number of systemic therapies, and receipt of prior platinum-based chemotherapy. Sample sizes were small, but no outlier subgroups were identified.

Of 7 patients with *ROS1* fusion-positive NSCLC who have never had previous systemic therapy, all 7 responded.

Gene fusion partner subgroups showed responses in all categories, including 10 responses in 12 patients with unknown *ROS1* gene fusion partner.

Intracranial responses: The interpretation of intracranial response data is limited due to the small sample size. Of 19 patients who had CNS disease at Baseline, 12 had measurable disease. Of the 12 who had measurable disease, 5 had received radiation to the brain within 2 months of their first dose of entrectinib, and an effect on CNS response cannot be ruled out. In the remaining 7 patients with *ROS1* fusion-positive NSCLC who had measurable CNS disease at Baseline per BICR and had not received brain radiation within two months of first entrectinib dose, there were 5 confirmed responses.

Of the 12 patients with *ROS1* fusion-positive NSCLC who had measurable CNS disease at Baseline, regardless of proximity of brain radiotherapy to entrectinib therapy, 9 had intracranial responses. A third of these had lasted at least a year, and the remaining two thirds had lasted at least 6 months, by the data cut-off date.

Efficacy in patients who had previously received crizotinib: Very limited entrectinib activity was seen in 27 ROS1-positive NSCLC patients treated across the STARTRK-1 (n = 9) and STARTRK-2 trials (n = 18) who had previously received crizotinib, and were excluded from the formal efficacy populations. Three responses were seen in this group (2 responses out of 19 patients who had CNS only progression and 1 response out of 8 patients who had overall systemic progression.

Neurotrophic tropomyosin receptor kinase integrated efficacy analysis

Methodology

The integrated efficacy analysis for *NTRK* that was submitted by the sponsor included data for the first consecutive 54 patients with extracranial *NTRK* fusion-positive solid tumours who were enrolled in the ALKA, STARTRK-1 or STARTRK-2 trials who had not previously been treated with a TRK inhibitor, who had measurable disease by RECIST;**Error! Bookmark not defined.** v1.1 per investigator, and who had at least 6 months of follow-up from the time of first dose of entrectinib (Table 13, Table 14, Table 15 and Table 17).

Patients with an additional 'oncodriver' mutation, for example one likely to confer a mechanism of resistance (such as concurrent *EGFR* or *KRAS* mutation), were not considered efficacy-evaluable for the integrated analysis.

In the STARTRK-1 and ALKA trials (which contributed 3 patients to the NTRK cohort), patients could only be enrolled for whom no alternative effective standard therapy was available or for whom standard therapy was considered unsuitable or intolerable. In the STARTRK-2 trial, this was not stated to be an inclusion criterion but is implicit in enrolment in a single-arm clinical trial. As part of their review, the FDA evaluated additional information they requested from the sponsor to confirm patients were all 'last-line':[14]

> '… additional justification to show that patients who enrolled in the entrectinib trials prior to receipt of systemic chemotherapy for metastatic or unresectable disease had no standard available therapy or satisfactory treatment options.'

There were 68 patients with *NTRK* fusion-positive cancers enrolled across the studies, and they all had at least 6 months follow-up available. However, seven were excluded from the NTRK Efficacy Population due to not meeting eligibility criteria ('non-evaluable cohort') for the following reasons:

- Received prior TRK inhibitor (n = 1)
- ECOG PS > 2 (n = 1)
- NTRK biomarker ineligibility (n = 3) (see section below, diagnostic testing in the NTRK efficacy set)
- Co-morbid conditions (n = 2):
  - Pericardial effusion
  - Peripheral neuropathy Grade > 2

A further 7 patients who were included in the NTRK Efficacy Population were not included in the NTRK Efficacy *Evaluable* Population for the following reasons:

- Non-measurable disease (n = 1)
- CNS primary tumours (n = 6), which were assessed for response using RANO criteria, and efficacy was therefore described separately

The pivotal data supporting the use of entrectinib in paediatric patients with *NTRK* fusion positive tumours is the same as for the adult indication. Supporting, descriptive data is available from the paediatric study, STARTRK-NG trial.

In addition to the main efficacy analysis in the NTRK Efficacy Evaluable Population, efficacy was assessed in the subsets of that population who had CNS metastases at Baseline per investigator (the CNS Metastases Analysis Set, n = 12), and those who did not (the No CNS Metastases Analysis Set, n = 42).

Efficacy measures

The main efficacy measures that contributed to the TGA risk-benefit analysis were the same for the NTRK indication as they were for the ROS1 indication:

- ORR
  - The proportion of patients with confirmed complete response (CR) or partial response (PR) by RECIST;**Error! Bookmark not defined.** v1.1
  - Non-responders included:
    - Response not confirmed
    - Missing baseline or post Baseline tumour assessment
    - Discontinued for any reason prior to post Baseline response evaluation
- Duration of Response (in months) in responders
  - Date of first objective response to first documentation of radiographic disease progression or death due to any cause, whichever was earlier.
  - If no death or progression: censored at last tumour assessment date prior to cut-off
- Intracranial ORR (IC-ORR)
  - Confirmed ORR in patients with CNS metastases at Baseline
  - Reported for measurable and non-measurable disease
- Intracranial DOR (IC-DOR, months) in intracranial responders
  - Date of first intracranial response to first documentation of radiographic CNS disease progression or date of death due to any cause, whichever was earlier.
  - If no death within 30 days of last dose, and no CNS disease progression censored at the last tumour assessment date prior to any date of subsequent anticancer therapy, including surgery or radiotherapy to the brain.

Results presented by histological subgroup were also considered.

As was the case for the ROS1+ NSCLC indication, due to the single arm nature of the data, a number of study endpoints were not considered to contribute robustly to the TGA benefit-risk consideration of the NTRK indication and are not further discussed herein (includes CBR, time-to-event endpoints and patient reported outcomes (PROs)).

Statistical analysis plan

A sample size of 56 was chosen to give a 95% CI with precision of ± 14% that would exclude 30% based on an assumed true ORR of 60%. This pre-specified threshold for clinical significance was agreed to by the FDA (page 158, multidisciplinary FDA review for NTRK indication;[14]), and was selected based on the sponsor's review of expected response rates to later lines of treatment in patients with *EGFR*/*ALK* negative NSCLC, colorectal cancer, breast including secretory breast cancer, salivary gland including mammary analogue secretory carcinoma (MASC), and soft tissue sarcoma.

Consecutive enrolment was chosen to minimise selection bias.

Point estimates with 95% 2 sided CIs were reported, but formal significance testing was not performed and p-values not reported. Multiplicity and subgroup effect loss due to

pooling of data were also not addressed, justified based on the rarity of the population and expectation of significant clinical benefit.

Enrolled neurotrophic tropomyosin receptor kinase fusion-positive solid tumour population

Disposition: Death was the most common reason for study discontinuation (70%) and progressive disease was the most common reason for treatment discontinuation (74%), consistent with the studied patient group.

Protocol deviations: Protocol deviations were reviewed, and are not likely to have materially altered the assessment of efficacy or safety.

Baseline characteristics: Baseline demographics, disease and treatment characteristics of the 54 patients in the NTRK efficacy evaluable set are summarised in Table 12.[14]

Table 16: Baseline demographics and characteristics of the NTRK efficacy evaluable set

Baseline characteristics	NTRK efficacy evaluable set (n = 54)	Baseline characteristics			NTRK efficacy evaluable set (n = 54)
Age, years		**Disease stage**			
Median (min, max)	57.5 (21, 83)	Metastatic			52 (96%)
Age group, n		Locally advanced			2 (4%)
> 65	34 (63%)	**Baseline CNS lesions by investigator**			
≤ 65	20 (37%)	Absent			42 (78%)
Gender, n		Present			10 (19%)
Female	32 (59%)	Measurable			2 (4%)
Male	22 (41%)	**Tumour type**			
Race, n		Sarcoma: MPNST (1), GIST (1), chondrosarcoma			13 (24%)
Asian	7 (13%)	NSCLC: Adeno and squamous cell (1)			10 (19%)
Not reported	4 (7%)	Salivary gland (MASC)			7 (13%)
White	43 (80%)	Breast: nonsecretory (1)			6 (11%)
Ethnicity		Thyroid: papillary, anaplastic			5 (9%)
Hispanic or Latino	4 (7%)	Colorectal			4 (7%)
Not Hispanic or Latino	45 (83%)	Neuroendocrine			3 (6%)
Missing	1 (2%)	Pancreatic			3 (6%)
Unknown or Not Reported	4 (7%)	Gynaecological: endometroid, ovarian			2 (4%)
ECOG performance status		Cholangiocarcinoma			1 (2%)
0	23 (43%)	**Prior Radiotherapy of the Brain**			
1	25 (46%)	Yes			7 (13%)
2	6 (11%)	No			47 (87%)
Smoking status		**Prior systemic therapy for this cancer**			
Never	30 (57%)	*No*		0	6 (11%)
Former/Current	17 (31%)	*Yes*	*48 (89%)*	1	2 (4%)
Current	6 (11%)			2	10 (19%)
				3	8 (15%)
				≥ 4	28 (52%)
		Prior lines of therapy for metastatic disease*			
		0			20 (37%)
		1			11 (20%)

Baseline characteristics	NTRK efficacy evaluable set (n = 54)	Baseline characteristics	NTRK efficacy evaluable set (n = 54)
		2	14 (26%)
		3	4 (7%)
		≥ 4	5 (9%)

Source: derived from the FDA multidisciplinary review;[14] for NTRK indication.

*Or for the two patients with locally advanced disease, for locally advanced disease.

Diagnostic testing in the neurotrophic tropomyosin receptor kinase efficacy set

All 54 patients in the NTRK efficacy evaluable set had an *NTRK* gene fusion that was predicted to translate into a fusion protein with a functional kinase domain (other mutations or evidence of second drivers such as *EGFR* alterations could receive treatment but were considered in the non-evaluable basket).

Patients were enrolled based on a variety of nucleic acid based testing. Of the 54 patients, the majority (52) were identified by NGS testing, whilst the other two (4%) had a fusion detected by other nucleic acid based tests.

In brief:

- 30 (55%) were identified by RNA based NGS (mostly Trailblaze Pharos;[24], n = 21)
- 19 (35%) were identified by DNA based NGS (mostly FoundationOne;[25], n = 13)
- 3 (6%) were identified by both DNA and RNA based NGS (FoundationOne Heme;[26])
- 1 (2%) was identified by polymerase chain reaction (PCR), and
- 1 (2%) was identified by Nanostring;[27]

Of the 54 patients in the NTRK efficacy evaluable set, 45 (85%) patients had an *NTRK* fusion mutation confirmed centrally using the Trailblaze Pharos (Igynta) clinical trial assay (RNA based NGS), according to the sponsor's application for provisional designation.

The fusion genes that were identified in the NTRK efficacy evaluable set are listed in Table 13.

To be included in the NTRK efficacy evaluable set, according to the protocol, tumours were required to have an in frame fusion of *NTRK1*, *NTRK2* or *NTRK3* with a functional kinase domain and without a second oncodriver. Molecular pathology reports provided by the sponsor after an information request were reviewed by the FDA, who commented that:[14]

> 'Preliminarily, many of the provided molecular pathology reports (both local and Pharos) did not provide NTRK fusion breakpoints or indicated finding of an in frame fusion, and secondary oncodrivers were not systematically assessed in all patients…'

The FDA state that no information on frameness was available for 8 of the 54 patients, and that concomitant oncodrivers were not assessed for 29 patients. Perhaps these data were assessed locally but not reported within the trial.

[25] FoundationOne is the first FDA-approved tissue-based broad companion diagnostic (CDx) that is clinically and analytically validated for all solid tumours.
[26] FoundationOne Heme is a comprehensive genomic profiling (CGP) test combining DNA and RNA sequencing for patients with hematologic malignancies, sarcomas or solid tumors where RNA sequencing is desired.
[27] Nanostring is an amplification-free technology that measures nucleic acid content by counting molecules directly.

Three patients were identified to have tumours harbouring a second oncodriver or out of frame fusion (one of each and a third with both). These were the 3 patients noted above to be excluded from the NTRK efficacy evaluable set due to failure to meet inclusion criteria (NTRK biomarker ineligibility: presence of one or more other oncogenic drivers for example *EGFR* or *KRAS* was considered likely to confer a mechanism of resistance).

No tissue was available for retesting.

Table 17: Fusion genes identified in the NTRK efficacy evaluable set

***NTRK* gene**	**Fusion gene**	**N (%)**
NTRK3 ***Total n = 31 (57%)***	*ETV6-NTRK3*	25 (81%)
	EML4-NTRK3	2
	AKAP13-NTRK3	1
	FAM19A2-NTRK3	1
	KIF7-NTRK3	1
	RBPMS-NTRK3	1
NTRK1 ***Total n = 22 (41%)***	*TPM3-NTRK1*	4
	TPR-NTRK1	4
	SQSTM1-NTRK1	2
	LMNA-NTRK1	2
	PEAR1-NTRK1	2
	ERC1-NTRK1	1
	EPS15L1-NTRK1	1
	CGN-NTRK1	1
	CDC42BPA-NTRK1	1
	PDIA3-NTRK1	1
	PLEKHA6-NTRK1	1
	CD74-NTRK1	1
	TRIM33-NTRK1	1
NTRK2 ***Total n = 1 (2%)***	*SQSTM1-NTRK2*	1

N = number of patients

Results in patients with neurotrophic tropomyosin receptor kinase fusion-positive solid tumours

Overall Response Rate and Duration of Response: The results for ORR and DOR according to BICR for the NTRK efficacy evaluable set are summarised in Table 14. The clinical cut off date was 31May 2018. Updated data was sent to the FDA with an additional 5 months'

follow up (clinical cut off date 31 October 2018), and the rates of responses lasting longer than 6 and 12 months, calculated by FDA based on that data, are also included below where they could be determined from the FDA report.[14]

Table 18: Efficacy analysis in the neurotrophic tropomyosin receptor kinase efficacy evaluable set by blinded independent central review

Objective response rate (ORR)	entrectinib (n = 54)	
Responders, n	31	
CR	4 (7.4%)	
PR	27 (50%)	
ORR (95%CI)	57.4% (43.2, 70.8)	
Date of Data cutoff	*May 31, 2018*	*Oct 31, 2018*
Median DOR in months (95% CI) [range]	10.4 (7.1, NE) [1.9+, 20.3+]	
DOR ≥ 6 months	17 (55% of 31)	21 (68%)
DOR ≥ 12 months	9 (39% of 23)	14 (45%)
DOR ≥ 18 months	3 (29% of 11)	

NE = not evaluable.

Subgroup analyses based on baseline characteristics were conducted. Sample sizes were small, but no outlier subgroups were identified. Results in tumour location groupings are summarised in Table 15,

With regard to line of therapy:[14]

> 'An exploratory analysis of ORR was conducted in patients who received prior systemic therapy for metastatic disease versus those who did not. The ORR was 53% for both populations.'

Table 19: Overall response rate and duration of response results by tumour location in NTRK fusion-positive tumours

Tumor type	Patients N = 54	ORR		DOR
		N (%)	95% CI	Range (months)
Sarcoma	13	6 (46%)	19%, 75%	2.8, 15.1
Non-small cell lung cancer	10	7 (70%)	35%, 93%	1.9*, 20.1*
Salivary (MASC)	7	6	NA	2.8, 16.5*
Breast cancer**	6	5	NA	4.2, 14.8*
Thyroid cancer	5	PR	NA	7.9
Colorectal cancer	4	PR	NA	4.8*
Neuroendocrine cancers	3	PR	NA	5.6*

Tumor type	Patients N = 54	ORR		DOR
		N (%)	95% CI	Range (months)
Pancreatic cancer	3	PR, PR	NA	7.1, 12.9
Gynecological cancers	2	PR	NA	20.3*
Cholangiocarcinoma	1	PR	NA	9.3

* Censored

** Four of the breast cancers were ETV6-NTRK3 positive secretory breast cancer, for example MASC. Of the two non-secretory breast cancers, there was one non-response and one PR.

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

Derived from 'Table 43' of the FDA multidisciplinary review.[14]

Intracranial responses: The interpretation of intracranial response data in patients with *NTRK* fusion-positive solid tumours is limited due to the small sample size.

Subgroup analyses of the primary efficacy outcome, per investigator assessment, were conducted:

- In the CNS metastases at Baseline (per investigator) subgroup (n = 12), the ORR (95% CI) was 50.0% (21.09, 78.91), with median duration of response not evaluable due to small sample size (3 ongoing responses at clinical cut-off date).
- In patients without CNS metastases at Baseline, the ORR (95% CI) was 59.5% (43.28, 74.37) and median duration of response 12.9 months.

Of the 12 patients with *NTRK* fusion-positive solid tumours who had CNS disease at Baseline per investigator, 11 were confirmed by BICR to have metastatic disease. In this group, the IC-ORR was 54.5% (95% CI: 23.4, 83.3), median duration not estimable.

Of the 11 that had CNS disease at Baseline per BICR, 7 had measurable CNS metastases. Of the 7 who had measurable disease, 3 had received radiation to the brain within 2 months of their first dose of entrectinib, and an effect on CNS response can't be ruled out. In the remaining four, there were 3 responses in intracranial lesions.

Of the 7 patients with *NTRK* fusion-positive solid tumours who had measurable CNS disease at Baseline per BICR, regardless of proximity of brain radiotherapy to entrectinib therapy, 4 had durable intracranial responses (median duration not estimable).

Efficacy in primary central nervous system tumours: Patients with primary CNS tumours harbouring *NTRK* fusions were not included in the NTRK efficacy evaluable set but five such adult patients were treated across the ALKA, STARTRK-1 and STARTRK-2 trials. In this group per RANO or RANO Brain Metastases criteria, there was 1 PR, 2 SD and 3 PD.

A publication of preliminary data from a Phase I/Ib trial in a paediatric cohort of 6 patients with CNS primaries from the STARTRK-NG trial indicates responses have been observed in all four of those who were evaluable for confirmed response at time of reporting: one CR in a patient with an *ETV6-NTRK3* fusion and 3 PRs in patients with an *TPR-NTRK1, EEF1G-ROS1,* or *EML1-NTRK*2 fusion.[28]

[28] Robinson GW, Gajjar AJ, Gauvain KM, Basu EM, Macy ME, Maese LD, Sabnis AJ, Foster JH, Shusterman S, Yoon J, Weiss BD, Abdelbaki M, Farid-Kapadia M, Meneses-orente G, Cardenas A, Hutchinson K, Bergthold G, Maneval EC, Fox E and Desai AV. Phase I/1B trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumors including central nervous system (CNS) tumors. Journal of Clinical Oncology 2019 37:15_suppl, 10009-10009.

The Delegate concurs with the FDA's conclusions on this subject:[14]

> 'Although limited, these data suggest activity in the CNS. This limited clinical data, together with nonclinical pharmacology data indicating that entrectinib crosses the blood brain barrier achieving levels that would inhibit TRK activity, support the decision not to include in product labeling a limitation of use for patients with primary CNS tumors.'

Efficacy-related conclusions

Evidence supporting efficacy for proposed indication consists of pooled data from patients who received entrectinib at various doses (but mostly at 600 mg daily) across three single arm clinical trials. Consecutive enrolment was used to reduce potential for bias.

ROS1 fusion-positive NSCLC

The ROS1 Primary Analysis Set consisted of the first 51 patients enrolled across three single arm clinical studies who had ROS1 fusion-positive NSCLC; had not previously received anti-ROS1 therapy; had a sole known oncodriver; had measurable disease per RECIST;**Error! Bookmark not defined.** v1.1; had an ECOG PS no higher than 2; and had at least 12 months of follow-up from the first post-treatment tumour assessment.

A large, clinically meaningful, and durable confirmed ORR per BICR was demonstrated. The ORR (95% CI) was 78% (65%, 89%). There was a CR rate of 6% and a PR rate of 73%. The median DOR (95% CI) was 15.7 months (11.4, 34.8) with minimum 12 months follow up. At a data cut-off date of 31 Oct 2018, 75% of responses had lasted at least 6 months, and 55% of responses had lasted at least 12 months.

Although subgroups are small, response rates were consistent between patients who had not received previous (non-anti-ROS1) systemic therapy for metastatic disease and those who had.

The rarity of ROS1 fusion-positive NSCLC renders randomised trials in this population infeasible. The single arm design and size limitations of this dataset are therefore acceptable. To determine whether efficacy is comparable to available therapies, cross-trial comparison is undertaken.

Crizotinib is the only therapy registered specifically for ROS1-positive NSCLC, and this indication was registered based on single arm data (n = 53). The response rate and proportion of responders with at least 12 months response duration for entrectinib are comparable to those seen for crizotinib for the treatment of ROS1 fusion positive NSCLC (n = 53). Intracranial activity has not been demonstrated for crizotinib and the most common site of progression on crizotinib is the CNS. Of seven patients with measurable CNS metastases at Baseline per BICR who had not received radiation to the brain within two months of their first dose of entrectinib, five had a confirmed response. Although the sample size necessitates caution over the precision of the point estimate, this pre-specified descriptive analysis indicates intracranial activity of entrectinib in humans, and is supported by preclinical findings.

For patients in whom testing for targetable mutations is negative or not available, the preferred first-line treatment is an anti-programmed death-ligand 1 (PD-L1) agent plus chemotherapy. The response rate reported for entrectinib in the ROS1 Primary Analysis Set had a lower 95% confidence bound of 65% according to the FDA analysis. This is higher than the response rates observed in ROS1 agnostic NSCLC populations treated with preferred first-line therapy, for example anti-PD-L1 therapy with or without concurrent chemotherapy, in other trials (48% to 58%, see Table 16).

Table 20: Summary of response rates and durations seen with current preferred first-line treatments for first-line non-small cell lung cancer, where driver mutations are unknown

	KEYNOTE-189	KEYNOTE-407	KEYNOTE -024
Treatment	pembrolizumab;[29] + chemo	pembrolizumab + chemo	pembrolizumab monotherapy
Histology	non-squamous only no EGFR or ALK	squamous only	squamous (18%) and non-squamous (82%) no EGFR or ALK
PD-L1	31% had TPS 1% (negative)	35% had TPS 1% (negative)	all TPS > 50% by 22C3 pharmDx test
ORR (95% CI)	48% (43, 53)	58% (52, 64)	45% (37, 53)
Median DOR, months (range)	11.2 (1.1+, 18.0+)	7.7 (1.1+, 14.7+)	not reached (1.9+, 14.5+)
KaplanMeier estimate response durability	81% at least 6 months	62% at least 6 months	88% at least 6 months

TPS = tumour proportion score.

The magnitude of response rate and durability of responses demonstrated in the submission are sufficient to establish efficacy for the proposed usage, based on the clinical benefit associated with tumour responses in NSCLC, the infeasibility of conducting randomised studies in this indication due to the rarity of its occurrence, and cross-trial comparisons which indicate that efficacy is likely to be acceptable to patients with ROS1 fusion-positive NSCLC.

Neurotrophic tropomyosin receptor kinase fusion positive solid tumours

The NTRK efficacy evaluable set consisted of the first 54 patients enrolled across three single arm clinical studies who had NTRK fusion-positive extracranial solid tumours and did not have any satisfactory treatment options or had progressed after any acceptable therapy. This group of patients had not previously received anti-TRK therapy; had a sole known oncodriver; had measurable disease by RECIST;**Error! Bookmark not defined.** v1.1; had an ECOG;[19] performance status no higher than 2; and had at least 6 months of follow-up from the time of first dose of entrectinib.

A large and durable confirmed ORR per BICR was demonstrated. The ORR (95% CI) was 57% (43%, 71%). There was a CR rate of 7.4% and a PR rate of 50%. The median DOR (95% CI) was 10.4 months (7.1, not estimable) with minimum 6 months follow up. At a data cut-off date of 31 Oct 2018, 68% of responses had lasted at least 6 months, and 45% of responses had lasted at least 12 months. Very limited data also supports activity against intracranial metastases, as well as efficacy in CNS primary disease.

The rarity of this diagnosis and the heterogeneity of histologies in which *NTRK* rearrangements are seen renders randomised trials in this population infeasible. Additionally, there is strong preclinical rationale, supported by nonclinical data, for the

[29] Australian product information for pembrolizumab. Last revised 20 Nov 2019. Accessed via TGA site.

pooling of efficacy data across histologies based on genetic subtyping. The single arm, pooled design and size limitations of this dataset are acceptable based on the above, however, the estimates of response rate and duration in the overall *NTRK*-positive population as well as in subgroups based on histology are imprecise due to the small overall population and very small subgroup sizes.

In patients with treatment-refractory solid tumours, either no treatment options remain or those that do are usually associated with significant morbidity and/or poor efficacy, with response rates generally less than 30%.[14] In this context, the magnitude of response rate and durability of responses demonstrated in this submission are considered sufficient to provisionally establish efficacy for the proposed usage, based on the clinical benefit associated with tumour responses in refractory solid tumours and the infeasibility of conducting randomised studies in this indication due to the rarity of its occurrence.

Additional data is expected to be collected through further enrolment and follow-up of the the STARTRK-2 and STARTRK-NG clinical trials. This confirmatory data is expected to improve the precision of the estimates for response rate and duration in NTRK fusion-positive solid tumours overall, as well as in subgroups based on histology, and in paediatric patients.

Safety

Total safety population

The FDA reviewed coding and accuracy of the original safety datasets submitted to them by the sponsor, and conducted an independent safety analysis using the revised datasets. Broadly, the conclusions on clinical safety reached by the sponsor reviewer and the FDA clinical review team are similar.

Of the studies described in Table 3, above, the ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG trials involved similar design, treatment and study populations, and so contributed data to the main integrated safety analysis in support of the proposed registration. The ALKA, STARTRK-1 and STARTRK-2 trials are described in efficacy section, above. A description of STARTRK-NG trial can be found in section below. Supporting safety data were submitted from a compassionate use program (for 5 adult and 3 paediatric patients), from midazolam DDI Study RXDX-101-14 (14 adult patients), and from the dedicated clinical pharmacology studies (which enrolled healthy volunteers), but these were not included in the main integrated safety analysis as they were not suitable for pooling due to various differences in study purposes, designs and populations.

The FDA integrated review of safety included all enrolled patients as at 30 Nov 2017 who received at least one dose of entrectinib (n = 355: 338 adult and 17 paediatric patients): 57 from the ALKA trial, 76 from the STARTRK-1 trial, 206 from the STARTRK-2 trial (2 of whom were under the age of 18), and 16 from the STARTRK-NG trial (15 of whom were under the age of 18).

Study RXDX-101-03/CO40778 (STARTRK-NG trial)

Table 21: Study RXDX-101-03/CO40778 (STARTRK-NG trial) description

Study description	
Population (enrolled = 16)	Phase I/Ib (dose escalation/dose expansion) study in paediatric/adolescent patients (aged 2 to 22) with recurrent or refractory solid tumours or primary brain tumours, with or without TRK, ROS1 or ALK fusions. Inclusion criteria (abridged): Different inclusion criteria applied across parts, as outlined in Table 21, below.

Study description	
	In addition to the criteria in the table below, all patients were required to have: • Archival tumour tissue, preferably from relapse • Performance status: Lansky or Karnofsky score at least 60% • Life expectancy at least 4 weeks Prior therapy was allowed with specific limitations for recency. Exclusion criteria (abridged): • Standard (significant medical/surgical illnesses, inadequate organ function, reproductive status) • Congenital long QT • All Phase Ib parts: prior antiTRK/ROS1/ALK therapy • Only part C: bone marrow space-only disease Location: multicentre Ongoing. Commenced 2016. Data cut-off for interim report 31 May 2018. Sample size: • Phase I (Part A – solid tumours) o Planned: approximately 6 to 30 patients o Enrolled: 16 patients • Phase Ib (Part B – primary brain tumours and D – solid tumours with *NTRK/ROS1/ALK* fusions) o Planned: approximately 13 patients per basket (for example tumour type and molecular alteration combination) for the first stage. Up to an additional 49 patients into the second stage.
Intervention	Formulation: Formulation: F1 (3 patients got F2B at 250 mg/m^2 (the first dose level)) Doses (BSA based dosing): escalations – starting at 250 mg/m^2, next group 400 mg/m^2, then 550 mg/m^2, then 750 mg/m^2 Dose schedule: administered orally with food once daily, in 28 day cycles
Endpoints	Primary: • DLT, MTD and RP2D in paediatric patients Secondary: • Safety • PK • Efficacy, including intracranial (these are beyond the scope of the submitted interim report)

Table 22: Inclusion criteria (abridged) for the STARTRK-NG trial

Phase	1	1b (dose expansion)
	Part	

Phase	1			1b (dose expansion)		
Inclusion criteria	A	A exp	B	C	D	E
Relapsed/refractory solid tumours						
extracranial except neuroblastoma	ü	ü			ü	ü
neuroblastoma	ü			ü		ü
primary brain			ü			ü
NTRK 1/2/3, ROS or ALK alterations						
gene fusions*			ü		ü	ü
other alterations		ü	ü			ü
Measurable or evaluable disease						
per RECIST v1.1	ü	ü			ü	
per RANO			ü			ü
per RECIST v1.1, ± Curie Scale				ü		ü
Other						
Body surface area at least 0.45 m^2 (at enrolment)	ü	ü	ü	ü	ü	
Age at least 2 years	ü	ü	ü	ü	ü	
Able to swallow capsules	ü	ü	ü	ü	ü	

* predicted to translate into functional fusion kinase, with no concomitant second oncodriver (such as *EGFR/KRAS*), as determined by any nucleic acid-based diagnostic testing method, for example NGS, Sanger, RT-PCR, NanoString, EdgeSeq.

Integrated safety analysis

Populations and exposure

The FDA safety review presents data for four main datasets within the integrated safety population, with a data cut-off date of 31 May 2018, defined in the FDA review as follows.[14]

Adult safety datasets:

- NTRK fusion-positive analysis set (n = 68): Patients from the ALKA, STARTRK-1, and STARTRK-2 trials in the safety population who have *NTRK* fusion-positive solid tumours
- ROS1-positive NSCLC analysis set (n = 133): Patients from the ALKA, STARTRK-1, and STARTRK-2 trials in the safety population who have *ROS1*-positive NSCLC

- Other adult analysis set (n = 137): Patients from the ALKA, STARTRK-1, and STARTRK-2 trials in the safety population with either ROS1-positive non-NSCLC, *ALK* fusion-positive tumours, or no gene fusion identified.

Main paediatric safety dataset:

- Paediatric analysis set (n = 17): Includes 15 paediatric patients from STARTRK-NG trial and 2 paediatric patients from the STARTRK-2 trial.

Exposure and baseline demographics in the four datasets described above are summarised in Table 17 and Table 18.

Table 23: Summary of entrectinib exposure in the integrated safety population

Parameter	*NTRK* Adult (n = 68)	*ROS1* NSCLC Adult (n = 133)	Other adult (n = 137)	Pediatric (n = 17)	All (n = 355)
Median treatment duration (Months)	7.9 (0.1, 24.7)	8.3 (0.1, 42.1)	2.0 (0.0, 37.0)	1.9 (0.2,12.7)	5.5 (0.0, 42.1)
Median no. of cycles	9.5 (1.0, 49.0)	10.0 (1.0, 92.0)	3.0 (1.0, 70.0)	4.0 (1.0, 16.0)	7.0 (1.0, 92.0)
Median no. of missed doses	1.0 (0.0, 34.0)	1.0 (0.0, 24.0)	0.0 (0.0, 17.0)	2.0 (0.0, 37.0)	1.0 (0.0, 37.0)
Median dose intensity, %*	94.1 (40.5, 105.3)	96.5 (29.8, 133.3)	98.6 (12.6, 388.3)	96.3 (32.6, 115.1)	96.9 (12.6, 388.3)

Source: reformatted FDA table.[14]

*Total cumulative dose received/total planned dose x 100%. Factors contributing to dose intensity > 100% included patients enrolled during the dose finding portion of the Phase I studies who underwent intra-patient dose escalation after determination of the recommended Phase II dose.

Table 24: Summary of baseline demographics in the integrated safety population

Parameter	*NTRK* Adult (n = 68)	*ROS1* NSCLC Adult (n = 133)	Other Adult (n = 137)	Pediatric (n = 17)	All (n = 355)
Sex					
Male (%)	46	40	49	62	45
Female (%)	54	60	51	38	55
Age					
Median (years)	58	53	55	10	55
Range	21-83	15-86	15-80	4-20	4-86

Parameter	*NTRK* Adult (n = 68)	*ROS1* NSCLC Adult (n = 133)	Other Adult (n = 137)	Pediatric (n = 17)	All (n = 355)
Age group (years)					
< 65 (%)	63	76	76	100	75
>65 (%)	37	24	24	0	25
Ethnicity					
Hispanic or Latino (%)	6	2	3	6	3
Not Hispanic or Latino	86	92	88	81	89
Not stated (%)	6	2.5	1	6	3
Unknown (%)	1.5	4	8	6	5
Race					
White (%)	77	53	72	81	66
Asian (%)	13	38	16	0	23
Black or African American (%)	1.5	5	4	19	4.5
Not reported (%)	9	3	4	0	4.5
ECOG PS (%)					
0	38	39	45	0	41
1	49	50	51	0	50
2	10	8	4	0	7
3	3	0.7	0	0	0.9
4	0	0.7	0	0	0.3

Source: reformatted FDA table.[14]

*Total cumulative dose received/total planned dose x 100%. Factors contributing to dose intensity > 100% included patients enrolled during the dose finding portion of the Phase I studies who underwent intra-patient dose escalation after determination of the recommended Phase II dose

Adverse events and laboratory abnormalities

An overview of adverse events across the integrated safety population are summarised in Table 19. Treatment emergent adverse events and laboratory abnormalities, including

Common Terminology Criteria for Adverse Events;[30] (CTCAE) Grade 3 or higher are summarised in Table 20 and Table 21, respectively. Those relating to the nervous system class were the most notable treatment emergent adverse events.

For both haematology and biochemistry, the majority of shifts that were reported were low grade. The most common clinically relevant shifts (defined as a change from Grade 0, 1 or 2 at Baseline to Grade 3 or 4 post-Baseline) were Grade 3 anaemia (9%), neutropaenia (7%), hypophosphataemia (12%), hyponatraemia (4%) and hypoalbuminaemia (3%), hyperuricaemia is discussed further in section adverse events of special interest.

Elevated serum creatinine was common but renal failure was not reported, raising the possibility of a secretory cause, assay effect, or entrectinib influence on catabolism.

Table 25 Overview of adverse events in the integrated safety population

Parameter	*NTRK* Adult (n = 68)	*ROS1* NSCLC Adult (n = 133)	Other Adult (n = 137)	Pediatric (n = 17)	All (n = 355)
Patients with AE (%)	100	100	99	100	99
Patients with treatment related AE (%)	100	100	98	100	99
Patients with SAE (%)	47	37	40	13	39
Patients with related SAE (%)	10	13	5	6	9
Patients with Grade ≥ 3 AE (%)	74	61	56	50	61
Patients with AE leading to discontinuation (%)	13	9	6	6	9
Patients with AE leading to dose reduction (%)	41	34	16	25	28
Patients with AE leading to drug interruption (%)	56	45	43	38	46
Patients with AE leading to death (%)	9	7	4	0	6

AE = adverse event, SAE = serious adverse event.

Source: reformatted FDA table.[14]

Table 26. Treatment emergent adverse events by groupings of Preferred Term that occurred in at least 10% of patients in the integrated safety population

System organ class **Adverse event**	**Entrectinib N = 355**	
	All grades (%)	**Grade ≥ 3 * (%)**
General		
Fatigue[1]	48	5
Edema[2]	40	1.1

[30] The **Common Terminology Criteria for Adverse Events** (**CTCAE**) are a set of criteria for the standardised classification of adverse effects of drugs used in cancer therapy.

System organ class **Adverse event**	**Entrectinib N = 355**	
	All grades (%)	**Grade ≥ 3 * (%)**
Pyrexia	21	0.8
Gastrointestinal		
Constipation	46	0.6
Diarrhea	35	2.0
Nausea	34	0.3
Vomiting	24	0.8
Abdominal pain[3]	16	0.6
Nervous system		
Dysgeusia	44	0.3
Dizziness[4]	38	0.8
Dysesthesia[5]	34	0.3
Cognitive impairment[6]	27	4.5
Peripheral sensory neuropathy[7]	18	1.1
Headache	18	0.3
Ataxia[8]	17	0.8
Sleep[9]	14	0.6
Mood disorders[10]	10	0.6
Respiratory, thoracic and mediastinal		
Dyspnea	30	6*
Cough	24	0.3
Musculoskeletal and connective tissue		
Myalgia[11]	28	1.1
Arthralgia	21	0.6
Muscular weakness	12	0.8
Back pain	12	1
Pain in extremity	11	0.3

System organ class **Adverse event**	**Entrectinib N = 355**	
	All grades (%)	**Grade ≥ 3 * (%)**
Metabolism and nutritional		
Increased weight	25	7
Decreased appetite	13	0.3
Dehydration	10	1.1
Eye		
Vision disorders[12]	21	0.8
Infections		
Urinary tract infection	13	2.3
Lung infection[13]	10	6*
Vascular		
Hypotension[14]	18	2.8
Skin and Subcutaneous Tissue		
Rash[15]	11	0.8

Source: reformatted FDA table.[14] Preferred Terms based on clinical judgement and agreed between FDA and the US sponsor.

*Grades 3 to 5, inclusive of fatal adverse reactions, including 2 events of pneumonia and 2 events of dyspnea.

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

Table 27: Laboratory abnormalities that worsened from Baseline in at least 20% of patients in the integrated safety population

Laboratory abnormality	Entrectinib NCI-CTCAE Grade N = 355[1]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Anemia	67	9
Lymphopenia	40	12
Neutropenia	28	7
Chemistry		
Increased creatinine[2]	73	2.1
Hyperuricemia[3]	52	8
Increased AST	44	2.7
Increased ALT	38	2.9
Hypernatremia	35	0.9
Hypocalcemia	34	1.8
Hypophosphatemia	30	7
Increased lipase	28	10
Hypoalbuminemia	28	2.9
Increased amylase	26	5.4
Hyperkalemia	25	1.5
Increased alkaline phosphatase	25	0.9
Hyperglycemia[4]	NE[3]	3.8

Source: reformatted FDA table.[14]

AST: aspartate aminotransferase; ALT: alanine aminotransferase

[1] Denominator for each laboratory parameter is based on the number of patients with a Baseline and post-treatment laboratory value available which ranged from 111 to 346 patients.

[2] Based on NCI CTCAE v5.0

[3] Based on NCI CTCAE v4.03 using laboratory dataset (ALB), adverse event dataset (AAE) and concomitant medication dataset (ACM)

[4] NE = Not evaluable. Grade 1 and 2 could not be determined per NCI CTCAE v5.0, as fasting glucose values were not collected.

Serious adverse events and high grade (≥3) adverse events

Adverse events that were serious (Table 22) occurred in 39% of the integrated safety population. Serious adverse events were defined in the study protocol using standard definitions, although the FDA review notes that the definition did not include adverse events that, if they had occurred in a more severe form or were allowed to continue, may have caused death (for example 'near misses').

Table 28: Serious adverse events with incidence > 1% by System Organ Class and Preferred Term

SOC/Preferred Term	***NTRK*** **Adult (n = 68) (%)**	**ROS1 NSCLC** **Adult n = 133 (%)**	**Other Adult nonNTRK, nonROS1** **n = 137 (%)**	**Paediatric n = 17 (%)**	**All n = 355 (%)**
Total n (%)	32 (47)	50 (37)	53 (39)	2 (13)	137 (39)
Respiratory and mediastinal disorders	11 (16)	16 (12)	17 (12)	2 (13)	46 (13)
Dyspnea	2 (2.9)	6 (4.5)	5 (3.6)	0	13 (3.7)
Acute respiratory failure/respiratory distress	3 (4.4)	0	4 (2.9)	0	7 (2)
Pleural effusion	3 (4.4)	5 (3.7)	3 (2.1)	2 (13)	12 (3.4)
Pulmonary embolism	2 (2.9)	3 (2.2)	3 (2.1)	0	8 (2.2)
Infections and infestations	11 (16)	13 (10)	11 (8)	1 (6)	36 (10)
Pneumonia	2 (2.9)	2 (1.5)	10 (7)	0	14 (3.9)
Sepsis	2(2.9)	1 (0.7)	6 (4.4)	0	9 (2.5)
Nervous system and psychiatric disorders	8 (12)	16 (12)	11 (8)	0	35 (10)
Cognitive disorder	1 (1.5)	2(1.5)	2 (1.4)	0	5 (1.4)
Syncope	0 (0)	2 (1.5)	1 (0.7)	0	3 (0.8)
Ataxia	1 (1.5)	1 (0.7)	1 (0.7)	0	3 (0.8)
Dizziness	1 (1.5)	1 (0.7)	0	0	2 (0.6)
Mental status changes/confusion	1 (1.5)	2 (1.5)	3 (2.1)	0	5 (1.4)
Depression	1 (1.5)	0	0	0	1 (0.3)
Cardiac disorders	5 (7)	6(4.5)	2 (1.4)	0	13 (3.7)

SOC/Preferred Term	*NTRK* Adult (n = 68) (%)	ROS1 NSCLC Adult n = 133 (%)	Other Adult nonNTRK, nonROS1 n = 137 (%)	Paediatric n = 17 (%)	All n = 355 (%)
Vascular disorders	2 (2.9)	3(2.2)	2 (1.4)	0	7 (2)
Hypotension	2 (2.9)	3(2.2)	1	0	6 (1.7)
Gastrointestinal disorders	0	4 (3)	10 (7)	0	14 (4)
General and administration site disorders	2 (2.9)	6 (4.4)	7 (5)	0	15 (4.2)
Pyrexia	0	4 (3)	3 (2.1)	0	7 (2)

Source: reformatted FDA table.[14] SOC = System Organ Class.

Discontinuations, interruptions and dose reductions due to adverse events

Adverse events that most commonly led to drug discontinuation, interruption or reduction of dosing for patients in the integrated safety population are summarised in Table 23.

Table 29: Adverse events that led to discontinuations, interruptions and dose changes in the integrated safety population, all reported as percentages

Preferred Term	*NTRK* Adult (n = 68)	*ROS1* NSCLC Adult (n = 133)	Other Adult non-*NTRK*, non-*ROS1* (n = 137)	Pediatric (n = 17)	All (n = 355)
*System Organ Classes in which AEs that led to **treatment discontinuation** occurred in at least 1% of patients in the integrated safety population*					
Total for all SOCs, %	13	9	6	6	9
Respiratory and mediastinal disorders					
Total	**3**	**2**	**0.7**	**6**	**2.0**
Dyspnea	0	0.7	0	6	0.6
Acute respiratory failure	3	0	0	0	0.6
Pneumonitis	0	0.7	0	0	0.3
Pulmonary edema	0	0	0.7	0	0.3
Pulmonary embolism	0	0.7	0	0	0.3
Cardiac Disorders					
Total	**4.4**	**1.5**	**1.5**	**0**	**2.0**

Preferred Term	*NTRK* Adult (n = 68)	*ROS1* NSCLC Adult (n = 133)	Other Adult non-*NTRK*, non-*ROS1* (n = 137)	Pediatric (n = 17)	All (n = 355)
Cardio-respiratory arrest	2.9	0	0	0	0.6
CHF	1.5	0	0	0	0.3
A Fib/Extrasystoles	0	0	0.7	0	0.3
Myocarditis	0	0.7	0	0	0.3
Cardiogenic shock	0	0.7	0	0	0.3
Pericardial Effusion	0	0.7	0	0	0.3
Infections and Infestations					
Total	**3**	**0.7**	**0.7**	**0**	**1.1**
Pneumonia/Lower RTI/Lung infection	1.5	0.7	0.7	0	0.8
Sepsis	1.5	0	0	0	0.3
General disorders and administrative site conditions					
Total	**1.5**	**0.7**	**1.5**	**0**	**1.1**
Fatigue	1.5	0	0.7	0	0.6
Malaise	0	0	0.7	0	0.3
Peripheral edema	0	0.7	0	0	0.3
*AEs that led to **treatment interruption** in at least 1% of patients in the integrated safety population*					
Total %	**56**	**45**	**43**	**38**	**46**
Increased creatinine/AKI	6	4	1.5	12.5	3.9
Fatigue	7	1.5	4	6	3.7
Anemia	9	0	4	0	3.1
Diarrhea	3	2	3	6	2.8
Pyrexia	3	2	4	0	2.8
Dizziness	1.5	5	0.7	0	2.5
Nausea	4	1.5	2	0	2.3

Preferred Term	*NTRK* Adult (n = 68)	*ROS1* NSCLC Adult (n = 133)	Other Adult non-*NTRK*, non-*ROS1* (n = 137)	Pediatric (n = 17)	All (n = 355)
Dyspnea	3	3	1.5	0	2.3
Pneumonia	3	2	3	6	2.3
Cognitive disorder	0	4.5	0.7	0	2.0
Neutropenia	0	0.7	1.5	6	2.0
AST increase	3	1.5	1.5	0	1.7
Pleural effusion	1.5	3	0.7	0	1.7
Vomiting	0	1.5	3	6	1.4
ALT increase	3	1.5	0.7	0	1.4
Lipase increase	0	0.7	3	0	1.4
UTI	1.5	1.5	1.5	0	1.4
Peripheral edema	1.5	2	0	0	1.1
Ataxia/fall/gait disturbance	4	2	3	0	1.1
Confusional state/mental status change	1.5	0.7	3	0	1.1
Decreased appetite	1.5	0	1.5	0	1.1
Hypotension	0	0	0.7	0	1.1
Hypoxia	4	0	0	0	0.8
*AEs that led to **dose reduction** in at least 1% of patients in the integrated safety population*					
Total %	41	34	16	25	28
Dizziness	4.4	6	2.2	0	3.9
Increased creatinine	6	4	0.7	6	3.1
Fatigue	6	2	0.7	0	2.3
Anemia	7	0	0.7	0	1.7
Increased weight	1.5	0.7	0.7	6	1.4

Preferred Term	*NTRK* Adult (n = 68)	*ROS1* NSCLC Adult (n = 133)	Other Adult non-*NTRK*, non-*ROS1* (n = 137)	Pediatric (n = 17)	All (n = 355)
Ataxia/ gait disturbance/balance disorder	3	3	1.5	0	1.0
Cognitive disorder	1.5	2	0	0	1.0
Peripheral sensory neuropathy/paresthesia / peripheral neuropathy	3	4	1.5	0	1.0
Gait disturbance	3	0.7	0.7	0	1.0
Arthralgia	0	1.5	1.5	0	1.0
Confusional state/mental status change/somnolence/ depressed level of consciousness /depression/agitation/ disturbance in attention	1.5	4	1.5	0	1.0

CHF: congestive heart failure; RTI: respiratory tract infection; AKI: acute kidney injury; AST: aspartate aminotransferase; ALT: alanine aminotransferase; UTI: urinary tract infection.

Source: FDA tables 54, 55 and 56 of the FDA multidisciplinary review, reformatted and merged.[14]

Deaths and fatal adverse events

Deaths in the integrated safety population are summarised in Table 24. Of the 20 adverse events that occurred within 30 days of last dose of entrectinib and resulted in death (Table 25) none were attributed to entrectinib by the investigators, however, the FDA reviewers state:[14]

> 'While the reviewers agree that the majority of deaths are unlikely to be related to entrectinib, due to the single arm nature of these studies and temporal relationship between the onset of death and initiation of entrectinib in some cases, it is possible that there is a causal relationship for entrectinib in some of these deaths.
>
> Additionally, FDA does not agree with the attribution of certain fatal events as noted above. Therefore, the package insert will include information regarding all Grade 5 AEs (deaths).'

Notably:[14]

> 'One patient committed suicide in the hospital subsequent to confirmation of disease progression. Given the documented CNS effects of entrectinib, this event is possibly/probably attributable to entrectinib.'

Table 30: Overview of deaths in the in the integrated safety population

Cause of Death	*NTRK* Adult N = 68 (%)	*ROS1* NSCLC Adult n = 133 (%)	Other Adult non-*NTRK*, non*ROS1* n = 137 (%)	Paed. nN = 17 (%)	All N = 355 (%)
Total no. of deaths (%)	22 (32)	29 (22)	37 (27)	5 (31)	93 (26)
Total no. of deaths due to AE	6 (9)	9 (7)	5(4)	0 (0)	20 (6)
Death < 30 days of last dose					
Total	8 (12)	21 (16)	17(12)	2 (13)	48 (14)
Progression of disease	4 (6)	15 (11)	11(8)	2(3)	32 (9)
Other	4 (6)	3 (2.2)	1 (0.7)	0	8(2.3)
Unknown	0	3 (2.2)	5 (3.6)	0	8(2.3)
Death > 30 days of last dose					
Total	14 (21)	8(6)	20 (15)	3 (19)	45 (13)
Progression of disease	12 (18)	7 (5)	12 (9)	3 (19)	34 (10)
Other	1 (1.5)	1 (0.7)	8(6)	0	10 (3)
Unknown	1(1.5)	0	0	0	1 0.3)

Source: FDA table.[14]

Table 31. Grade 5 adverse events (adverse events that led to death) in the integrated safety population

Preferred Term	NTRK Adult n = 68 (%)	ROS1 NSCLC Adult n = 133 (%)	Other Adult nonNTRK, nonROS1 n = 137 (%)	Pediatric n = 17 (%)	All n = 355 (%)
Total(%)	6 (9)	9 (7)	5 (4)	0 (0)	20 (6)
Acute Respiratory Failure	2 (3)	0 (0)	1 (0.7)	0 (0)	2 (0.6)
Cardio-respiratory Arrest	2 (3)	0 (0)	0 (0)	0 (0)	2 (0.6)
Dyspnea	0 (0)	1 (0.7)	1 (0.7)	0 (0)	2 (0.6)
Meningeal Metastases	0 (0)	2 (1.4)	0 (0)	0 (0)	2 (0.6)
Pneumonia	1 (1.5)	1 (0.7)	0 (0)	0 (0)	2 (0.6)
Sepsis/Septic Shock	1 (1.5)	1 (0.7)	1 (0.7)	0 (0)	3 (0.9)
Cardiogenic Shock	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.3)
Cerebral Infarction	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.3)
Completed Suicide	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.3)
Large Intestine Perforation	0 (0)	1(0.7)	0 (0)	0 (0)	1 (0.3)
Pulmonary Embolism	0 (0)	1 (0.7)	0 (0)	0 (0)	1(0.3)
Tumor Lysis Syndrome	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.3)

Source: FDA table.[14]

Adverse events of special interest

A number of adverse events of special interest (AESI) were identified, based on scientific literature describing clinical experience, neurobiology/mechanism of action and safety profile of drugs with similar targets.

QT prolongation including sub-study of STARTRK-2 trial

In Study 1091319, the concentration QTc analysis did not demonstrate a relationship between increased plasma concentration and prolongation of QTc.

A cardiac ECG sub-study of STARTRK-2 trial included all patients enrolled in STARTRK-2 trial from US and Japanese sites (n = 113). ECGs were performed at screening, throughout treatment cycles, end of treatment visits, and if clinically indicated. Readings were taken in triplicate and centrally assessed. A dedicated FDA review team concluded that no large (> 20 ms) QTc prolongation effect was observed, and the data did not support an exposure response analysis due to the narrow exposure range and limitations of the PK/ECG sampling schedule. Therefore, the relevance of the observed prolongations in this single arm cohort is not clear.

Within the integrated safety population (n = 355), of the patients who had at least one post-Baseline ECG assessment, 2.8% had QTc interval prolongation of > 60 ms and 1.7% had a QTc interval > 500 ms after starting entrectinib. Two patients had both features, and neither had confounders recorded in their narratives that would explain the QT prolongation.

The sponsor's draft Australian PI includes Warning/Precaution text that addresses this, including the avoidance of use in patients with congenital long QT;**Error! Bookmark not defined.** or on QT prolonging medications; also reflective of trial exclusions. The draft text does not include clinically significant bradyarrhythmias, or severe or uncontrolled heart failure (which is particularly significant, given this is another class of adverse event associated with entrectinib), and will require revision to include these.

As the data don't support an assessment of exposure response, a recommendation for a specific time point for ECG monitoring is not considered warranted at this time, noting such recommendations are not present in the EMA or FDA label documents.

Neurotoxicity

Entrectinib is known to have CNS penetrance and based on its mechanism of action, neurological adverse events were predicted to occur. Adverse event terms were grouped by FDA clinical reviewers into clinically relevant categories as below. Neurotoxicity generally appeared to be manageable with dose changes: at the data cut-off, 60% of the reported events of neurotoxicity had resolved. A small number (8%) were treated with medications for the event. One patient discontinued due to neurotoxicity – this was a patient in the STARTRK-2 trial who had a Grade 1 hallucination soon after commencing treatment, with a gradual decline in mental status until Day 9 when he ceased treatment due to Grade 3 cognitive disorder and concurrent Grade 3 pneumonia. Ten days later he developed Grade 2 agitation and Grade 1 vasogenic cerebral oedema, and an MRI two days later showed interval increase in the size of a transcallosal lesion. The presence of infection and CNS disease confound the causality of the Grade 3 cognitive disorder that led to discontinuation.

The FDA reviewers found the incidence of CNS adverse reactions was not different between patients with and without CNS metastases. In patients with CNS metastases, however, they did note imbalances in reports of dizziness (38% versus 31%), headache (21% versus 13%), paraesthesia (20% versus 6%), balance disorder (13% versus 4%) and confusional state (11% versus 2%) when comparing those who had received prior CNS irradiation (n = 90) to those who had not (n = 48).

Cognitive impairment: Cognitive impairment, including amnesia, aphasia, cognitive disorder, confusional state, delirium, disturbance in attention, hallucinations, visual hallucination, memory impairment, mental disorder and mental status changes, occurred in 27% of patients. Drug interruption, dose reduction, and discontinuation were required for 13%, 18% and 1% of patients, respectively.

Mood disorders: Mood disorders occurred in 10% of patients, including anxiety (4.8%), depression (2.8%) and agitation (2%). Grade 3 events occurred in 0.6% of patients (n = 2), and one patient completed suicide 11 days after the last dose of entrectinib (ceased due to disease progression). Dose interruption and reduction each occurred in 6% of patients with mood disorders.

Dizziness, syncope, ataxia, gait disturbance and hypotension: In 108 out of 135 reported cases of dizziness, underlying explanatory causes were not identified by clinical review of narratives, and entrectinib causality is considered reasonably plausible. Syncope was reported in 14 cases, around half confounded (for example, hypotension and/or dehydration, QT prolongation, cardiac disease with medical history of arrest, and Prinzmetal's angina). Ataxia was reported in 17 cases and gait disturbance in 24 cases: for most of these patients multiple other events were concurrently reported (such as vertigo, insomnia, fatigue, cognitive disturbance and confusion), suggesting presentation of an entrectinib related neurological syndrome.

Hypotension mostly occurred in conjunction with explanatory factors such as dehydration, diarrhoea, vomiting, acute infections, and cardiac events.

Sleep disturbances: Sleep disturbance was reported in 14% of patients, including reports of insomnia (7%), somnolence (7%), hypersomnia (1.1%), and sleep disorder (0.3%). Two patients reported Grade 3 events, and entrectinib dose was reduced in 6%.

Dyspnoea: Adverse events of dyspnoea were reported in 106 patients (30%), and for around half these cases, no clear alternative aetiology or underlying cause was apparent from case review. The FDA concluded these were likely to be entrectinib related.[14] There was not a higher rate of dypsnoea with NSCLC compared to other tumours, suggesting primary histology was not a risk factor for dyspnoea. Whether these are CNS attributable is unclear.

Congestive heart failure

There were 12 events (3.4%) consistent with congestive heart failure in the integrated safety population (n = 355), 8 of which were Grade 3 (2.3%). These cases included:

- decreased ejection fraction (EF) (n = 4), two of which were Grade 3
- pulmonary oedema (n = 4)
- cardiac failure (n = 3)
- congestive cardiac failure (n = 3)
- acute right ventricular failure, cardiogenic shock and chronic ventricular failure (each n = 1)

Eight of these heart failure events were Grade 3 in severity, and seven were serious, all of whom presented with dyspnoea or fluid overload, and five of whom were treated with systemic diuretics.

As described in the FDA review:[14]

> 'Entrectinib was interrupted in 3 patients, reduced in 1 patient, and withdrawn in 3 patients. Five of 7 patients with serious congestive heart failure events recovered. Per the summary of clinical safety, of the 12 patients with congestive heart failure events, 7 patients had a past medical cardiac history at Baseline and/or concurrent conditions that may have predisposed them to congestive cardiac failure events. Overall, congestive heart failure events were generally manageable with entrectinib dose interruption or reduction.
>
> One Grade 5 adverse event of cardiogenic shock was reported in a patient with NSCLC due to pericardial effusion and pericardial tamponade. The patient

> developed cardiogenic shock two days after starting entrectinib and died. It was noted that the patient had suspected pericardial, bilateral pleural, omental and peritoneal carcinomatosis at Baseline, as well as diffused lung, liver, and bone metastases. This patient was not included in the analysis of cardiac events because Genentech did not consider the adverse event to be drug related, and instead attributed the AE to underlying disease.
>
> One Grade 4 AE of eosinophilic myocarditis was reported in a 40 year old male… with metastatic NSCLC after receiving treatment with one dose of entrectenib at 800mg/m^2.
>
> …
>
> Congestive heart failure (CHF) was added to the warnings and precautions (W&P) section of the entrectinib product label because CHF is a serious adverse event. Although it is challenging to assess relatedness of cardiac events to entrectenib based on the single arm trials and most of the affected patients had a prior medical history of cardiac risk factors, it is unusual to observe clinically detected CHF at an incidence of 2.3% even in clinical trials enrolling patients with refractory cancers. [One patient in STARTRK-1], who developed Grade 4 myocarditis, had a biopsy consistent with eosinophilic myocarditis possibly related to entrectinib as this is an unusual adverse event for which no such events are expected in clinical trials. A post marketing requirement (PMR) will be conducted by Genentech to further assess the contribution of entrectenib to cardiac risk and characterize cardiac adverse events. Genentech plans to conduct additional assessments for left ventricular ejection fraction (LV ECOG no worse than 2) at screening and Cycle 3 Day 1 in clinical trial(s) of entrectinib to better assess cardiac function prior to and during treatment.'

Congestive heart failure has been included in the draft Australian PI under warnings/precautions, but the text is very limited by comparison to the detail included in the FDA label.

Vision disorders

Preclinical data indicated that entrectinib could cause neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium, and eye examinations were included in all ongoing clinical trials.

Visual disorders were reported in 21% of the integrated safety population; most cases were Grade 1, with 14% Grade 2 and 0.8% Grade 3 severity. The disorders spanned a range of events: The spectrum of AEs related to vision disorders including blurred vision (9%), photophobia (5%), diplopia (3.1%), visual impairment (2%), photopsia (1.3%), vitreous floaters (1.1%), cataract (1.1%), vitreous detachment (0.8%) and 1 patient (0.3%) each with vitreous adhesions, blindness, corneal erosion, keratitis and retinal haemorrhage. Periorbital edema and eyelid swelling also occurred. Entrectinib was continued in most cases.

An FDA ophthalmology review advised that severe visual disturbances were unlikely to be related to a direct effect on the eye, and were more likely to be related to CNS metastases or the effect of entrectinib on the CNS (similarly to crizotinib).

Entrectinib causality is considered likely for many of the visual disorders reported, based on biological plausibility, the observed neurological effects in other organ systems, positive temporality, and a number of positive dechallenges. In addition to CNS effects, a subset of the observed events are consistent with dry eye syndrome or allergic response, whilst the remainder of events were considered attributable to normal aging.

Skeletal fractures

In addition to central roles in nervous system development and maintenance, TRKA, TRKB and TRKC are also implicated in skeletal tissue formation and healing. Particularly, TRKA signalling is required for communication between osteoblasts and sensory nerves during load induced bone formation in mice.[31] Neither fractures nor tooth problems were observed with entrectinib in toxicology studies.

Reports of bilateral femoral neck fractures in paediatric patients presented at the annual American Society of Clinical Oncology meeting in June 2019;[32] prompted additional scrutiny of this concern. A signal analysis was requested by FDA and performed by the sponsor using data from 528 patients (498 adults and 30 patients under 18 years of age) treated up until 8 March 2019 in ALKA or STARTRK-1 trial, or 3 May 2019 in STARTRK-2 or STARTRK-NG trial.

From this signal analysis, 34 patients with fractures (27 adult and 7 paediatric) were identified, 15 of them serious (3 serious paediatric cases). In all paediatric cases, the fractures involved minimal or no trauma. Two were cases of bilateral femoral neck fractures (in a 4 year old female and a 9 year old male). For both paediatric and adult cases, the median time of onset was around 4 months. Entrectinib was interrupted for 44% of patients and not discontinued for any patient. Complete healing had occurred for 71% of the paediatric and 63% of the adult cases at time of data cut-off. No data are available on how entrectinib affects healing of known fractures or risk of future fractures.

For many of the cases there were confounding factors such as pre-existing osteopenia, steroid use or bone metastases. A specialist case review by FDA concluded that most fractures did not appear to be due to tumour pathology at the fracture site, but there was limited data available from which to conclude this (lack of biopsies). A history of osteoporosis was present in 5 of the 27 adults with fractures.

The rate of fractures in entrectinib treated adults (about 5%) does not appear larger than the background rate the FDA estimates for adults with solid tumours (up to 18%), but for the paediatric patients, the FDA estimates a background rate of 6%. The observed rate of about 23% incidence in paediatric patients is therefore of significant concern, and it may be that there is more reliance on TRK signalling in paediatric bone biology.

A specific postmarket requirement has been agreed to by the sponsor with the FDA to address this safety concern.[14] Additional detail regarding FDA recommendations for clinical data collection and study methodology are contained on pages 209-210 of the multidisciplinary review document for the NTRK indication.[14]

Hepatotoxicity

Toxicology studies suggested hepatotoxicity could be a clinical concern.

Although AST and ALT elevations were very common (around 40%), the majority were low grade (for each, the incidence of Grade 3 to 4 elevations was about 3%). AST elevation and ALT elevation both led to dose interruption in around 10% of patients and dose reduction in around 2% of patients, but no discontinuations. No cases consistent with Hy's

[31] Tomlinson RE, Li Z, Li Z, Minichiello L, Riddle RC, Venkatesan A, Clemens TL. NGF-TrkA signaling in sensory nerves is required for skeletal adaptation to mechanical loads in mice. *Proc Natl Acad Sci U S A.* 2017 May 2;114(18): E3632-E3641.

[32] Robinson GW, Gajjar AJ, Gauvain KM, Basu EM, Macy ME, Maese LD, Sabnis AJ, Foster JH, Shusterman S, Yoon J, Weiss BD, Abdelbaki M, Farid-Kapadia M, Meneses-orente G, Cardenas A, Hutchinson K, Bergthold G, Maneval EC, Fox E and Desai AV. Phase I/IB trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumors including central nervous system (CNS) tumors. *Journal of Clinical Oncology* 2019 37:15_suppl, 10009-10009.

Law;[33] (for example suggestive of drug induced liver injury) were reported: there were five (1.4%) cases who had concurrent elevations ALT or AST (> 3 times ULN) and elevated total bilirubin (> 2 times ULN), but in all of these, there were significant confounding factors preventing a conclusion of Hy's Law being met.

Hyperuricaemia

Hyperuricaemia was reported as an adverse event in 32 patients (9%) in the integrated safety population. The majority of cases were CTCAE Grade 1, except 6 cases which were all Grade 4. One occurred in the context of tumour lysis syndrome which was fatal. All the cases except one Grade 4 case had resolved at the time of data cut-off: 2 (6%) required dose reduction, another 2 (6%) required dose interruption, and the remainder were able to be managed with urate reducing medication.

Of 259 patients that had baseline and post-treatment urate levels available, there were 134 (52%) patients with hyperuricemia of any grade. Of these, 24 had levels above 10 g/dL (defined as Grade 4 elevation by the reviewers) and 3 had post-Baseline levels that weren't higher than 10 g/dL but had an AE reported and were treated with allopurinol (defined as 'physiological consequences' and therefore Grade 3 elevation per CTCAE by the reviewers).

Embryofetal toxicity

Based on mechanism of action, embryofetal toxicity is predicted and appropriate warnings regarding females of reproductive potential should be included in the Australian PI.

Weight changes

TRKB is implicated in appetite control, and clinical events of weight gain could be predicted to occur with entrectinib based on mechanism of action. Weight changes were reported by around 25% of patients, 7% at Grade 3 severity (defined by the CTCAE as >20% from Baseline). Fluid retention or oedema was co-reported for a number of cases and may have contributed.

Paediatric safety

The adverse event profile of entrectinib in paediatric patients (defined as patients less than 18 years of age, n = 30) was compared to that for adults (n = 338), noting that the size of the populations and trial design limits interpretation (see Table 26).

The FDA report characterises this group, in summary, as follows:

> 'Of these 30 patients, 7% were < 2 years (n = 2), 77% were 2 to < 12 years (n = 23), 17% were 12 to < 18 years (n = 5); 57% had metastatic disease (n = 17) and 44% had locally advanced disease (n = 13); and all patients had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common cancers were neuroblastoma (47%), primary CNS tumors (30%), and sarcoma (10%). The median duration of exposure for all pediatric patients was 4.2 months (range: 0.2 to 22.7 months).'

[33] Hy's law is a observation that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury with jaundice.

Table 32: Overview of Grade 3 or 4 adverse events that were at least 5% more frequent in patients under than over the age of 18 years in the integrated safety population

Event/laboratory abnormality	Paediatric (n = 30)	Adult (n = 338)
Neutropenia	8 (27%)	7 (2%)
Bone fractures	7 (23%)	17 (5%)
Increased weight	6 (20%)	24 (7%)
Thrombocytopenia	3 (10%)	1 (0.3%)
Lymphopenia	2 (7%)	3 (1%)
Increased gamma-glutamyl transferase	2 (7%)	0

Source: FDA multidisciplinary review.[14]

Grade 3 or 4 device related infections were also higher in paediatric patients than adults (7% versus 3%).

Three discontinuations due to an adverse reactions occurred in the paediatric group due to a Grade 4 pulmonary oedema, Grade 3 dyspnoea, and Grade 4 pancreatitis.

Skeletal fractures and effects on bone and tooth development are considered possible risks attributable to entrectinib in paediatric patients based on the mechanism of action of entrectinib, and findings in toxicology studies. Juvenile rats treated with entrectinib showed growth delay (including shorter bones) and impaired learning and memory. Dose dependent toxicity (especially bone related) was also seen in foetal rat development, though mainly at a dose three times the human exposure at the proposed dosage. No fractures or tooth problems were seen in animal studies, but as noted in section above, skeletal fractures, two patients (a 9 year old and a 4 year old) treated with entrectinib in STARTRK-NG trial developed bilateral leg fractures.

Safety-related conclusions

The safety dataset is limited, both in population size (355 patients) and duration of exposure (median 5.5 months and maximum 42 months). It is also demographically heterogeneous, although ECOG performance status was mainly 0 or 1. The database is considered adequate to evaluate safety of entrectinib for the proposed usage in adults, in context of the rarity of both *NTRK* fusion-positive tumours and *ROS1* fusion-positive NSCLC, and the magnitude of the observed response rates.

The safety profile of entrectinib in the paediatric population is based on limited data (n = 30). The FDA reviewer commented:[14]

> 'In addition to the increased incidence of skeletal fractures, cytopenias, and elevated liver enzymes, infections appeared to be more common in the pediatric population; however, pediatric patients are prone to seasonal illnesses such upper respiratory infections and the symptoms that accompany them such as cough, nasal congestion.
>
> As noted above, due to the small number of pediatric patients, the modest size of the safety database in adults (n = 338), the single arm design of clinical studies of entrectinib, and confounding factors such as differences in susceptibility to

> infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse reactions to entrectinib are related to patient age or other factors.'

The adverse effect profile observed across the trials appears to be consistent with the mechanism of action of the drug, and the studied population. As entrectinib crosses the blood-brain barrier and neurotoxicity appears to be a TRK inhibitor class effect, the high rate of observed neurological adverse events was foreseeable. Adverse effects included cognitive, mood, sensory (visual, proprioceptive, satiety), dyspnoea and sleep disorders, as well as cardiac failure and skeletal fractures (particularly in the paediatric population). Monitoring will be required for QT;**Error! Bookmark not defined.** prolongation, liver enzyme elevation and hyperuricaemia.

Serious and fatal adverse events predominantly appear consistent with disease progression, cancer related conditions or oncology treatment related adverse effects, but causality in a case of completed suicide can't be discounted due to the observed potential for neurological adverse events including mood and cognitive change. Another fatal adverse event concerned a patient who died from tumor lysis syndrome, and for whom Grade 4 uric acid elevation was also present. Given the lack of a comparator arm and the small safety database (too small to reliably detect rare events), the interpretation of safety data is difficult, and safety data represented in the PI should be comprehensive, regardless of causality attribution.

Of the adverse events of special interest reviewed by the FDA, a number were not included in labelling:[34]

> 'AESI that were not included in the W&P section of the entrectinib product label included weight changes and clinically relevant adverse reactions occurring in < 10% of patients such as dysphagia (10%), fall (8%), pleural effusion (8%), syncope (3.9%), pulmonary embolism (4%), and hypoxia (4%). After assessment of the narratives and review of Genentech's responses to multiple FDA IRs, the reviewers decided that inclusion of these adverse events in the W&P section was not warranted either because a causal relationship between the AE and entrectinib was unclear or inclusion in the W&P section was not necessary given that oncologists are typically skilled in managing a variety of adverse reactions to drugs, including those described above.'

The FDA analyses of events, including term grouping, and label content for adverse effects and warnings/precautions was developed in consultation with expert clinicians (neurology, bone, ophthalmology) in the relevant fields. The Australian Product Information wording should be aligned with the FDA labelling for international harmonisation, and based on the clinical expertise that was involved in the development of the content.

Risk management plan

The sponsor has submitted the draft EU-risk management plan (RMP) version 1.0 (dated 18 December 2018; data lock point (DLP) 15 November 2018) and Australian specific Annex (ASA) version 1.0 (dated May 2019) in support of this application. At the second round of evaluation, the sponsor submitted updated versions: EU-RMP version 1.2 (dated 6 November 2019; DLP 31 October 2018) and ASA version 2.0 (dated December 2019). Following the second round of evaluation, the sponsor submitted an updated ASA version 3.0 (dated February 2020) and an updated conversion strategy for full registration.

[34] FDA Prescribing Information for Rozlytrek. Accessed via FDA.gov.

The RMP summary of safety concerns and their associated risk monitoring and mitigation strategies (versions as at December 2019) are summarised in Table 27.[35]

Table 33: Sponsor's summary of safety concerns list with monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Congestive heart failure	ü	ü	ü	–
	QT prolongation	ü	ü	ü	–
	Fractures	ü	ü	ü	–
Important potential risks	Severe neurologic reactions	ü	ü	ü*	–
	Neuro-developmental impairment in paediatric patients	ü	ü	ü*	–
Missing information	Safety in long term use	–	ü	–	
	Use in patients with hepatic impairment	ü	ü–	ü	–

* Jointly under the description 'cognitive disorders'

Confirmatory data requirements

Confirmatory data requirements for Australian provisional registration relate to the NTRK indication only.

Confirmatory data commitments made to the FDA were:[14]

- Postmarketing requirement (PMR) 3689-1 (expected availability June 2021): submission of a final report and datasets for the group of 54 patients whose data supported initial registration with at least 2 years follow-up from onset of response or until disease progression, whichever comes first.
- PMR 3689-2 (expected availability March 2027): submission of a final report and datasets with additional NTRK-positive patients recruited across studies, with minimum follow-up of 12 months from onset of response for responders, requiring:
    - A sufficient number of patients to provide more precise estimates of response rates and durability for paediatric solid tumors, colorectal cancer, CNS system cancers, gynecological cancers, and melanoma

[35] [35] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[35] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

- A minimum of 40 patients with cancers other than the above, and other than soft tissue sarcoma, non-small cell adenocarcinoma lung cancer, mammary analogue secretory carcinoma, and secretory breast cancer.

For the purposes of confirmatory data for Australian provisional registration, the sponsor proposes to provide the same data. This proposal is acceptable, noting the TGA require the final reports but not full datasets.

In Australia, provisional registration is granted for two years, with a maximum of two extensions, so that the entire length of provisional registration allowable is six years. Recognising that the rate of accrual is affected by the rarity of the condition, the provisional registration of an NTRK indication may lapse before the data required by the FDA are available. In this circumstance, there are three main possible courses of action foreseen:

- The sponsor could do nothing and the provisional indication would lapse.
- The sponsor could apply for a new provisional registration designation and if approved, submit a new extension of indication application to register the same provisional indication.
- The sponsor could submit a conversion to full registration application based on whatever evidence is available at that time. If this path was taken, the TGA Delegate would have to make a risk-benefit assessment based on the available data, incorporating residual uncertainty.

Proposed wording for the conditions of registration is located in section below, '*Conditions of registration'*.

Other postmarket activities

In addition to routine pharmacovigilance and risk minimisation activities, and in line with commitments made to the FDA, the sponsor proposes to undertake analyses of data from ongoing clinical trials to address the risks of congestive heart failure, QT;**Error! Bookmark not defined.** prolongation, fractures, severe neurologic reactions, neuro-developmental impairment in pediatrics patients, and longer term and developmental safety. A dedicated study is planned to investigate use in patients with moderate or severe hepatic impairment. Outcomes of the above activities should be reported to the TGA as (non-provisional registration specific) conditions of registration. Proposed wording is outlined in section below, '*Conditions of registration*'.

As entrectinib is a new chemical entity and is being considered for a provisionally registered indication, it will also be included in the Black Triangle Scheme.[1]

Risk-benefit analysis

Delegate's considerations

In vitro diagnostic issues

Clinical trial assay

Diagnostic testing in the *ROS1* and *NTRK* efficacy sets are described in detail in the '*Clinical*' section, above, diagnostic testing in the ROS1 efficacy set and diagnostic testing in the NTRK efficacy sets.

A single site RNA based NGS test (Trailblaze Pharos)[24] was developed specifically for use in entrectinib studies, and was designed and operated at Ignyta, the former sponsor of entrectinib. This test was used to centrally confirm identified fusions where possible:

- Of the 51 patients in the ROS1 Primary Analysis Set, 30 (59%) had a Pharos result.
- Of the 54 patients in the NTRK efficacy evaluable set, 45 (85%) had a Pharos result.

No tissue for retesting was available for any samples.

All *NTRK* fusions were identified by nucleic acid based testing, whilst 24% of *ROS1* fusions (n = 12) were identified by FISH alone. The use of FISH to identify ROS1 in NSCLC is in keeping with current clinical practice.

Companion diagnostic testing for selection for entrectinib therapy

Currently, there is no FDA approved companion diagnostic for identification of *ROS1* rearranged tumours. A DNA based FoundationOne NGS companion diagnostic (F1CDx) was under development at the time of FDA approval and has since been submitted to the FDA for both the *ROS1* and *NTRK* indications in the USA.

Australian availability of FoundationOne CDx testing

A summary of the issues around testing in Australia was given by the sponsor in their submission for provisional designation of the NTRK indication:

> 'FoundationOne CDx (F1CDx) is an NGS based assay for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumour mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumour tissue specimens. The F1CDx assay is a single site assay performed at Foundation Medicine, Inc.
>
> …
>
> is currently available in Australia as a service whereby patient samples are transported to the USA for testing. As the testing occurs outside Australia, there is currently no regulatory framework to register the test here.'

The sponsor stated in a response to the TGA clinical evaluator that no discussions with laboratory service providers in Australia are underway with respect to developing an accredited laboratory test for the gene rearrangements in Australia, however:

> '…the sponsor has developed FoundationOne CDx as a global companion test for Rozlytrek which is available commercially in Australia, but with the testing performed in the US. The sponsor also understands that alternative, comparable tests are currently available in Australia. The sponsor did not provide performance comparisons for these tests.'

FoundationOne Heme appears to be an NGS test that incorporates both RNA and DNA sources, and therefore increases sensitivity, however, it is not the diagnostic intended for companion status in the US.

Testing for ROS1 in the absence of a companion diagnostic

The FDA's rationale for approval of entrectinib despite the absence of a companion diagnostic was as follows:[14]

> 'Given the efficacy of entrectinib in patients with ROS1 gene fusion-positive unresectable or metastatic NSCLC, the low prevalence of this subset of NSCLC (1-2% of all NSCLC) and the availability of non-companion diagnostic testing for ROS1 fusions in NSCLC, the clinical review team determined that it is in the best interest of U.S. patients to approve entrectinib before one or more companion diagnostic assays are ready for premarket approval application (PMA) submission. Since a PMA for an *in vitro* companion diagnostic device was not submitted for contemporaneous approval with this NDA, approved labeling will state that there

> is no FDA-approved for detection of ROS1 rearrangement(s) in NSCLC for selecting patients for treatment with entrectinib. Genentech has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect ROS1 rearrangements for identifying patients who may benefit from entrectinib.'

The TGA Delegate is in agreement with this approach.

The most sensible current approach to *ROS1*-positive tumour identification appears to be the approach used to identify patients for crizotinib therapy of the same indication. That is: use of immunohistochemistry (IHC) as a screening tool (with positivity cut-offs defined for high sensitivity), then using FISH to confirm positive or unclear IHC results.[36] In Australia, *ROS1* testing by FISH (for determination of eligibility for treatment with crizotinib) is subsidised for patients with a documented absence of both EGFR and ALK mutations, who are *ROS1*-positive by IHC. Direct DNA sequencing can be used to identify the fusion gene partner in confirmed cases or to adjudicate where FISH and IHC are in disagreement.

This approach is predicted by the sponsor to be used for identification of patients with *ROS1* mutations for the purposes of treatment with entrectinib.

Development and validation of a companion diagnostic test for ROS1 rearrangement should nevertheless be a condition of entrectinib registration as a broad range of tests were used in the clinical trial, and this will provide a reference standard. Proposed registration condition wording is outlined in the section below, '*Conditions of registration*'.

Testing for neurotrophic tropomyosin receptor kinase in the absence of a companion diagnostic

The FDA indicates in their multidisciplinary review that the post-marketing requirement agreed to by the US sponsor incorporates development of a testing approach with acceptable sensitivity and specificity, noting that addition of RNA sequencing to the DNA NGS methodologies for *NTRK* fusions improved its performance:[14]

> '… the most popular commercially available DNA next generation sequencing (NGS panels, such as FoundationOne CDx, may not detect certain NTRK gene fusions.[37] However, the addition of RNAseq to NGS testing has resulted in high sensitivity and specificity rates, 93% and 100% respectively, in detecting clinically actionable gene fusions. In addition, RNAseq requires no prior knowledge of fusion partners or intronic/exonic break points. For this reason, FDA requested and Genentech agreed to a post-marketing requirement to identify an analytically validated test for detection of NTRK in-frame gene fusions.
>
> …
>
> Genentech did not submit (or identify a corporate partner to develop and submit) a PMA for an *in vitro* companion diagnostic device contemporaneously with these NDAs (212725 and 212726). Therefore, approved labeling will state that there is no approved companion diagnostic test for the identification of patients with NTRK-fusion solid tumors. DOP2 consulted the Center for Devices and Radiologic Health (CDRH) regarding use of local tests for determination of NTRK fusion status. Given the efficacy of entrectinib in patients with NTRK gene fusions in unresectable or metastatic solid tumor specimens and the availability of non-companion diagnostic testing for NTRK fusions in solid tumors, the clinical review

[36] Rossi G, Jocollé G, Conti A, et al. Detection of ROS1 rearrangement in non-small cell lung cancer: current and future perspectives. *Lung Cancer (Auckl).* 2017;8:45–55.
[37] Ed S. Kheder and David S. Hong. Emerging Targeted Therapy for Tumors with NTRK Fusion Proteins. *Clin Cancer Res*. 2018 (24) (23) 5807-5814.

> team and CDRH agreed that it is in the best interest of U.S. patients to approve entrectinib before one or more companion diagnostic assays are ready for a PMA submission.'

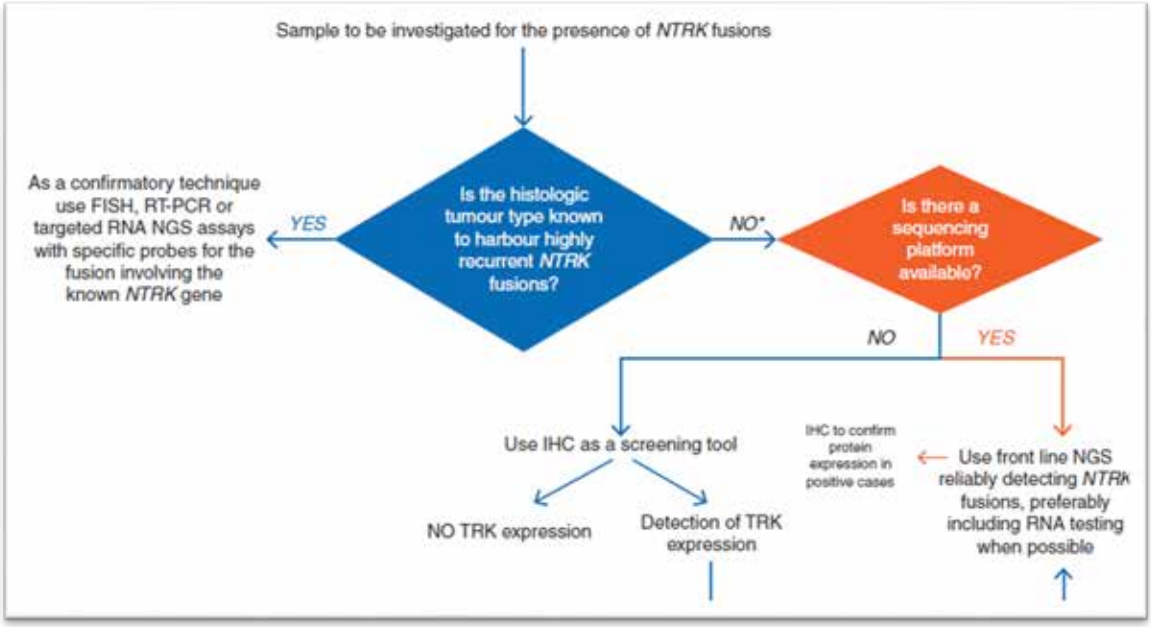
The TGA Delegate agrees with the FDA approach that the lack of an approved companion diagnostic should not be a barrier to registration given the magnitude of efficacy observed and the rarity of the condition. The risks of non-companion diagnostic testing are mediated by the non TGA regulatory controls to which laboratory testing in Australia is subject, noting also that false positives are very unlikely based on the nature of the mutation. Development and validation of a companion diagnostic test for NTRK rearrangement should, however, be a condition of entrectinib registration as a broad range of tests were used in the clinical trial, and this will provide a formal reference standard.

The small study population makes it impossible to draw conclusions about efficacy within diagnostic test or histology subgroups. However, an European Society for Medical Oncology (ESMO) expert panel was convened to consider the best approach to the detection of *NTRK* fusions in daily practice and clinical research. Their recommendations were published in 2019, concluding:[38]

> 'In tumours where *NTRK* fusions are highly recurrent, FISH, RT-PCR or RNA based sequencing panels can be used as confirmatory techniques, whereas in the scenario of testing an unselected population where *NTRK1/2/3* fusions are uncommon, either front line sequencing (preferentially RNA sequencing) or screening by immunohistochemistry followed by sequencing of positive cases should be pursued.'

These recommendations, summarised in the published infographic (reproduced below as Figure 2), form a useful guide.**Error! Bookmark not defined.**

Figure 2: Infographic ('Figure 2') from the ESMO Translational Research and Precision Medicine Working Group publication. Error! Bookmark not defined.



[38] Marchiò C, Scaltriti M, Ladanyi M, Iafrate AJ, Bibeau F, Dietel M, Hechtman JF, Troiani T, López-Rios F, Douillard JY, Andrè F, Reis-Filho JS. ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. Ann Oncol. 2019; 30(9):1417-1427.

As the proposed companion diagnostic remains in development and validation, and may not be a feasible option for Australian patients depending on access and funding arrangements, the most appropriate current approach to identification of *NTRK* appears to be the algorithmic approach suggested by ESMO, or the similar one suggested by Penault-Llorca *et al*.[39]

Risk-benefit analysis

ROS1 fusion-positive non-small cell lung cancer

After a minimum follow-up of 12 months, the ORR (95% CI) in 51 consecutively enrolled patients with ROS1 fusion-positive NSCLC across three clinical trials (the ALKA, STARTRK-1 and STARTRK-2 trials) was 78.4% (64.7%, 88.7%), including a CR rate of 6% and PR rate of 73%, with a median (95% CI) DOR of 15.7 (11.4, 34.8) months. At a data cut-off date of 31 October 2018, 75% of responses had lasted at least 6 months, and 55% of responses had lasted at least 12 months. Subgroup sizes were small, but support conclusions of presence of intracranial activity, and similarity of response rates between patients who had and had not received previous (non-anti-ROS1) systemic therapy for metastatic disease.

Head to head comparative data against other therapies is not available as *ROS1*-positive NSCLC is too rare for a randomised study to be feasible. Crizotinib is the only currently registered therapy for *ROS1*-fusion positive NSCLC in Australia, and was registered based on single arm data (n = 53), but has not demonstrated intracranial efficacy. The response rates and durability demonstrated with entrectinib appear in keeping with those seen with crizotinib, and higher than those reported for first-line ROS1-agnostic therapy of NSCLC patients (anti-PD-L1 plus chemotherapy).

The major limitations of the submitted dataset are short duration of follow-up and small size; median duration of response is therefore not able to be precisely estimated. Despite the limitations of the data, the magnitude of response rate and durability of responses demonstrated are considered sufficient to establish efficacy for the proposed usage, based on the clinical benefit associated with tumour responses in NSCLC, the infeasibility of conducting randomised studies in this indication due to the rarity of its occurrence, and cross-trial comparisons which indicate that efficacy is likely to be acceptable to patients with *ROS1* fusion-positive NSCLC. Additional data is expected to be collected through further recruitment of patients with *ROS1*-positive NSCLC and further follow-up of the patients included in the registration dataset, to provide a more precise estimate of ORR and DOR.

The sponsor has also made post-market commitments to development and validation of a companion diagnostic. In view of the magnitude of clinical benefit observed and lack of other therapy with intracranial effectiveness, and noting that non-companion diagnostic testing is available and false positives on sequencing are very unlikely with this type of mutation, addressing this post-approval is acceptable.

The risks of therapy with entrectinib have been assessed from a database limited in size and duration of exposure (n = 355, mediation duration of exposure 5.5 months). The lack of comparative, randomised data also limits interpretability of the safety profile. Despite its shortcomings, the safety dataset is considered adequate to evaluate safety of entrectinib for the proposed usage, in context of the rarity of *ROS1* fusion-positive NSCLC and the magnitude and duration of the observed response rates. Due to the limitations of the data (single arm, small population and short follow up), conservative representation of safety data in the PI is advisable.

[39] Penault-Llorca F, Rudzinski ER, Sepulveda AR. Testing algorithm for identification of patients with TRK fusion cancer. *J Clin Pathol*. 2019 Jul;72(7):460-467.

The safety population was demographically heterogeneous, although ECOG PS was mainly 0 or 1. Noting the limited sample sizes, significant differences in safety were not identified between in subgroups based on demographics.

Based on the observed clinical data, the most significant risks appear to include:

- Congestive cardiac failure
- Neurotoxicity: cognitive, mood, sensory and sleep disorders, ataxia, dizziness and headaches (entrectinib crosses the blood-brain barrier and neurotoxicity appears to be a TRK inhibitor class effect)
- Skeletal fractures (these were most notable in the paediatric population to whom the ROS1 NSCLC indication is not relevant)
- Hepatotoxicity, QT;**Error! Bookmark not defined.** prolongation and hyperuricemia: these require precautionary PI text to ensure appropriate monitoring and treatment.

Common (≥ 20%) but less serious reported toxicities included fatigue, oedema, gastrointestinal effects (diarrhoea, constipation, nausea and vomiting), weight gain, cough, pyrexia, and arthralgia. Fatal adverse events included a case of completed suicide, and a case of tumour lysis syndrome with concurrent Grade 4 uric acid elevation.

Most patients who discontinued treatment did so due to disease progression, with 9% of patients discontinuing due to adverse effects.

The sponsor has committed to further clinical study to better characterise the risk of congestive heart failure, skeletal fractures, off target effects, and the effect of moderate or severe hepatic impairment on entrectinib PK.

Neurotrophic tropomyosin receptor kinase fusion- positive solid tumours

After a minimum follow-up of 6 months, in a group of 54 consecutively enrolled patients across three clinical trials (the ALKA, STARTRK-1 and STARTRK-2 trials) who had NTRK fusion-positive extracranial solid tumours, had not received prior anti-NTRK therapy, and who did not have any satisfactory treatment options or had progressed after any acceptable therapy, the ORR (95% CI) was 57% (43%, 71%), including a CR rate of 7% and a PR rate of 50%, with a median (95% CI) DOR of 10.4 months (7.1, not estimable). At a data cut-off date of 31 October 2018, 68% of responses had lasted at least 6 months, and 45% of responses had lasted at least 12 months. Very limited data also supports activity against intracranial metastases, as well as efficacy in CNS primary disease. Data in a very small subgroup supports conclusions of activity against intracranial metastases. Although patients with primary CNS tumours were excluded from the main NTRK efficacy set, limited additional information is able to support a decision not to exclude such patients from the provisional indication.

Renal and hepatic maturity in people aged between 12 years and 18 years is similar enough to adults (people over the age of 18 years) to allow extrapolation of the efficacy data for entrectinib in last-line therapy of *NTRK*-positive solid tumours, based on comparable PK profiles in adults (in the ALKA, STARTRK-1 and STARTRK-2 trials) and adolescent patients (in a fourth entrectinib trial in paediatric patients: STARTRK-NG trial). The BSA based dosing approach approved by the FDA in this age group is preferred to the sponsor's proposed BSA based dosing, as it better fits the observed data and provides a smoother dose adjustment across BSA categories. There was insufficient data available in patients younger than 12 years to allow a safe and effective dose to be determined.

The rarity of this diagnosis and the heterogeneity of histologies in which *NTRK* rearrangements are seen renders randomised trials in this population infeasible. The single arm, pooled design and size limitations of this dataset are therefore acceptable, and able to support a regulatory decision.

Approval of histology agnostic indications represents a new paradigm in regulatory medicine. In the case of entrectinib, there is strong scientific rationale that TRK inhibition should induce regression in tumours harbouring an *NTRK* fusion mutation regardless of fusion gene partner, and supportive preclinical data indicating such an effect across multiple cell lines.

In patients with treatment refractory solid tumours, either no treatment options remain or those that do are usually associated with significant morbidity and/or poor efficacy, with response rates generally less than 30%. The magnitude of response rate and durability of responses demonstrated with entrectinib in this treatment context are considered likely to predict clinically meaningful benefit in such patients. However, the estimates of response rate and duration in the overall *NTRK*-positive population as well as in subgroups based on histology are imprecise due to the small overall population and very small subgroup sizes. There also remains a risk that efficacy is not present in some histologies, though responses appear to be consistent across tumour histologies from the limited data available. This risk is considered acceptable in context of the therapy being used last-line, for example an effective alternative therapy is not available.

Additional data is expected to be collected through further enrolment and follow-up of the STARTRK-2 and STARTRK-NG clinical trials. This confirmatory data is expected to allow a more precise estimate of response rate and duration of response in *NTRK* fusion-positive solid tumours overall, in histological subgroups, including CNS primary disease, and in paediatric patients.

The sponsor has also made post-market commitments to development and validation of a companion diagnostic. In view of the magnitude of response rate observed and lack of available therapies for these treatment refractory patients, and noting that non companion diagnostic testing is available and false positives on sequencing are very unlikely with this type of mutation, addressing this post-approval is acceptable.

The safety profile for entrectinib in the treatment of *NTRK* fusion-positive solid tumours is based on the same safety dataset as for ROS1 fusion-positive NSCLC (see above). Pooling of the safety data, as presented in the FDA label, is considered appropriate in this instance based on the size and single arm nature of the safety dataset: separate presentation would not provide additional meaningful clinical guidance for prescribers.

Safety for paediatric patients with *NTRK* fusion-positive solid tumours over the age of 12 years is extrapolated from that seen in the main *NTRK* efficacy population in conjunction with PK modelling.

Very limited supporting data is available from 30 paediatric patients treated with entrectinib in STARTRK-NG trial. Interpretation of this data is limited based on the very small sample size, but descriptively, higher grade (CTCAE Grade 3 or 4) adverse events that occurred more frequently (at least by 5%) compared with the adult safety database (n = 338) were neutropaenia (27% versus 2%), fractures (23% versus 5%), thrombocytopaenia (10% versus 0.3%), lymphopaenia (7% versus 1%), increased gamma-glutamyl transferase (7% versus 0%), device related infection (7% versus 0.3%), and increased weight (20% versus 7%). Three such events (Grade 3 dyspnoea, Grade 4 pulmonary oedema and Grade 4 pancreatitis) led to discontinuation.

Safety data in patients under the age of 12 is very sparse, and PK modelling was unable to support identification of a safe and effective dose for this patient group.

Based on mechanism of action and preclinical data, the potential for on and off target effects in a developing human and the short duration of clinical follow up in the paediatric safety population to date raise concerns around developmental toxicities.

A further toxicity of specific concern in the paediatric population is adverse effects on bones and teeth. Fractures were reported in 23% of paediatric patients (all associated

with minimal or no trauma) compared to 5% of adults (in whom confounders such as steroid use or bone metastases were present, although evidence of fracture at site of bone metastasis was not available).

Further collection of safety data is expected as outlined above for the ROS1 indication, including specific addressing of the fracture risk in paediatric patients. Additional to these, the sponsor has committed to further clinical study to better characterise longer term effects of entrectinib on growth and development when used in paediatric patients.

Conditions of registration

Confirmatory data requirements for provisional registration

Confirmatory data commitments made to the FDA relating to the accelerated approval of the *NTRK* indication are outlined in the '*Confirmatory data requirements*' section above**.** For the purposes of Australian provisional registration, the sponsor proposes to provide the same confirmatory data. This proposal is acceptable (noting the TGA request to receive reports but not original datasets).

In Australia, provisional registration is granted for two years, with a maximum of two extensions, so that the entire length of provisional registration allowable is six years. Provisional registration may lapse before all of the information outlined in Appendix 1 is available. The possible actions that the Delegate foresees sponsor could take if this scenario occurs are outlined in section above, confirmatory data requirements.

In recognition of the predicted timeframes, the uncertainty around these and the possibility that provisional registration lapse may precede final report availability, the Delegate proposes to not specify a date by which submission of a final report for the NTRK indication is expected.

The Delegate proposes the following wording for the condition of registration specific to confirmatory data requirements for Australian provisional registration (for the NTRK indication only, submission PM-2019-01809-1-4):

> Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided. Specifically, the sponsor must:
>
> - Conduct studies as described in the clinical study plan in version 3.0, dated February 2020, of the Australia-specific Annex;
> - Submit, by June 2021, a final report for the group of 54 patients whose data supported initial registration of the NTRK solid tumour indication, with at least 2 years of follow-up from onset of response or until disease progression, whichever came first;
> - Submit annual interim progress reports (recruitment status) and interim clinical study reports incorporating data for patients with NTRK fusion-positive solid tumours enrolled across the ALKA, STARTRK-1 and STARTRK-2 trials, with minimum follow-up of 12 months from onset of response for responders, and requiring:
>   - A sufficient number of patients to provide more precise estimates of response rates and durability for paediatric solid tumours, colorectal cancer, CNS system cancers, gynaecological cancers, and melanoma; and
>   - A minimum of 40 patients with cancers other than the above, and other than soft tissue sarcoma, non-small cell adenocarcinoma lung cancer, mammary analogue secretory carcinoma, and secretory breast cancer.
> - Submission of an interim clinical study report is expected by 2024

Additional conditions for submission PM-2019-01808-1-4

The Delegate proposes the following additional conditions of registration for the ROS1 indication only (submission PM-2019-01808-1-4):

> The sponsor must submit to TGA all of the same reports that are submitted to the FDA in fulfilling their postmarket requirements and commitments relevant to the FDA registration of entrectinib for *ROS1*-positive NSCLC. The reports are expected to include:
>
> - Analytical and clinical validation of a companion diagnostic device to detect *ROS1* rearrangements for the identification of patients who may benefit from entrectinib (submission expected during 2020)
> - A study of off-target activation or inhibition by entrectinib including receptors involved in suicidal ideation (submission expected September 2020)
> - A final report characterising response rates and duration of responses in a group of at least 92 patients with *ROS1*-positive NSCLC enrolled across ALKA, STARTRK-1 and STARTRK-2 trials, including the 51 patients whose data supported initial registration of the ROS1-positive NSCLC indication, once all responders have been followed for at least 18 months from the date of initial response (submission expected June 2021)
> - A study of the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of entrectinib (submission expected December 2021)
> - A study of cardiac risks and sequelae (submission expected June 2022)
> - A study of fracture risks and sequelae (submission expected March 2025).

Additional conditions for submission PM-2019-01809-1-4

The Delegate proposes the following additional conditions of registration for the NTRK indication only (submission PM-2019-01809-1-4):

The sponsor must submit to TGA all of the same reports that are submitted to the FDA in fulfilling their postmarket requirements and commitments relevant to the FDA registration of entrectinib for *NTRK*-positive solid tumours. The reports are expected to include:

- Analytical and clinical validation of a companion diagnostic device to detect *NTRK* rearrangements for the identification of patients who may benefit from entrectinib (submission expected during 2020)
- A study of off target activation or inhibition by entrectinib including receptors involved in suicidal ideation (submission expected September 2020)
- A study of the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of entrectinib (submission expected December 2021)
- A study of cardiac risks and sequelae (submission expected June 2022)
- A study of fracture risks and sequelae (submission expected March 2025)
- A final clinical study report incorporating data for patients with *NTRK* fusion-positive solid tumours enrolled across the ALKA, STARTRK-1 and STARTRK-2 trials, with minimum follow-up of 12 months from onset of response for responders, and requiring:
  - A sufficient number of patients to provide more precise estimates of response rates and durability for paediatric solid tumours, colorectal cancer, CNS system cancers, gynaecological cancers, and melanoma; and

- A minimum of 40 patients with cancers other than the above, and other than soft tissue sarcoma, non-small cell adenocarcinoma lung cancer, mammary analogue secretory carcinoma, and secretory breast cancer.

(submission expected March 2027)

- A study of longer term effects of entrectinib on growth and development in paediatric patients 12 years of age and older (submission expected August 2029).

Proposed action

ROS1 fusion-positive non-small cell lung cancer

The benefit-risk balance for the proposed usage is considered favourable for the purposes of Australian registration. The durable responses observed with entrectinib treatment in *ROS1* fusion-positive NSCLC, in context of the morbidity and mortality associated with this disease and alternative treatments, are likely to make treatment with entrectinib acceptable to patients, despite the serious risks. The lack of randomised data to support assessment of time to response endpoints and provide head to head comparison is acceptable due to the rarity of the condition and therefore infeasibility of randomised trials.

Neurotrophic tropomyosin receptor kinase fusion-positive solid tumours

The benefit-risk balance for the proposed usage is considered favourable for the purposes of Australian provisional registration. Durable responses have been observed with entrectinib treatment in this population of patients with *NTRK* fusion-positive solid tumours who have refractory disease or no acceptable therapeutic options and no concurrent alternative driver mutation that may confer resistance. In context of the morbidity and mortality associated with refractory cancer, the clinical benefit associated with durable response is likely to make treatment with entrectinib acceptable to patients, despite the serious risks. The lack of randomised data to support assessment of time to response endpoints is acceptable due to the rarity of the condition and therefore infeasibility of randomised trials. Uncertainty remains over the precision of the estimate of response rates and durability in specific histologies, as well as usage in paediatric patients.

Due to a paucity of suitable paediatric data and the failure of allometric scaling using a fixed exponent of 0.75 to adequately predict observed exposure in adult and adolescent patients, a safe and effective dose couldn't be established, and safety and efficacy for the intended use could not be established for paediatric patients under the age of 12.

Advisory Committee considerations[40]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

[40] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Outcome

Submission PM-2019-01808-1-4 (non-small cell lung cancer indication)

Based on a review of quality, safety and efficacy, the TGA approved the registration of Rozlytrek (entrectinib) 100 mg and 200 mg hard capsules for oral administration, indicated for:

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

Submission PM-2019-01809-1-4 (solid tumour indication)

Based on a review of quality, safety and efficacy, the TGA approved the provisional registration of Rozlytrek entrectinib for 100 mg and 200 mg hard capsule for oral administration, for the following extension of indications:

> *Solid tumours*
>
> *Rozlytrek is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours that:*
>
> - *have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation,*
> - *are metastatic or where surgical resection is likely to result in severe morbidity, and*
> - *have either progressed following treatment or have no satisfactory alternative therapy.*
>
> *This indication was approved via the provisional approval pathway, based on objective response rate and duration of response in single arm trials. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.*

As such, the full indications at this time were:

> ***Non-small cell lung cancer (NSCLC)***
>
> *Rozlytrek is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours are ROS1-positive.*
>
> ***Solid tumours***
>
> *Rozlytrek is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours that:*
>
> - *have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation,*
> - *are metastatic or where surgical resection is likely to result in severe morbidity, and*
> - *have either progressed following treatment or have no satisfactory alternative therapy.*
>
> *This indication was approved via the provisional approval pathway, based on objective response rate and duration of response in single arm trials. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.*

Specific conditions of registration applying to these goods

Submission PM-2019-01808-1-4 (non-small cell lung cancer indication)

- Rozlytrek (entrectinib) is to be included in the Black Triangle Scheme[1]. The PI and Consumer Medicines Information (CMI) for Rozlytrek must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product, or for the entire period of provisional registration, whichever is longer.
- The sponsor must submit to TGA all of the same reports that are submitted to the FDA in fulfilling their postmarket requirements and commitments relevant to the FDA registration of entrectinib for ROS1-positive NSCLC. The reports are expected to include:
    - Analytical and clinical validation of a companion diagnostic device to detect ROS1 rearrangements for the identification of patients who may benefit from entrectinib (submission expected during 2020)
    - A study of off target activation or inhibition by entrectinib including receptors involved in suicidal ideation (submission expected September 2020)
    - A final report characterising response rates and duration of responses in a group of at least 92 patients with ROS1-positive NSCLC enrolled across ALKA, STARTRK-1 and STARTRK-2 trials, including the 51 patients whose data supported initial registration of the ROS1-positive NSCLC indication, once all responders have been followed for at least 18 months from the date of initial response (submission expected June 2021)
    - A study of the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of entrectinib (submission expected December 2021)
    - A study of cardiac risks and sequelae (submission expected June 2022)
    - A study of fracture risks and sequelae (submission expected March 2025)
- The Rozlytrek EU-Risk Management Plan (RMP) (version 1.2, dated 6 November 2019, data lock point 31 October 2018), with Australian Specific Annex (version 2.0, dated December 2019), included with submissions PM-2019-01808-1-4 to be revised to the satisfaction of the TGA, will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than nine calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than every six months from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Submission PM-2019-01809-1-4 (solid tumour indication)

- Rozlytrek (entrectinib) is to be included in the Black Triangle Scheme. The PI and CMI for Rozlytrek must include the black triangle symbol and mandatory accompanying

text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product, or for the entire period of provisional registration, whichever is longer.

- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided. Specifically, the sponsor must:
    - Conduct studies as described in the clinical study plan in version 3.0, dated February 2020, of the Australia-specific Annex;
    - Submit, by June 2021, a final report for the group of 54 patients whose data supported initial registration of the NTRK solid tumour indication, with at least 2 years of follow-up from onset of response or until disease progression whichever came first;
    - Submit annual interim progress reports (recruitment status) and one clinical study report incorporating data for patients with NTRK fusion-positive solid tumours enrolled across the ALKA, STARTRK-1, STARTRK-2, STARK-NG trials and potentially other studies, with minimum follow-up of 12 months from onset of response for responders, and aiming at enrolment of:
        - A sufficient number of patients to provide more precise estimates of response rates and durability for paediatric solid tumors, colorectal cancer, CNS system cancers, gynecological cancers, and melanoma; and
        - A minimum of 40 patients with cancers other than the above, and other than soft tissue sarcoma, non-small cell adenocarcinoma lung cancer, mammary analogue secretory carcinoma, and secretory breast cancer.

      Submission of an interim clinical study report is expected at latest by 2023
- The sponsor must submit to TGA all of the same reports that are submitted to the FDA in fulfilling their postmarket requirements and commitments relevant to the FDA registration of entrectinib for NTRK-positive solid tumours. The reports are expected to include:
    - Analytical and clinical validation of a companion diagnostic device to detect NTRK rearrangements for the identification of patients who may benefit from entrectinib (submission expected during 2020)
    - A study of off-target activation or inhibition by entrectinib including receptors involved in suicidal ideation (submission expected September 2020)
    - A study of the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of entrectinib (submission expected December 2021)
    - A study of cardiac risks and sequelae (submission expected June 2022)
    - A study of fracture risks and sequelae (submission expected March 2025)
    - A final clinical study report incorporating data for patients with NTRK fusion-positive solid tumours enrolled across the ALKA, STARTRK-1, STARTRK-2, STARK-NG trials and potentially other studies, with minimum follow-up of 12 months from onset of response for responders, and requiring:
        - A sufficient number of patients to provide more precise estimates of response rates and durability for paediatric solid tumors, colorectal cancer, CNS system cancers, gynecological cancers, and melanoma; and

- § A minimum of 40 patients with cancers other than the above, and other than soft tissue sarcoma, non-small cell adenocarcinoma lung cancer, mammary analogue secretory carcinoma, and secretory breast cancer.

  (submission expected at latest by March 2027)

- o A study of longer-term effects of entrectinib on growth and development in paediatric patients 12 years of age and older (submission expected August 2029)

- The Rozlytrek EU-Risk Management Plan (RMP) (version 1.2, dated 6 November 2019, data lock point 31 October 2018), with Australian Specific Annex (version 2.0, dated December 2019), included with submission PM-2019-01809-1-4, to be revised to the satisfaction of the TGA, will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than nine calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than every six months from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Rozlytrek approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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