



RESEARCH AND DEVELOPMENT

REPOTRECTINIB

RISK MANAGEMENT PLAN

Version Number: 0.3

Data-lock Point for this RMP:15-Oct-2023

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LIST OF ABBREVIATIONS

Term	Definition
AE(s)	adverse event(s)
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
ATC	Anatomical Therapeutic Chemical
ATP	adenosine triphosphate
AUC	Area under the concentration vs time curve
AUCinf	area under the concentration time curve extrapolated from 0 to infinity
BICR	Blinded Independent Central Review
BID	twice daily
BMS	Bristol Myers Squibb
C1D1	Cycle 1 Day 1
CHO	Chinese hamster ovary (cells)
COPD	Chronic Obstructive Pulmonary Disease
Cmax	maximum (or peak) concentration
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events (NCI-CTCAE)
CYP3A	cytochrome P450 3A
CYP3A4	cytochrome P-450 3A family isozyme 4
DLT	dose-limiting toxicity
ECG	electrocardiogram
EEA	European Economic Area
EPAR	European public assessment report
FISH	fluorescence in situ hybridization
GLP	Good Laboratory Practice
hERG	human Ether-a-go-go related gene
ICH	International Council for Harmonisation
ILD	interstitial lung disease
INN	International Nonproprietary Name
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
N/A	not applicable
NOEL	no-observed-effect level
NSCLC	non-small cell lung cancer

Term	Definition
<i>NTRK</i>	neurotrophic tyrosine receptor kinase
ORR	objective response rate
PFS	progression-free survival
PI	Package Insert
PIL	Patient Information Leaflet
PK	pharmacokinetics
PL	Patient Leaflet
PND	postnatal day
PR interval	Interval from onset of atrial depolarization “P wave” to onset of ventricular depolarization.
PT	Preferred term
QD	once daily
QPPV	Qualified Person Responsible for Pharmacovigilance
QT interval	Time Between the Start of the Q Wave and the End of the T Wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected using Fridericia’s method
RMP	Risk Management Plan
<i>ROS1</i>	receptor tyrosine kinase encoded by the <i>ROS1</i> gene
RP2D	Recommended Phase 2 dose
RTKs	receptor tyrosine kinases
SAE	serious adverse event
SEER	United States Surveillance, Epidemiology and End Results (Program)
SFM	solvent front mutation
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event.
TKIs	Tyrosine kinase inhibitors
TRK	tropomyosin receptor tyrosine kinases
US	United States
WOCBP	Women of childbearing potential

EU RISK MANAGEMENT PLAN (RMP) FOR REPOTRECTINIB

RMP version to be assessed as part of this application:

Version Number: 0.3

Data-lock Point for this RMP: 15-Oct-2023

Date of Final Sign-off: 26-Sep-2024

Rationale for submitting an updated RMP: Not applicable.

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	N/A	V0.3 / pending
SII Non-clinical part of the safety specification	N/A	V0.3 / pending
SIII Clinical trial exposure	N/A	V0.3 / pending
SIV Populations not studied in clinical trials	N/A	V0.3 / pending
SV Post-authorization experience	N/A	V0.3 / pending
SVI Additional EU requirements for the safety specification	N/A	V0.3 / pending
SVII Identified and potential risks	N/A	V0.3 / pending
SVIII Summary of the safety concerns	N/A	V0.3 / pending
Part III Pharmacovigilance Plan	N/A	V0.3 / pending
Part IV Plan for post-authorization efficacy studies	N/A	V0.3 / pending
Part V Risk Minimisation Measures	N/A	V0.3 / pending
Part VI Summary of the Risk Management Plan	N/A	V0.3 / pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	N/A	V0.3 / pending
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	N/A	V0.3 / pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
ANNEX 4 Specific adverse drug reaction follow-up forms	N/A	V0.3 / pending
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	N/A	V0.3 / pending
ANNEX 6 Details of proposed additional risk minimisation activities	N/A	V0.3 / pending
ANNEX 7 Other supporting data	N/A	V0.3 / pending
ANNEX 8 Summary of changes to the risk management plan over time	N/A	V0.3 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP:

Version Number: N/A

Approved with procedure: N/A

Date of approval (opinion date): N/A

EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Repotrectinib
Pharmacotherapeutic group(s) (ATC Code)	L01EX28
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	AUGTYRO
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Small molecule tyrosine kinase inhibitor Summary of mode of action: Repotrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1, the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC, and anaplastic lymphoma kinase (ALK). Additionally, the kinases JAK2, FYN, LYN, YES, FGR, TXK, ARK5, SRC, DDR1, and FAK have <i>in vitro</i> IC50's of >10nM. Fusion proteins that include ROS1 or TRK kinase domains can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation. Repotrectinib has demonstrated a dose-dependent suppression of phosphorylation of the targeted oncogenic fusion proteins, their downstream signal effectors, and inhibition of cell proliferation of many human cancer cell lines expressing the targeted fusion oncogenes ROS1, TRKA, TRKB, TRKC, and corresponding mutations. Repotrectinib was designed to be smaller in size than the currently available ROS1, TRKA-C, and ALK inhibitors. Repotrectinib has a rigid, three-dimensional macrocycle structure that precisely anchors the molecule completely inside the ATP adenosine binding site of the cocrystal structure of ROS1, TRKA-C, and ALK, with a predefined bioactive binding conformation and avoids steric interference from both solvent front and gatekeeper mutations. Important information about its composition: None
Hyperlink to the Product Information	Refer to proposed PI

Table 1-1: Product Details

Indication(s) in the EEA	Current: AUGTYRO as monotherapy is indicated for the treatment of adult patients with <i>ROS1</i>-positive locally advanced or metastatic non-small cell lung cancer (NSCLC). AUGTYRO as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with advanced solid tumours expressing a <i>NTRK</i> gene fusion and • who have received a prior NTRK inhibitor, or • have not received a prior NTRK inhibitor and treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted (See SmPC Sections 4.4 and 5.1).
Dosage in the EEA	Current <u><i>ROS1</i>-positive NSCLC</u> The recommended dose in adults is 160 mg repotrectinib once daily for 14 days, followed by 160 mg repotrectinib twice daily until disease progression or unacceptable toxicity. <u><i>NTRK</i> gene fusion-positive solid tumours</u> The recommended dose in adults and paediatric patients 12 years and older is 160 mg repotrectinib once daily for 14 days, followed by 160 mg repotrectinib twice daily until disease progression or unacceptable toxicity. <u>Method of administration</u> AUGTYRO is for oral use. The capsules should be swallowed whole at the same time every day. The capsules must not be opened, crushed, or chewed, and the contents of the capsule must not be dissolved.
Pharmaceutical form (s) and strength(s)	Current Hard gelatin capsule dose of 40 mg or 160 mg
Is/will the product be subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

2.1.1 Locally advanced or metastatic ROS1-positive NSCLC

Table 2.1.1-1: Epidemiologic Characteristics of Locally Advanced or Metastatic ROS1-Positive NSCLC

Locally Advanced or Metastatic <i>ROS1</i> -Positive NSCLC				
Incidence and prevalence	Lung cancer remains the leading cause of cancer-related death, with an estimation of 1.8 million in 2020 globally. ^{1,2} In Europe, total of 375,569 lung cancer related deaths were reported in 2021 (251,006 male and 124,563 female). ^{3,2} NSCLC represents 80% to 85% of lung cancer. ⁴ The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Approximately 1% to 2% of NSCLC patients harbor a <i>ROS1</i> chromosomal rearrangement. ^{5,6,7}			
Demographics of the population: age, gender, racial, and/or ethnic origin	Well-characterized demographic data were not available specifically for <i>ROS1</i> -positive NSCLC given the rarity of the mutation. The below tables summarize the incidence (incidence rates, numbers of cases, and distribution of cases) for advanced/metastatic NSCLC (represented by GLOBOCAN) by age and gender in Europe. Five-Year Age-Adjusted Incidence Rates, Numbers of Cases, and Percentage Distributions by Age Group for Lung cancer and NSCLC in Europe, GLOBOCAN 2022			
Lung cancer and NSCLC^a				
Age at Diagnosis	Rate per 100.000^b	Number of Cases of Lung cancer^b	Number of cases of NSCLC^a	Percentage Distribution of Cases^c
< 50	2.3	15,820	13,447	3.3%
50-64	92.5	146,181	124,253	30.2%
65+	213.4	322,553	274,170	66.5%
Overall	28.8	484,554	411,871	100%

Table 2.1.1-1: Epidemiologic Characteristics of Locally Advanced or Metastatic ROS1-Positive NSCLC

Locally Advanced or Metastatic <i>ROS1</i> -Positive NSCLC			
	^a Data was retrieved for lung cancer and adjusted by 0.85 for NSCLC. ^b Derived from Global Cancer Observatory: Cancer Today, 2022, age standardized IR by selecting trachea, bronchus and lung cancer rates to estimate IR in lung cancer. ^c Approximately 1% to 2% of NSCLC patients are <i>ROS1</i>-positive.^{5,6} Source: Derived from Global Cancer Observatory: Cancer Today, 2022.²		
	Five-Year Age-Adjusted Incidence Rates, Numbers of Cases, and Percentage Distributions by Gender for NSCLC in Europe		
	NSCLC ^a		
	Gender	Rate per 100.000 ^b	Percentage Distribution of Cases ^c
	Male	36.4	65.4%
	Female	15.2	34.6%
	^a Data was retrieved for lung cancer and adjusted by 0.85 for NSCLC. ^b Age-standardized IR per 100, 000 derived from Globocan, by selecting Trachea, bronchus and lung cancer estimates IR in lung cancer and adjusted by 0.85 for NSCLC. ^c Approximately 1% to 2% of NSCLC patients are <i>ROS1</i>-positive.^{5,6} Source: Derived from Global Cancer Observatory: Cancer Today, 2022.²		
Risk factors for the disease	In general, risk factors for NSCLC include cigarette smoking, second-hand/passive smoking, certain foods (cured meat, deep-fried cooking, chili), alcohol, low physical activity, urban air pollution, occupational exposure (eg, smoke, dust, silicone, asbestos), and lung cancer susceptibility genes.⁸ There are specific patients who are more prone to NSCLC with oncogenic driver mutations. <i>ROS1</i> alterations specifically are more likely to be found in patients with adenocarcinoma, younger age, female gender, and without a history of smoking, and are not known to occur in the presence of another driver mutation.^{9,10}		

Table 2.1.1-1: Epidemiologic Characteristics of Locally Advanced or Metastatic ROS1-Positive NSCLC

Locally Advanced or Metastatic <i>ROS1</i>-Positive NSCLC	
Main treatment options	Despite being recommended in major lung cancer guidelines, molecular testing (including for <i>ROS1</i> fusions) uptake remains variable and sub-optimal. Reasons include cost, lack of awareness, long turnaround time, technical and organizational challenges.^{11,12,13} Treatment of patients with NSCLC depends on tumor stage, molecular characteristics, and an assessment of the patient's overall medical condition. NSCLC patients with Stage I, II, or III are generally treated with curative intent using surgery, chemotherapy, radiation therapy, or a combined-modality approach. Systematic therapy is indicated for patients with advanced and metastatic disease (Stage IV). The identification of oncogenetic activation of particular tyrosine kinase in some NSCLC tumours including <i>ROS1</i> gene, has led to targeted therapy in these patients. The current ESMO clinical practice guidelines for oncogene-addicted advanced-stage NSCLC (2023) recommends molecular testing for nine predictive biomarkers for approved targeted therapy.¹⁴ These therapies include crizotinib and entrectinib to treat <i>ROS1</i>+ advanced stage NSCLC. Currently, FDA approved crizotinib,¹⁵ and entrectinib,¹⁶ and repotrectinib¹⁷ for the treatment of <i>ROS1</i>-positive NSCLC.¹⁸ The <i>ROS1</i> tyrosine kinase is highly sensitive to the <i>ROS1</i>/MET inhibitor crizotinib as well as the <i>ROS1</i>/TRK inhibitors entrectinib and repotrectinib; these agents are indicated in patients with the <i>ROS1</i> translocation, including those who have received chemotherapy and those who are treatment naïve.^{19,20,21,22} If a patient has experienced progression on crizotinib, lorlatinib is suggested as next-line therapy. Lorlatinib, approved in ALK-positive NSCLC after progression on other ALK inhibitors, appears to also overcome acquired resistance to crizotinib in <i>ROS1</i>-positive NSCLC.^{23,24} Overall, <i>ROS1</i> inhibitors are indicated in the first-line setting rather than chemotherapy or chemoimmunotherapy. However, if treatment was initiated prior to knowledge of the genetic alteration, chemotherapy may be used upon progression on initial therapy.^{15,16,17}
Mortality and morbidity (natural history)	In the advanced or metastatic setting, the 5-year survival rate for NSCLC is approximately 7%.²⁵
Important comorbidities	Based on a global literature review in patients with lung cancer, the estimated prevalence of individual comorbid conditions sequentially ordered by proportion was: hypertension (35.2%), COPD (23.5%), chronic bronchitis (17.2%), ischemic heart disease (16.6%), peripheral vascular disease (13.1%), asthma (12.9%), diabetes (12.5%), advanced COPD (stage 3 and 4) (10.7%), bronchiectasis (4.5%), stroke (2.2%), and pulmonary fibrosis (0.5%).²⁶ In general, compared with other types of solid tumours, the comorbidity burden in lung cancer patients has been described to be higher along with the high prevalence of smoking.²⁷ In a population-based study in Sweden, the most common co-morbid conditions among NSCLC patients were malignancies other than lung cancer (13.2%), chronic pulmonary disease (12.6%), cerebrovascular disease (9.0%), myocardial infarction (8.1%), and diabetes without complications (7.4%). The corresponding prevalence data in lung cancer-free controls were 9.6%, 3.9%, 7.9%, 6.2%, and 5.5%, respectively.²⁸ The prevalence and frequency of comorbid conditions is not expected to be different in the target population of <i>ROS1</i>-positive NSCLC.

Table 2.1.1-1: Epidemiologic Characteristics of Locally Advanced or Metastatic ROS1-Positive NSCLC

Locally Advanced or Metastatic *ROS1*-Positive NSCLC

The highest worldwide incidences of lung cancer and NSCLC have been reported in Hungary and New Caledonia. Hungary and Turkey had the highest estimated age-adjusted mortality rates due to lung cancer; 39.8 per 100.000 in Hungary and 35.1 per 100.000 in Turkey. The age-standardized (world) estimated 2022 incidence rates for lung cancer is 23.6 per 100.000.²

The estimated number of prevalent cases worldwide for lung cancer in 5 years ranged in 2022 from 0.55 per 100.000 in Niger to 136.5 per 100.000 in Hungary, lowest and highest incidence rates, respectively. The age-adjusted mortality rate for lung cancer was 0.93 to 39.8 per 100.000 cases in Niger and Hungary, respectively.²

Estimated Age-Adjusted Incidence Rates by Age Group in Different Continents/Regions for NSCLC in 2022^{a,b,c}

Age at Diagnosis	Asia	Europe	North America	Latin America & Caribbean	Africa	Oceania	World
< 50	2.2	1.9	1.4	0.8	0.6	1.4	1.8
50-64	58.3	78.6	75.9	27.4	16.1	15.1	55.8
65+	172.4	181.4	231.0	85.9	41.0	175.5	162.7
Overall	21.4	24.5	27.1	10.3	5.3	19.9	20.0

^a Age-standardized rates per 100.000.

^b Data was retrieved for lung cancer and adjusted by 0.85 for NSCLC.

^c Derived from Global Cancer Observatory: Cancer Today, 2022.²

Note: Approximately 1% to 2% of NSCLC patients are *ROS1*-positive.^{5,6}

Sources:^{2,29}

Table 2.1.1-1: Epidemiologic Characteristics of Locally Advanced or Metastatic ROS1-Positive NSCLC**Locally Advanced or Metastatic *ROS1*-Positive NSCLC****Estimated Age-Adjusted Incidence Rates by Gender in Different Continents/Regions for NSCLC in 2022^{a,b}**

Gender	World age-adjusted incidence rate for NSCLC per 100.000					
	Asia	Europe	North America	Latin America & Caribbean	Africa	Oceania
Male	29.1	36.0	28.7	13.4	8.4	23.2
Female	14.4	15.2	25.8	7.8	2.7	16.9

^a Data was retrieved for lung cancer and adjusted by 0.85 for NSCLC.

^b Derived from Global Cancer Observatory: Cancer Today, 2022.²

Note: Approximately 1% to 2% of NSCLC patients are *ROS1*-positive.^{5,6}

Sources:^{2,29}

Estimated Age-Standardized Incidence Rates for NSCLC 2022, Males and Females Combined, All Ages

Region	Age-standardized incidence rates NSCLC ^{a,b}
Europe	24.5 per 100.000
The 6 European countries with the highest estimated ASR	Bosnia and Herzegovina: 31.1 per 100.000 Poland: 31.0 per 100.000 Montenegro: 31.2 per 100.000 Croatia: 31.5 per 100 000 Serbia: 34.3 per 100.000 Hungary: 40.5 per 100.000
Central and Eastern Europe	23.5 per 100.000
Western Europe	26.5 per 100.000
Northern Europe	23.8 per 100.000
Southern Europe	23.5 per 100.000

^a Data was retrieved for lung cancer and adjusted by 0.85 for NSCLC.

^b Derived from Global Cancer Observatory: Cancer Today, 2022.²

Note: Approximately 1% to 2% of NSCLC patients are *ROS1*-positive.^{5,6}

Sources:^{2,29}

Table 2.1.1-1: Epidemiologic Characteristics of Locally Advanced or Metastatic ROS1-Positive NSCLC

Locally Advanced or Metastatic ROS1-Positive NSCLC	
<i>Co-mediations in the target population:</i>	
The treatment choices for NSCLC are based mainly on the stage of the cancer but are also based on other factors such as lung function, age, and pre-existing comorbidities. Therapy choices may be considered for pre-operative patients in earlier stage of lung cancer before surgery or to treat the pre-existing conditions such as COPD.³⁰ Advanced lung cancer requires more aggressive therapy which may lead to severe side effects such as cardiac toxicity, and may affect therapy choices in those patients with pre-existing cardiac diseases. Having cardiovascular disease as a pre-condition may increase the toxicity of specific treatments. It is also possible that the negative prognostic impact of severe comorbidity is due to the use of aggressive therapy. Due to that, patients with multiple comorbidities, often in decompensation, cannot receive appropriate therapy.³¹	

2.1.2 NTRK-Positive Solid Tumours

Table 2.1.2-1: Epidemiologic Characteristics of NTRK-Positive Solid Tumours

NTRK-Positive Solid Tumours	
Incidence	To estimate the Age-Standardized Incidence Rate of solid tumours in Europe data from Globocan were used.² The list of cancers that comprises the solid tumours included in Globocan are: <u>Female cancers:</u> lip, oral cavity, salivary glands, oropharynx, nasopharynx, hypopharynx, oesophagus, stomach, colorectum, liver, gallbladder, pancreas, larynx, lung, melanoma of skin, mesothelioma, Kaposi sarcoma, breast, cervix uteri, corpus uteri, kidney, ovary, thyroid, vagina, vulva, bladder, brain, CNS. <u>Male cancers:</u> lip, oral cavity, salivary glands, oropharynx, nasopharynx, hypopharynx, oesophagus, stomach, colorectum, liver, gallbladder, pancreas, larynx, lung, melanoma of skin, mesothelioma, Kaposi sarcoma, kidney, thyroid, bladder, brain, CNS, testis, penis, prostate. <u>Age-adjusted incidence rate for all solid tumours in Europe:</u> Male: 287.8 per 100.000 Female: 217.4 per 100.000
Prevalence	NTRK gene fusions occur in 0.3% of all solid tumours, though frequencies vary by cancer type.^{32,33} Based on the study report from data from > 295,000 solid tumour cancer patients through the FoundationCORE® database (Foundation Medicine Inc., Cambridge, MA, USA), a total of 889 patients had NTRK fusion-positive tumour with the prevalence of 0.30% among 45 cancer types. The prevalence of NTRK-positive tumours varies by age: 0.28% in adults (aged ≥ 18 years) and 1.34% in paediatrics and cancer type: 0.05% in CNS-non-Glioma and 2.62% in salivary gland tumours.³²

Table 2.1.2-1: Epidemiologic Characteristics of *NTRK*-Positive Solid Tumours

<i>NTRK</i>-Positive Solid Tumours				
5-Year Prevalence of <i>NTRK</i>-positive Solid Tumours in Europe				
Continent / Country	5-Year Prevalence Male^{a,b}	5-Year Prevalence Female^{a,b}	Total Country 5-year Prevalence for Solid Tumours^{a,b}	Total Country Prevalence for <i>NTRK</i>+ Solid Tumour^c
Europe	1684.5	1581.3	1895.1	5.7
Germany	2080.6	1938.9	2336.5	7.0
Russian Federation	1067.7	1239.3	1344.2	4.0
France	2157.1	1902.5	2353.1	7.1
United Kingdom	1919.4	1790.5	2156.4	6.5
Italy	1971.1	1847.1	2216.7	6.6
Spain	1854.3	1517.0	1956.4	5.9
Poland	1540.5	1456.7	1739.4	5.2
Netherlands	2245.1	2269.7	2626.4	7.9
Ukraine	784.7	917.8	992.3	3.0
Romania	1525.2	1340.1	1661.6	5.0
Belgium	2059.8	1955.3	2334.7	7.0
Sweden	2264.0	1885.8	2415.3	7.2
Czechia	1818.4	1637.6	2007.6	6.0
Greece	1743.2	1588.8	1935.0	5.8
Portugal	1932.4	1654.0	2072.0	6.2
Hungary	1959.4	1809.6	2183.1	6.5
Switzerland	2152.2	1833.8	2316.9	6.9
Austria	1626.6	1457.3	1791.8	5.4
Denmark	2479.5	2344.7	2805.4	8.4
Norway	2372.6	2130.3	2623.3	7.9
Serbia	1223.5	1144.8	1375.5	4.1
Finland	2003.3	1891.4	2263.6	6.8
Belarus	1396.5	1218.6	1508.8	4.5

a Prevalence proportions are per 100.000.

b As per Global Cancer Observatory 2022.²

c Calculated based on 0.3% of solid tumours.³²

Demographics of the population: age, gender, racial and/or ethnic origin

Five-year Prevalence Proportions per 100.000 population Categorized by Gender and Age for All Solid Tumour and *NTRK*+ Solid Tumours in Europe

Table 2.1.2-1: Epidemiologic Characteristics of *NTRK*-Positive Solid Tumours

<i>NTRK</i> -Positive Solid Tumours				
Age at Diagnosis	5-year Prevalence Female (Solid Tumour) ^{a,b}	5-year Prevalence Female (<i>NTRK</i> +) ^c	5-year Prevalence Male (Solid Tumour) ^{a,b}	5-year Prevalence Male (<i>NTRK</i> +) ^c
<20	23.4	0.3	18.5	0.2
20-39	285.4	0.8	132.5	0.4
40-64	1663.2	4.7	1270.7	3.6
>64	3242.9	9.1	5644.7	15.8
Overall ^a	1348.8	4.0	1397.6	4.2

a Prevalence proportions are per 100.000.

b As per Global Cancer Observatory.²

c *NTRK*+ solid tumour was calculated based on 0.3% for any age (0-85), 0.28% for adults and 1.34% in paediatrics.³²

Risk factors for the disease

NTRK gene fusions occur in 0.3% of all solid tumours, though frequencies vary by cancer type.^{32,33} The prevalence of *NTRK*-positive tumours varies by age, higher in paediatrics; and by cancer type.³² It is highly seen in rare tumours such as mammary secretory carcinoma, mammary analogue secretory carcinoma of the salivary gland, congenital infantile fibrosarcoma (fusion prevalence is almost 100%), and other rarer tumours. *NTRK* fusion is present in approximately 40% of high-grade non-brainstem paediatric gliomas.^{34, 35} Mean age at the time of diagnosis of overall patients in FoundationCORE was 60.5 years, whereas the mean age for children and for adults was 5 years and 62 years, respectively, and 57.5% were female in the total cohort (n=889).³²

Main treatment options

Larotrectinib and entrectinib are 2 oral targeted agents currently available for unresectable locally advanced or metastatic cancer patients harboring an *NTRK* gene fusion.^{16,36} The accurate and timely identification of TRK fusions is of immediate therapeutic importance given that TRK inhibitors have been shown to have robust activity in TRK fusion-positive solid tumours.^{37,38} In addition to advanced/metastatic disease, both larotrectinib and entrectinib have also been approved for the treatment of the disease “where surgical resection is likely to result in severe morbidity”.³⁹ Other available treatments may vary by individual tumour type and include chemotherapy, immunotherapy, non-TRK targeted therapy.^{30,40,41,42,43,44,45}

Mortality and morbidity (natural history)

Age-Standardized Mortality Rate for solid tumour in Europe⁴⁶
Male 118.6 per 100.000
Female 72.1 per 100.000
Overall, 92.30 per 100.000

Table 2.1.2-1: Epidemiologic Characteristics of *NTRK*-Positive Solid Tumours

<i>NTRK</i>-Positive Solid Tumours	
Important co-morbidities	A recent report by Westphalen et al with more than 295,000 cancer patients from the FoundationCORE database (Foundation Medicine Inc., Cambridge, MA, USA), identified 889 patients harboring the <i>NTRK</i> gene fusions.³² The most common <i>NTRK</i>-positive solid tumour in adults and paediatric patients were salivary gland cancers (2.60% and 2.43%, respectively), soft tissue sarcomas (1.51% and 1.20%, respectively), and thyroid cancer (1.60% and 1.25%, respectively).³² Common comorbidities observed in <i>NTRK</i>-positive tumour patients are related either to the underlying disease or are associated with the co-medications used to treat it. In this context, systemic therapy regimens that are commonly used for individual tumour types include: platinum/doxorubicin, paclitaxel, vinorelbine, mitoxantrone, cetuximab + cisplatin, gefitinib + lapatinib as first line therapy for advanced/ metastatic salivary gland carcinoma⁴³; doxorubicin ± olaratumab or ifosfamide or docetaxel, paclitaxel, gemcitabine for advanced/metastatic soft tissue sarcoma (with or without <i>NTRK</i> fusion)⁴⁴; and doxorubicin, sorafenib, lenvatinib for non-modularly advanced thyroid cancer (with or without <i>NTRK</i> fusion).⁴² Extrapolating data from the Dutch Nationwide Network and Registry; van Herk-Sukel et al. estimated the most common comorbidities in 533 adult patients soft tissue sarcoma.⁴⁷ The most common comorbidities at baseline were cardiovascular disease (33%), respiratory disease (10%), diabetes mellitus (7%) followed by anemia and depression (6%).⁴⁷ In this study, in addition to risk factors for cardiovascular disease, a clear association was demonstrated between the use of chemotherapy in the first 6 months after diagnosis and the onset of anemia during follow up. It is well recognized that anemia might arise during or shortly after myelotoxic chemotherapy.⁴⁷ In a study including 378 thyroid cancer patients, Kuijpers, et al. showed that the prevalence of comorbidities increased with age. Hypertension was the most frequent comorbidity (18%), followed by other malignancies (7%), cardiovascular diseases (6%),diabetes mellitus (6%),COPD and tuberculosis (5%)⁴⁸ Importantly, the number of comorbidities in patients with thyroid cancer influenced the type of treatment used (surgery, radiotherapy, and/or chemotherapy).⁴⁸

2.2 Nonclinical Part of the Safety Specification

Repotrectinib has been evaluated in accordance with the ICH S9 Guideline “Nonclinical Evaluation for Anticancer Pharmaceuticals”⁴⁹ in a comprehensive nonclinical safety program encompassing single- and repeat-dose exploratory toxicology studies, definitive 28- and 91-day toxicology studies conducted in two mammalian species (rat and monkey), a preliminary non-GLP embryo-foetal toxicity study in pregnant rats, juvenile toxicity studies in juvenile rats, a phototoxicity study in pigmented rats, as well as genotoxicity and safety pharmacology studies, including in vitro hERG and ECG testing in monkeys.

Toxicology and Safety Pharmacology:

Toxicities of repotrectinib were observed in the CNS, skin, bone marrow, and gastrointestinal tract in the rat and/or monkey. These effects generally exhibited reversibility or a trend toward reversibility during the recovery phase. Repotrectinib was not mutagenic but induced micronuclei in genotoxicity studies. Detailed testing suggests that repotrectinib is aneugenic and associated with a threshold, below which there is no induction of genotoxic events. Repotrectinib caused

teratogenicity and embryo-foetal toxicity in rats, and CNS, bone marrow and decreased femur bone length effects in juvenile rats.

Table 2.2-1: Key Safety Findings from Nonclinical Studies and Relevance to Human Use

Key Safety Findings	Relevance to human usage
Toxicity <i>Skin effects:</i> Scabbed areas and/or abrasions of the skin primarily in the cervical, cranial, face, ear, shoulder, jaw, and/or thoracic regions that microscopically correlated with surface serocellular crusts, dermal granulation tissue with subacute inflammation, and epidermal hyperplasia and hyperkeratosis adjacent to the erosion/ulceration were observed in repeat-dose toxicity studies in rats. <i>CNS:</i> Ataxia and tremors that were not accompanied by any microscopic findings were observed in the 28-day and 91-day repeat-dose toxicity studies in rats. Many of the animals with ataxia or tremors had intolerability issues evident weeks after the clinical observations and had to be euthanized early; those that survived to terminal necropsy had complete recovery of any CNS findings. In the juvenile rats, CNS signs of toxicity (ataxia) were observed after 2 to 3 days at ≥ 10 mg/kg and resulted in moribundity and early euthanasia of the entire 10 mg/kg and 30 mg/kg groups by day 3. Based on comparison exposure (AUC) at the low observed effect level in juvenile versus adult rats, there appeared to be increased sensitivity of the developing rodent nervous system. However, the deaths in these very young juvenile rats may have been due to their small body size, high metabolic rate and rapid growth resulting in fast decline in general condition and death (a recognized and accepted disadvantage of the juvenile rat test species as noted in ICH S11, 2020) and are therefore considered not likely relevant to a human infant. <i>Bone marrow:</i> Decreased red cell mass (erythrocyte counts, hemoglobin, and hematocrit) and reticulocyte counts and increased platelet counts were observed in rats and monkeys. Bone marrow hypocellularity (sternal and femoral) and increased megaokaryopoiesis was observed only in the rat and correlated with the decreased red cell mass and reticulocyte counts and increased platelet counts. <i>Gastrointestinal:</i> Emesis and watery feces that correlated with microscopic changes of minimal subacute/chronic inflammation and/or minimal to mild mucosal gland hyperplasia in the large intestines (cecum, colon, and rectum) were observed in monkeys. Subacute/chronic inflammation was also seen within the jejunum. Inflammatory changes in the intestines correlated with markers of inflammation in the clinical pathology assessment including increased fibrinogen, globulin, inflammatory cells (neutrophils, monocytes, eosinophils, and basophils), and decreased albumin.	The skin effects in rats are considered attributed to TRK inhibition resulting in potential loss of sensation, altered behavior and/or local inflammation, and secondary bodily harm. There have been no clinically significant reports of skin findings in subjects participating in clinical trials with repotrectinib. Peripheral neuropathy has been reported in subjects participating in clinical trials. The CNS effects in rats are likely mediated by TRK inhibition in the CNS and are relevant to humans. CNS effects, including dizziness and ataxia, have been reported in clinical trials with repotrectinib. The bone marrow effects in rats and monkeys are common with TKIs and are relevant to humans. Anemia and other cytopenias have been reported in clinical trials with repotrectinib. The gastrointestinal effects in monkeys are common with TKIs. Gastrointestinal events were observed in clinical trials with repotrectinib and mostly consisted of mild constipation, nausea, vomiting, and diarrhea.

Table 2.2-1: Key Safety Findings from Nonclinical Studies and Relevance to Human Use

Key Safety Findings	Relevance to human usage
<u>Reproductive and developmental toxicity</u> <i>Embryo-foetal development:</i> Teratogenic effects (foetal external malformation of malrotated hindlimbs) were observed in a preliminary non-GLP embryo-foetal toxicity study in rats at ≥ 12 mg/kg/day. In addition, repotrectinib-related maternal effects were observed at dose levels ≥ 12 mg/kg/day and included increased body weight, scabbing/abrasions in the cervical and thoracic regions, and decreased mean foetal body weight values for females and for the combined sexes. <u>Juvenile toxicity</u> The effect of repotrectinib on juvenile rats was investigated in dose range-finding and definitive repeat-dose toxicology studies. Similar to what observed in sexually mature rats in general toxicity studies, CNS and bone marrow findings were observed in juvenile rats; however, the CNS effects in juvenile rats were more severe than what was observed in sexually mature rats at similar exposures and resulted in acute mortality and early euthanasia at PND 13 to 15. In the definitive juvenile toxicity study, decreased body weight, food consumption, and femur length as well as increased platelet counts were observed at the high dose of 3 mg/kg. Body weight at the age of attainment of vaginal patency was lower and statistically significant at 1 and 3 mg/kg. There were no repotrectinib-related effects on the age or body weight at attainment of balanopreputial separation or age at attainment of vaginal patency nor any effects on auditory startle responsiveness, motor activity, and learning and memory (Biel maze) up to the highest dose of 3 mg/kg.	Relevance to human usage is unknown. Foetal and maternal effects occurred at less than 2-fold the human exposure at the highest recommended dose of 160 mg BID. Female patients of childbearing potential and male patients with female partners of reproductive potential must use contraception due to teratogenicity risk. Relevance to human usage is unknown. Juvenile rats aged PND 13 to 15 (developmentally approximately equivalent to a human infant [< 2 years of age]) had CNS-mediated mortality. However, the deaths in these very young juvenile rats may have been due to their small body size, high metabolic rate and rapid growth resulting in fast decline in general condition and death (a recognized and accepted disadvantage of the juvenile rat test species as noted in ICH S11)⁵⁰ and are therefore considered not likely relevant to a human infant. In a repeat-dose toxicity study in juvenile rats, where neurobehavioural development was assessed, no effects of repotrectinib on learning and memory, motor activity and auditory startle response were observed. Dose-dependent delays in development including decreases in the rate of body weight gain at the mid- and high-dose groups in males and females and in the growth rate (as measured by femur length) may have relevance to paediatric patients ≥ 12 years old.

Table 2.2-1: Key Safety Findings from Nonclinical Studies and Relevance to Human Use

Key Safety Findings	Relevance to human usage
<u>Genotoxicity</u> In a battery of genotoxicity studies, repotrectinib was not mutagenic or clastogenic, but aneugenic in vitro in the mammalian cell micronucleus assay in TK6 cells. Consistent with the threshold phenomenon expected from an aneugen, repotrectinib was positive in an in vivo mammalian erythrocyte micronucleus assay conducted in rats at doses of 500, 1000, and 2000 mg/kg/day but negative at or below the nominal dose of 100 mg/kg/day (C_{max} of 2300 ng/mL and AUC_{0-24} of 28400 hr*ng/mL).	The exposure of animals at the NOEL for aneugenicity was approximately 3.4-fold human exposure at recommended clinical dose (based on AUC). Female patients of childbearing potential and male patients with female partners of reproductive potential must use contraception for a defined time period.

2.3 Clinical Trial Exposure

Repotrectinib has been studied in Phase 1 and Phase 2 studies. An overview of the repotrectinib clinical program summarized in this RMP is provided in [Table 2.3-1](#).

Table 2.3-1: Repotrectinib Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number (Indication)	Study Title	Number Treated Subjects	Clinical Cutoff
TRIDENT-1 ^{a,51,52} (<i>ROS-1</i> -positive NSCLC and <i>NTRK</i> -positive Solid Tumours)	Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of TPX-0005 in Patients with Advanced Solid Tumors Harboring <i>ALK</i> , <i>ROS1</i> , or <i>NTRK1-3</i> Rearrangements	<i>ROS-1</i> + NSCLC ^b : 367 <i>NTRK</i> + Solid Tumours ^c : 144 Other treated Subjects ^d : 54 Total Subjects: 565	15-Oct-2023
CARE ^{e,53} (<i>NTRK</i> -positive Solid Tumours)	Phase 1/2, Open-Label, Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity Study of Repotrectinib in Pediatric and Young Adult Subjects with Advanced or Metastatic Malignancies Harboring <i>ALK</i> , <i>ROS1</i> , or <i>NTRK1-3</i> Alterations	<i>NTRK</i> + Cohort ^f : 19 Other Cohort ^g : 19 Total Subjects: 38	15-Oct-2023

^a TRIDENT-1 (Study TPX-0005-01, CA127-1024)

^b *ROS1*+ NSCLC Subjects included expansion cohorts EXP-1, EXP-2, EXP-3, and EXP-4 as well as those who enrolled into protocol versions 5, 6, 7, 8, and 9 as what was formally cohort EXP-3 but no longer met criteria for any cohort in protocol version 10.

^c *NTRK*+ Solid Tumor Subjects included expansion cohorts EXP-5 and EXP-6.

^d Other treated subjects included subjects with *ROS1*+ non-NSCLC, *ALK*+ gene fusions, and any gene fusions with discordant results between local FISH test and central laboratory test.

- ^e CARE (Study TPX-0005-07, CA127-1029)
- ^f NTRK cohort includes subjects with NTRK1-3 genetic mutation.
- ^g Other cohort includes subjects with ROS1 or ALK genetic mutation.

Table 2.3-2: Clinical Exposure in Person Time - All Treated Subjects (TRIDENT-1 Study)

ROS1+ NSCLC Subjects N = 367			NTRK+ Solid Tumor Subjects N = 144		Other Treated Subjects N = 54		Total N = 565	
	Persons (%)	Person Time of Exposure (months)(1)	Persons (%)	Person Time of Exposure (months)(1)	Persons (%)	Person Time of Exposure (months)(1)	Persons (%)	Person Time of Exposure (months)(1)
< 1 month	26 (7.1)		10 (6.9)		10 (18.5)		46 (8.1)	
1 to < 3 months	65 (17.7)		31 (21.5)		21 (38.9)		117 (20.7)	
3 to < 6 months	55 (15.0)		28 (19.4)		11 (20.4)		94 (16.6)	
6 to < 12 months	71 (19.3)		23 (16.0)		5 (9.3)		99 (17.5)	
12 to < 18 months	54 (14.7)		20 (13.9)		1 (1.9)		75 (13.3)	
18 to < 24 months	33 (9.0)		14 (9.7)		0		47 (8.3)	
24 to < 36 months	40 (10.9)		15 (10.4)		3 (5.6)		58 (10.3)	
≥ 36 months	26 (7.1)		3 (2.1)		3 (5.6)		29 (5.1)	
0 - ≤ 51.15 months (A)			144 (100.0)	1538.53				
0 - ≤ 70.11 months (A)					54 (100.0)	401.35		
0 - ≤ 71.23 months (A)	367 (100.0)	4665.66					565 (100.0)	6605.55

(1) Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date.

(A) Max clinical exposure. Includes data from TPX-0005-01 (Phase 1 and Phase 2).

Data Cutoff Date: 15-Oct-2023.

Table 2.3-3: Clinical Exposure in Person Time by Age Group and Gender - All Treated Subjects and by Subgroup (TRIDENT-1 Study)

Age Category (Years)	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 237	Female N = 328	Total N = 565	Male N = 237	Female N = 328	Total N = 565
All Treated Subjects						
>= 12 AND < 18	0	0	0	0.00	0.00	0.00
>= 18 AND < 65	179 (75.5)	246 (75.0)	425 (75.2)	2100.22	2971.86	5072.07
>= 65 AND < 75	39 (16.5)	66 (20.1)	105 (18.6)	304.10	934.47	1238.57
>= 75 AND < 85	18 (7.6)	16 (4.9)	34 (6.0)	123.60	164.93	288.53
>= 85	1 (0.4)	0	1 (0.2)	6.37	0.00	6.37
TOTAL	237 (100)	328 (100)	565 (100)	2534.29	4071.26	6605.55
Subgroup: ROS1+ NSCLC Subjects						
	Male N = 138	Female N = 229	Total N = 367	Male N = 138	Female N = 229	Total N = 367
>= 12 AND < 18	0	0	0	0.00	0.00	0.00
>= 18 AND < 65	111 (80.4)	180 (78.6)	291 (79.3)	111 (80.4)	180 (78.6)	291 (79.3)
>= 65 AND < 75	19 (13.8)	39 (17.0)	58 (15.8)	19 (13.8)	39 (17.0)	58 (15.8)
>= 75 AND < 85	7 (5.1)	10 (4.4)	17 (4.6)	7 (5.1)	10 (4.4)	17 (4.6)
>= 85	1 (0.7)	0	1 (0.3)	1 (0.7)	0.00	1 (0.3)
TOTAL	138 (100)	229 (100)	367 (100)	1703.33	2962.33	4665.66
Subgroup: NTRK+ Solid Tumor Subjects						
	Male N = 70	Female N = 74	Total N = 144	Male N = 70	Female N = 74	Total N = 144
>= 12 AND < 18	0	0	0	0.00	0.00	0.00
>= 18 AND < 65	43 (61.4)	47 (63.5)	90 (62.5)	565.06	556.68	1121.74
>= 65 AND < 75	17 (24.3)	21 (28.4)	38 (26.4)	124.16	197.42	321.58
>= 75 AND < 85	10 (14.3)	6 (8.1)	16 (11.1)	37.32	57.89	95.21
>= 85	0	0	0	0.00	0.00	0.00
TOTAL	70 (100)	74 (100)	144 (100)	726.54	811.99	1538.53

Table 2.3-3: Clinical Exposure in Person Time by Age Group and Gender - All Treated Subjects and by Subgroup (TRIDENT-1 Study)

	Persons (%)			Person Time of Exposure (Months) (1)		
Subgroup: Other Treated Subjects						
	Male N = 29	Female N = 25	Total N = 54	Male N = 29	Female N = 25	Total N = 54
>= 12 AND < 18	0	0	0	0.00	0.00	0.00
>= 18 AND < 65	25 (86.2)	19 (76.0)	44 (81.5)	81.71	266.05	347.77
>= 65 AND < 75	3 (10.3)	6 (24.0)	9 (16.7)	18.86	30.88	49.74
>= 75 AND < 85	1 (3.4)	0	1 (1.9)	3.84	0.00	3.84
>= 85	0	0	0	0.00	0.00	0.00
TOTAL	29 (100)	25 (100)	54 (100)	104.42	296.94	401.35

(1) Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date. Includes data from TPX-0005-01 (Phase 1 and Phase 2).

Data Cutoff Date: 15-Oct-2023.

Table 2.3-4: Clinical Exposure in Person Time by Starting Dose - All Treated Subjects (TRIDENT-1 Study)

ROS1+ NSCLC Subjects N = 364			NTRK+ Solid Tumor Subjects N = 144		Other Treated Subjects N = 54		Total N = 565	
Dose Level	Persons (%)	Person Time of Exposure (months)(1)	Persons (%)	Person Time of Exposure (months)(1)	Persons (%)	Person Time of Exposure (months)(1)	Persons (%)	Person Time of Exposure (months)(1)
40 mg QD	4 (1.1)	99.81	4 (2.8)	26.71	5 (9.3)	73.46	13 (2.3)	199.99
80 mg QD	3 (0.8)	42.81	0	0	9 (16.7)	53.36	12 (2.1)	96.17
160 mg QD	5 (1.4)	149.82	2 (1.4)	4.96	16 (29.6)	77.18	23 (4.1)	231.95
240 mg QD	1 (0.3)	36.60	0	0	9 (16.7)	21.19	10 (1.9)	57.79
160 mg BID	3 (0.8)	7.92	1 (0.7)	4.96	8 (14.8)	142.32	12 (2.1)	155.20
200 mg BID	0	0	0	0	2 (3.7)	3.55	2 (0.4)	3.55
120 mg QD with food	3 (0.8)	64.26	0	0	0	0	3 (0.5)	64.26
160 mg QD with food	3 (0.8)	42.32	1 (0.7)	36.80	2 (3.7)	14.06	6 (1.1)	93.18
160 mg QD/BID with food	10 (2.7)	120.05	1 (0.7)	51.15	1 (1.9)	1.84	12 (2.1)	173.04
RP2D (2)	335 (91.3)	4102.08	135 (93.8)	1413.95	2 (3.7)	14.39	472 (83.5)	5530.42
Total	367 (100.0)	4665.66	144 (100.0)	1538.53	54 (100.0)	401.35	565 (100.0)	6605.55

(1) Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date.

(2) The RP2D is 160 mg QD for 14 days followed by 160 mg BID.

Data Cutoff Date: 15-Oct-2023.

Table 2.3-5: Cumulative Dose of Repotrectinib by Starting Dose Level - All Treated Subjects and by Subgroup (TRIDENT-1 Study)

Starting Dose Level											
	40 mg QD (N=13)	80 mg QD (N=12)	160 mg QD (N=23)	240 mg QD (N=10)	160 mg BID (N=12)	200 mg BID (N=2)	120 mg QD with Food (N=3)	160 mg QD with Food (N=6)	160 mg QD/BID with Food (N=12)	RP2D (2) (N=472)	Total (N=565)
All Treated Subjects											
N. of Doses Received/ Subject											
Mean	523.0	238.8	386.7	166.0	609.1	99.5	648.7	456.2	772.8	594.1	570.1
(SD)	(684.15)	(275.62)	(807.47)	(327.42)	(1220.23)	(0.71)	(974.18)	(469.18)	(1123.59)	(579.63)	(622.20)
	102.0	137.5	88.0	52.5	136.5	99.5	117.0	288.0	357.5	410.5	329.0
Median											
Min- Max	29 - 2137	21 - 821	2 - 3816	8 - 1082	6 - 4151	99 - 100	56 - 1773	28 - 1109	17 - 3121	1 - 2668	1 - 4151
Cumulative Dose (mg) / Subject (1)											
Mean	63932.3	36606.7	65965.2	31400.0	74780.0	19900.0	91320.0	72840.0	108060.0	84440.9	81243.5
(SD)	(90960.80)	(53787.95)	(134744.51)	(55818.17)	(129306.51)	(141.42)	(138233.13)	(75162.91)	(148633.97)	(83728.68)	(88667.78)
	8640.0	13320.0	16640.0	12040.0	21520.0	19900.0	16400.0	45640.0	51020.0	54800.0	47920.0
Median											
Min- Max	1160 - 245760	1680 - 180400	320 - 610560	1920 - 186080	960 - 400280	19800 - 20000	6720 - 250840	4480 - 177440	2560 - 446000	160 - 401920	160 - 610560
Subgroup: ROS1+ NSCLC Subjects											
	40 mg QD (N=4)	80 mg QD (N=3)	160 mg QD (N=5)	240 mg QD (N=1)	160 mg BID (N=3)	200 mg BID (N=0)	120 mg QD with Food (N=3)	160 mg QD with Food (N=3)	160 mg QD/BID with Food (N=10)	RP2D ⁽²⁾ (N=335)	Total (N=367)
N. of Doses Received/ Subject											
Mean	734.5	432.0	1305.8	1082.0 (-)	154.7		648.7	401.7	614.6	628.8	632.9
(SD)	(967.56)	(304.37)	(1431.34)		(196.17)		(974.18)	(498.74)	(933.13)	(609.36)	(638.05)
	356.0	272.0	637.0	1082.0	62.0		117.0	209.0	357.5	434.0	426.0
Median											
Min- Max	89 - 2137	241 - 783	329 - 3816	1082 - 1082	22 - 380		56 - 1773	28 - 968	17 - 3121	4 - 2668	4 - 3816
Cumulative Dose (mg) / Subject (1)											
Mean	95720.0	58826.7	223888.0	186080.0 (-)	24746.7		91320.0	63973.3	91724.0	90261.1	91443.4
(SD)	(113783.71)	(41224.56)	(230396.87)		(31386.66)		(138233.13)	(79969.61)	(134014.05)	(88318.75)	(93365.42)
	65520.0	45280.0	101920.0	186080.0	9920.0		16400.0	32560.0	51020.0	64480.0	64240.0
Median											

Table 2.3-5: Cumulative Dose of Repotrectinib by Starting Dose Level - All Treated Subjects and by Subgroup (TRIDENT-1 Study)

Starting Dose Level											
Min-Max	6160 - 221680	26080 - 105120	46400 - 610560	186080 - 186080	3520 - 60800	6720 - 250840	4480 - 154880	2560 - 446000	640 - 401920	640 - 610560	
Subgroup: NTRK+ Solid Tumor Subjects											
	40 mg QD (N=4)	80 mg QD (N=0)	160 mg QD (N=2)	240 mg QD (N=0)	160 mg BID (N=1)	200 mg BID (N=0)	120 mg QD with Food (N=0)	160 mg QD with Food (N=1)	160 mg QD/BID with Food (N=1)	RP2D ⁽²⁾ (N=135)	Total (N=144)
N. of Doses Received/ Subject											
Mean	256.3		67.0 (26.87)		295.0 (-)			1109.0 (-)	3072.0 (-)	511.6	518.8
(SD)	(368.37)									(494.34)	(533.90)
	96.0		67.0		295.0			1109.0	3072.0	322.0	311.0
Median											
Min-Max	29 - 804		48 - 86		295 - 295			1109 - 1109	3072 - 3072	1 - 2032	1 - 3072
Cumulative Dose (mg) / Subject (1)											
Mean	35530.0		12600.0		47200.0 (-)			177440.0 (-)	370520.0 (-)	70584.3	71467.8
(SD)	(56036.57)		(5713.42)							(69970.97)	(73805.74)
	11120.0		12600.0		47200.0			177440.0	370520.0	43080.0	42980.0
Median											
Min-Max	1160 - 118720		8560 - 16640		47200 - 47200			177440 - 177440	370520 - 370520	160 - 304960	160 - 370520
Subgroup: Other Treated Subjects											
	40 mg QD (N=5)	80 mg QD (N=9)	160 mg QD (N=16)	240 mg QD (N=9)	160 mg BID (N=8)	200 mg BID (N=2)	120 mg QD with Food (N=0)	160 mg QD with Food (N=2)	160 mg QD/BID with Food (N=1)	RP2D ⁽²⁾ (N=2)	Total (N=54)
N. of Doses Received/ Subject											
Mean	567.2	174.3	139.4	64.2 (63.77)	818.8	99.5		211.5	56.0 (-)	354.0	280.6
(SD)	(694.23)	(250.25)	(222.42)		(1475.12)	(0.71)		(219.91)		(196.58)	(647.61)
	102.0	104.0	70.0	51.0	136.5	99.5		211.5	56.0	354.0	85.0
Median											
Min-Max	44 - 1516	21 - 821	2 - 912	8 - 214	6 - 4151	99 - 100		56 - 367	56 - 56	215 - 493	2 - 4151
Cumulative Dose (mg) / Subject (1)											
Mean	61224.0	29200.0	23285.0	14213.3	96990.0	19900.0		33840.0	8960.0 (-)	44880.0	37991.1
(SD)	(104547.42)	(57500.80)	(42841.55)	(13493.88)	(155717.12)	(141.42)		(35185.63)		(14820.96)	(76696.95)

Table 2.3-5: Cumulative Dose of Repotrectinib by Starting Dose Level - All Treated Subjects and by Subgroup (TRIDENT-1 Study)

	Starting Dose Level									
	8640.0	8320.0	11200.0	11840.0	21520.0	19900.0	33840.0	8960.0	44880.0	12040.0
Median										
Min-	1760 -	1680 -	320 - 178960	1920 -	960 -	19800 -	8960 - 58720	8960 - 8960	34400 -	320 -
Max	245760	180400		44480	400280	20000			55360	400280

(1) Cumulative dose (in mg) is sum of the doses (in mg) administered to a subject during the treatment period.

(2) The RP2D is 160 mg QD for 14 days followed by 160 mg BID.

Includes data from TPX-0005-01 (Phase 1 and Phase 2).

Data Cutoff Date: 15-Oct-2023.

Table 2.3-6: Clinical Exposure in Person Time by Race Origin and Gender - All Treated Subjects and by Subgroup (TRIDENT-1 Study)

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 237	Female N = 328	Total N = 565	Male N = 237	Female N = 328	Total N = 565
All Treated Subjects						
Caucasian	110 (46.4)	151 (46.0)	261 (46.2)	885.26	1539.74	2425.01
Asian	104 (43.9)	146 (44.5)	250 (44.2)	1372.03	2114.46	3486.49
Black or African American	8 (3.4)	7 (2.1)	15 (2.7)	53.19	105.82	159.02
Native Hawaiian or Other Pacific Islander	1 (0.4)	2 (0.6)	3 (0.5)	14.03	50.50	64.53
American Indian or Alaska Native	2 (0.8)	0	2 (0.4)	10.15	0.00	10.15
Other	1 (0.4)	3 (0.9)	4 (0.7)	1.84	57.53	59.37
Not Reported	9 (3.8)	18 (5.5)	27 (4.8)	174.00	199.75	373.75
Unknown	2 (0.8)	1 (0.3)	3 (0.5)	23.79	3.45	27.24
TOTAL	237 (100)	328 (100)	565 (100)	2534.29	4071.26	6605.55
Subgroup: ROS1+ NSCLC Subjects						
	Male N = 138	Female N = 229	Total N = 367	Male N = 138	Female N = 229	Total N = 367
Caucasian	55 (39.9)	104 (45.4)	159 (43.3)	529.02	1209.92	1738.94
Asian	70 (50.7)	109 (47.6)	179 (48.8)	1015.92	1593.26	2609.18
Black or African American	4 (2.9)	5 (2.2)	9 (2.5)	32.89	22.74	55.62
Native Hawaiian or Other Pacific Islander	1 (0.7)	2 (0.9)	3 (0.8)	14.03	50.50	64.53
American Indian or Alaska Native	2 (1.4)	0	2 (0.5)	10.15	0.00	10.15
Other	0	0	0	0.00	0.00	0.00
Not Reported	4 (2.9)	8 (3.5)	12 (3.3)	77.54	82.46	160.00
Unknown	2 (1.4)	1 (0.4)	3 (0.8)	23.79	3.45	27.24
TOTAL	138 (100)	229 (100)	367 (100)	1703.33	2962.33	4665.66

Table 2.3-6: Clinical Exposure in Person Time by Race Origin and Gender - All Treated Subjects and by Subgroup (TRIDENT-1 Study)

	Persons (%)			Person Time of Exposure (Months) (1)		
Subgroup: NTRK+ Solid Tumor Subjects						
	Male N = 70	Female N = 74	Total N = 144	Male N = 70	Female N = 74	Total N = 144
Caucasian	37 (52.9)	39 (52.7)	76 (52.8)	291.78	309.03	600.81
Asian	25 (35.7)	23 (31.1)	48 (33.3)	322.14	321.54	643.68
Black or African American	3 (4.3)	1 (1.4)	4 (2.8)	16.16	12.98	29.14
Native Hawaiian or Other Pacific Islander	0	0	0	0.00	0.00	0.00
American Indian or Alaska Native	0	0	0	0.00	0.00	0.00
Other	0	1 (1.4)	1 (0.7)	0.00	51.15	51.15
Not Reported	5 (7.1)	10 (13.5)	15 (10.4)	96.46	117.29	213.75
TOTAL	70 (100)	74 (100)	144 (100)	726.54	811.99	1538.53
Subgroup: Other Treated Subjects						
	Male N = 29	Female N = 25	Total N = 54	Male N = 29	Female N = 25	Total N = 54
Caucasian	18 (62.1)	8 (32.0)	26 (48.1)	64.46	20.80	85.26
Asian	9 (31.0)	14 (56.0)	23 (42.6)	33.97	199.66	233.63
Black or African American	1 (3.4)	1 (4.0)	2 (3.7)	4.14	70.11	74.25
Native Hawaiian or Other Pacific Islander	0	0	0	0.00	0.00	0.00
American Indian or Alaska Native	0	0	0	0.00	0.00	0.00
Other	1 (3.4)	2 (8.0)	3 (5.6)	1.84	6.37	8.21
TOTAL	29 (100)	25 (100)	54 (100)	104.42	296.94	401.35

(1) Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date. Includes data from TPX-0005-01 (Phase 1 and Phase 2).

Data Cutoff Date: 15-Oct-2023.

Table 2.3-7: Clinical Exposure in Person Time - Full Analysis Set (CARE Study)

Duration of Exposure	NTRK (N = 19)		Other (N = 19)		Overall Total (N = 38)	
	Persons (%)	Person Time of Exposure (months) (1)	Persons (%)	Person Time of Exposure (months) (1)	Persons (%)	Person Time of Exposure (months) (1)
0 - < 1 month	1 (5.3)		3 (15.8)		4 (10.5)	
1 - < 3 months	6 (31.6)		5 (26.3)		11 (28.9)	
3 - < 6 months	3 (15.8)		1 (5.3)		4 (10.5)	
6 - < 12 months	5 (26.3)		3 (15.8)		8 (21.1)	
12 - < 18 months	3 (15.8)		4 (21.1)		7 (18.4)	
18 - < 24 months	0		1 (5.3)		1 (2.6)	
24 - < 36 months	1 (5.3)		1 (5.3)		2 (5.3)	
≥ 36 months	0		1 (5.3)		1 (2.6)	
0 - ≤ 32.9 months (a)	19 (100)	148.11				
0 - ≤ 41.5 months (a)			19 (100)	196.50	38 (100)	344.61

Note: NTRK cohort includes subjects with NTRK1-3 genetic mutation. Other cohort includes subjects with ROS1 or ALK genetic mutation. Percentages are based on the number of subjects in the Full Analysis Set.

(1) Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date.

(a) Max clinical exposure for treatment group.

Data Cutoff Date: 15-Oct-2023

Table 2.3-8: Clinical Exposure in Person Time by Age Group - Full Analysis Set (CARE Study)

Duration of Exposure	Persons (%)	Person Time of Exposure (months) (1)	Persons (%)	Person Time of Exposure (months) (1)	Persons (%)	Person Time of Exposure (months) (1)
Age Group: < 12 years old						
	NTRK (N = 11)		Other (N = 11)		Overall Total (N = 22)	
0 - < 1 month	0		0		0	
1 - < 3 months	4 (36.4)		3 (27.3)		7 (31.8)	
3 - < 6 months	2 (18.2)		1 (9.1)		3 (13.6)	
6 - < 12 months	3 (27.3)		2 (18.2)		5 (22.7)	
12 - < 18 months	1 (9.1)		2 (18.2)		3 (13.6)	
18 - < 24 months	0		1 (9.1)		1 (4.5)	
24 - < 36 months	1 (9.1)		1 (9.1)		2 (9.1)	
≥ 36 months	0		1 (9.1)		1 (4.5)	
0 - ≤ 32.9 months (a)	11 (100)	90.64	11 (100)	150.51	22 (100)	241.15
0 - ≤ 41.5 months (a)						
Age Group: ≥ 12 years old						
	NTRK (N = 8)		Other (N = 8)		Overall Total (N = 16)	
0 - < 1 month	1 (12.5)		3 (37.5)		4 (25.0)	
1 - < 3 months	2 (25.0)		2 (25.0)		4 (25.0)	
3 - < 6 months	1 (12.5)		0		1 (6.3)	
6 - < 12 months	2 (25.0)		1 (12.5)		3 (18.8)	
12 - < 18 months	2 (25.0)		2 (25.0)		4 (25.0)	
18 - < 24 months	0		0		0	
24 - < 36 months	0		0		0	
≥ 36 months	0		0		0	
0 - ≤ 17.2 months (a)	8 (100)	57.46				
0 - ≤ 17.9 months (a)			8 (100)	46.00	16 (100)	103.46

NTRK cohort includes subjects with NTRK1-3 genetic mutation. Other cohort includes subjects with ROS1 or ALK genetic mutation. Percentages are based on the number of subjects in the Full Analysis Set. (1) Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date.

(a) Max clinical exposure for treatment group.

Data Cutoff Date: 15-Oct-2023

Table 2.3-9: Clinical Exposure in Person Time by Age Group and Gender - Full Analysis Set (CARE Study)

Age Category (Years)	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 9	Female N = 10	Total N = 19	Male N = 9	Female N = 10	Total N = 19
Cohort NTRK						
>= 0 AND < 12	5 (55.6)	6 (60.0)	11 (57.9)	29.47	61.17	90.64
>= 12 AND < 18	3 (33.3)	4 (40.0)	7 (36.8)	20.73	32.16	52.90
>= 18 AND < 26	1 (11.1)	0	1 (5.3)	4.57	0	4.57
>= 26	0	0	0	0	0	0
TOTAL	9 (100)	10 (100)	19 (100)	54.77	93.34	148.11
Cohort Other						
	Male N = 11	Female N = 8	Total N = 19	Male N = 11	Female N = 8	Total N = 19
>= 0 AND < 12	4 (36.4)	7 (87.5)	11 (57.9)	28.75	121.76	150.51
>= 12 AND < 18	7 (63.6)	0	7 (36.8)	45.14	0	45.14
>= 18 AND < 26	0	1 (12.5)	1 (5.3)	0	0.85	0.85
>= 26	0	0	0	0	0	0
TOTAL	11 (100)	8 (100)	19 (100)	73.89	122.61	196.50
Cohort Overall						
	Male N = 20	Female N = 18	Total N = 38	Male N = 20	Female N = 18	Total N = 38
>= 0 AND < 12	9 (45.0)	13 (72.2)	22 (57.9)	58.22	182.93	241.15155.04
>= 12 AND < 18	10 (50.0)	4 (22.2)	14 (36.8)	65.87	32.16	98.04
>= 18 AND < 26	1 (5.0)	1 (5.6)	2 (5.3)	4.57	0.85	5.42
>= 26	0	0	0	0	0	0
TOTAL	20 (100)	18 (100)	38 (100)	128.6650.27	215.95	344.61

Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date.

Data Cutoff Date: 15-Oct-2023

Table 2.3-10: Clinical Exposure in Person Time by Age Category and Gender and Age Group - Full Analysis Set (CARE Study)

Age Group: < 12 years old		Persons (%)		Person Time of Exposure (Months) (1)		
Cohort NTRK						
Age Category (Years)	Male N = 5	Female N = 6	Total N = 11	Male N = 5	Female N = 6	Total N = 11
>= 0 AND < 12	5 (100)	6 (100)	11 (100)	29.47	61.1743.14	90.64
>= 12 AND < 18	0	0	0	0	0	0
>= 18 AND < 26	0	0	0	0	0	0
>= 26	0	0	0	0	0	0
TOTAL	5 (100)	6 (100)	11 (100)	29.47	61.17	90.64
Cohort Other						
Age Category (Years)	Male N = 4	Female N = 7	Total N = 11	Male N = 4	Female N = 7	Total N = 11
>= 0 AND < 12	4 (100)	7 (100)	11 (100)	28.75	121.76	150.51
>= 12 AND < 18	0	0	0	0	0	0
>= 18 AND < 26	0	0	0	0	0	0
>= 26	0	0	0	0	0	0
TOTAL	4 (100)	7 (100)	11 (100)	28.75	121.76	150.51
Cohort Overall						
Age Category (Years)	Male N = 9	Female N = 13	Total N = 22	Male N = 9	Female N = 13	Total N = 22
>= 0 AND < 12	9 (100)	13 (100)	22 (100)	58.22	182.93	241.15
>= 12 AND < 18	0	0	0	0	0	0
>= 18 AND < 26	0	0	0	0	0	0
>= 26	0	0	0	0	0	0
TOTAL	9 (100)	13 (100)	22 (100)	58.22	182.93	241.15

Table 2.3-10: Clinical Exposure in Person Time by Age Category and Gender and Age Group - Full Analysis Set (CARE Study)

<i>Age Group: ≥12 years old</i>			Persons (%)			Person Time of Exposure (Months) (1)		
Age Category (Years)	Male N = 4	Female N = 4	Total N = 8	Male N = 4	Female N = 4	Total N = 8		
Cohort NTRK								
>= 0 AND < 12	0	0	0	0	0	0		
>= 12 AND < 18	3 (75.0)	4 (100)	7 (87.5)	20.73	32.16	52.90		
>= 18 AND < 26	1 (25.0)	0	1 (12.5)	4.57	0	4.57		
>= 26	0	0	0	0	0	0		
TOTAL	4 (100)	4 (100)	8 (100)	25.30	32.16	57.46		
Cohort Other								
Age Category (Years)	Male N = 7	Female N = 1	Total N = 8	Male N = 7	Female N = 1	Total N = 8		
>= 0 AND < 12	0	0	0	0	0	0		
>= 12 AND < 18	7 (100)	0	7 (87.5)	45.14	0	45.14		
>= 18 AND < 26	0	1 (100)	1 (12.5)	0	0.85	0.85		
>= 26	0	0	0	0	0	0		
TOTAL	7 (100)	1 (100)	8 (100)	45.14	0.85	46.00		
Cohort Overall								
Age Category (Years)	Male N = 11	Female N = 5	Total N = 16	Male N = 11	Female N = 5	Total N = 16		
>= 0 AND < 12	0	0	0	0	0	0		
>= 12 AND < 18	10 (90.9)	4 (80.0)	14 (87.5)	65.87	32.16	98.04		
>= 18 AND < 26	1 (9.1)	1 (20.0)	2 (12.5)	4.57	0.85	5.42		
>= 26	0	0	0	0	0	0		
TOTAL	11 (100)	5 (100)	16 (100)	70.44	33.02	103.46		

(1) Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date.

Data Cutoff Date: 15-Oct-2023

Table 2.3-11: Clinical Exposure in Person Time by Starting Dose - Full Analysis Set (CARE Study)

Dose Level	Persons (%)	Person Time of Exposure (months) (1)	Persons (%)	Person Time of Exposure (months) (1)	Persons (%)	Person Time of Exposure (months) (1)
Overall	NTRK (N = 19)		Other (N = 19)		Overall Total (N = 38)	
Dose Level 1	3 (15.8)	37.49	1 (5.3)	41.53	4 (10.5)	79.01
Dose Level 2	16 (84.2)	110.62	18 (94.7)	154.97	34 (89.5)	265.59
Total	19 (100)	148.11	19 (100)	196.50	38 (100)	344.61
Age Group: < 12 years old	NTRK (N = 11)		Other (N = 11)		Overall Total (N = 22)	
Dose Level 1	3 (27.3)	37.49	1 (9.1)	41.53	4 (18.2)	79.01
Dose Level 2	8 (72.7)	53.16	10 (90.9)	108.98	18 (81.8)	162.14
Total	11 (100)	90.64	11 (100)	150.51	22 (100)	241.15
Age Group: ≥12 years old	NTRK (N = 8)		Other (N = 8)		Overall Total (N = 16)	
Dose Level 1	0	0	0	0	0	0
Dose Level 2	8 (100)	57.46	8 (100)	46.00	16 (100)	103.46
Total	8 (100)	57.46	8 (100)	46.00	16 (100)	103.46

Note: NTRK cohort includes subjects with NTRK1-3 genetic mutation. Other cohort includes subjects with ROS1 or ALK genetic mutation.

Dose 1 Level: 160 mg Repotrectinib QD; Dose Level 2: 160 mg Repotrectinib QD for 14 days followed by 160 Repotrectinib BID. Dose Level 2 cohort consists of Phase 1 Dose Level 2 subjects as well as all subjects from Phase 2 (Cohort 1, Cohort 2, Cohort 3).

(1) Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date.

Data Cutoff Date: 15-Oct-2023

Table 2.3-12: Cumulative Dose of Repotrectinib by Starting Dose Level - Full Analysis Set (CARE Study)

Overall	NTRK (N=19)			Other (N=19)			Overall Total (N=38)		
	Dose Level 1	Dose Level 2	Total	Dose Level 1	Dose Level 2	Total	Dose Level 1	Dose Level 2	Total
Doses Received / Subject (1)									
n	3	16	19	1	18	19	4	34	38
Mean (SD)	379.3 (535.89)	387.3 (303.45)	386.0 (329.62)	1800.0 (NE)	495.7 (494.44)	564.4 (566.06)	734.5 (834.28)	444.7 (413.30)	475.2 (465.73)
Median	81.0	317.0	258.0	1800.0	383.5	479.0	539.5	332.0	332.0
Min, Max	59, 998	41, 1065	41, 1065	1800, 1800	1, 1632	1, 1800	59, 1800	1, 1632	1, 1800
Cumulative Dose (mg) / Subject (2)									
n	3	16	19	1	18	19	4	34	38
Mean (SD)	35129.6 (50262.46)	50173.2 (46738.66)	47797.9 (46183.15)	286340.0 (NE)	49628.4 (57869.52)	62086.9 (78178.68)	97932.2 (132139.61)	49884.8 (52136.49)	54942.4 (63744.82)
Median	8307.2	35500.8	29721.6	286340.0	17510.4	19660.8	50710.4	26140.8	26140.8
Min, Max	3968, 93114	6560, 170400	3968, 170400	286340, 286340	140, 181520	140, 286340	3968, 286340	140, 181520	140, 286340
Age Group: < 12 years old	NTRK (N = 11)			Other (N = 11)			Overall Total (N = 22)		
	Dose Level 1	Dose Level 2	Total	Dose Level 1	Dose Level 2	Total	Dose Level 1	Dose Level 2	Total
Doses Received / Subject (1)									
n	3	8	11	1	10	11	4	18	22
Mean (SD)	379.3 (535.89)	359.5 (263.14)	364.9 (325.57)	1800.0 (NE)	633.3 (532.12)	739.4 (615.29)	734.5 (834.28)	511.6 (444.99)	552.1 (517.18)
Median	81.0	291.0	206.0	1800.0	600.0	625.0	539.5	430.0	430.0
Min, Max	59, 998	82, 795	59, 998	1800, 1800	44, 1632	44, 1800	59, 1800	44, 1632	44, 1800
Cumulative Dose (mg) / Subject (2)									
n	3	8	11	1	10	11	4	18	22
Mean (SD)	35129.6 (50262.46)	35258.9 (30863.90)	35223.6 (34235.55)	286340.0 (NE)	48115.8 (54498.81)	69772.5 (88500.11)	97932.2 (132139.61)	42401.6 (44809.27)	52498.1 (67826.24)
Median	8307.2	22924.8	16128.0	286340.0	31228.8	42796.8	50710.4	24691.2	24691.2

Table 2.3-12: Cumulative Dose of Repotrectinib by Starting Dose Level - Full Analysis Set (CARE Study)

Min, Max	3968, 93114	8986, 86540	3968, 93114	286340, 286340	1971, 181520	1971, 286340	3968, 286340	1971, 181520	1971, 286340
Age Group: ≥12 years old	NTRK (N = 8)			Other (N = 8)			Overall Total (N = 16)		
	Dose Level 1	Dose Level 2	Total	Dose Level 1	Dose Level 2	Total	Dose Level 1	Dose Level 2	Total
Doses Received / Subject (1)									
n	0	8	8	0	8	8	0	16	16
Mean (SD)		415.0 (355.40)	415.0 (355.40)		323.8 (410.88)	323.8 (410.88)		369.4 (374.10)	369.4 (374.10)
Median		343.5	343.5		95.5	95.5		199.5	199.5
Min, Max		41, 1065	41, 1065		1, 1059	1, 1059		1, 1065	1, 1065
Cumulative Dose (mg) / Subject (2)									
n	0	8	8	0	8	8	0	16	16
Mean (SD)		65087.5 (56745.66)	65087.5 (56745.66)		51519.1 (65627.12)	51519.1 (65627.12)		58303.3 (59679.88)	58303.3 (59679.88)
Median		50670.0	50670.0		15280.0	15280.0		31920.0	31920.0
Min, Max		6560, 170400	6560, 170400		140, 169440	140, 169440		140, 170400	140, 170400

Note: Dose Level 1: 160 mg Repotrectinib QD; Dose Level 2: 160 mg Repotrectinib QD for 14 days followed by 160 Repotrectinib BID. Dose Level 2 cohort consists of Phase 1 Dose Level 2 subjects as well as all subjects from Phase 2 (Cohort 1, Cohort 2, Cohort 3).

Percentages are based on the number of subjects in the Full Analysis Set.

(1) To determine total number of doses received, 1 dose is assigned to QD dosing days; 2 doses are assigned to BID dosing days. Do not assign any doses for days where dose reported in 0mg.

(2) Cumulative dose (in mg) is sum of the doses (in mg) administered to a subject during the treatment period.

Data Cutoff Date: 15-Oct-2023

Table 2.3-13: Clinical Exposure in Person Time by Race Origin and Gender - Full Analysis Set (CARE Study)

Race	Persons (%)			Person Time of Exposure (Months) (1)		
	Male N = 9	Female N = 10	Total N = 19	Male N = 9	Female N = 10	Total N = 19
Cohort NTRK						
Caucasian	7 (77.8)	8 (80.0)	15 (78.9)	48.36	48.33	96.69
Asian	1 (11.1)	2 (20.0)	3 (15.8)	0.89	45.01	45.90
Black or African American	1 (11.1)	0	1 (5.3)	5.52	0	5.52
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Other	0	0	0	0	0	0
Multiple	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Not Reported	0	0	0	0	0	0
TOTAL	9 (100)	10 (100)	19 (100)	54.77	93.34	148.11
Cohort Other						
Race	Male N = 11	Female N = 8	Total N = 19	Male N = 11	Female N = 8	Total N = 19
Caucasian	5 (45.5)	4 (50.0)	9 (47.4)	28.12	69.42	97.54
Asian	4 (36.4)	1 (12.5)	5 (26.3)	17.15	9.69	26.84
Black or African American	1 (9.1)	1 (12.5)	2 (10.5)	10.74	0.85	11.60
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Other	0	0	0	0	0	0
Multiple	0	1 (12.5)	1 (5.3)	0	1.12	1.12
Unknown	0	0	0	0	0	0

Table 2.3-13: Clinical Exposure in Person Time by Race Origin and Gender - Full Analysis Set (CARE Study)

		Persons (%)			Person Time of Exposure (Months) (1)		
Not Reported	1 (9.1)	1 (12.5)	2 (10.5)	17.87	41.53	59.40	
TOTAL	11 (100)	8 (100)	19 (100)	73.89	122.61	196.50	
Cohort Overall							
Race	Male N = 20	Female N = 18	Total N = 38	Male N = 20	Female N = 18	Total N = 38	
Caucasian	12 (60.0)	12 (66.7)	24 (63.2)	76.48	117.75	194.23	
Asian	5 (25.0)	3 (16.7)	8 (21.1)	18.04	54.70	72.74	
Black or African American	2 (10.0)	1 (5.6)	3 (7.9)	16.26	0.85	17.12	
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	
American Indian or Alaska Native	0	0	0	0	0	0	
Other	0	0	0	0	0	0	
Multiple	0	1 (5.6)	1 (2.6)	0	1.12	1.12	
Unknown	0	0	0	0	0	0	
Not Reported	1 (5.0)	1 (5.6)	2 (5.3)	17.87	41.53	59.40	
TOTAL	20 (100)	18 (100)	38 (100)	128.66	215.95	344.61	

(1) Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date.

Data Cutoff Date: 15-Oct-2023

Table 2.3-14: Clinical Exposure in Person Time by Race Origin and Gender and Age Group - Full Analysis Set (CARE Study)

<i>Age Group: < 12 years old</i>	Persons (%)			Person Time of Exposure (Months) (1)		
Cohort NTRK						
Race	Male N = 5	Female N = 6	Total N = 11	Male N = 5	Female N = 6	Total N = 11
Caucasian	4 (80.0)	5 (83.3)	9 (81.8)	23.95	28.29	52.24
Asian	0	1 (16.7)	1 (9.1)	0	32.89	32.89
Black or African American	1 (20.0)	0	1 (9.1)	5.52	0	5.52
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Other	0	0	0	0	0	0
Multiple	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Not Reported	0	0	0	0	0	0
TOTAL	5 (100)	6 (100)	11 (100)	29.47	61.17	90.64
Cohort Other						
Race	Male N = 4	Female N = 7	Total N = 11	Male N = 4	Female N = 7	Total N = 11
Caucasian	2 (50.0)	4 (57.1)	6 (54.5)	16.16	69.42	85.59
Asian	1 (25.0)	1 (14.3)	2 (18.2)	1.84	9.69	11.53
Black or African American	1 (25.0)	0	1 (9.1)	10.74	0	10.74
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Other	0	0	0	0	0	0
Multiple	0	1 (14.3)	1 (9.1)	0	1.12	1.12
Unknown	0	0	0	0	0	0
Not Reported	0	1 (14.3)	1 (9.1)	0	41.53	41.53
TOTAL	4 (100)	7 (100)	11 (100)	28.75	121.76	150.51

Table 2.3-14: Clinical Exposure in Person Time by Race Origin and Gender and Age Group - Full Analysis Set (CARE Study)

Cohort Overall						
Race	Male N = 9	Female N = 13	Total N = 22	Male N = 9	Female N = 13	Total N = 22
Caucasian	6 (66.7)	9 (69.2)	15 (68.2)	40.11	97.71	137.82
Asian	1 (11.1)	2 (15.4)	3 (13.6)	1.84	42.58	44.42
Black or African American	2 (22.2)	0	2 (9.1)	16.26	0	16.26
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Other	0	0	0	0	0	0
Multiple	0	1 (7.7)	1 (4.5)	0	1.12	1.12
Unknown	0	0	0	0	0	0
Not Reported	0	1 (7.7)	1 (4.5)	0	41.53	41.53
TOTAL	9 (100)	13 (100)	22 (100)	58.22	182.93	241.15
Age Group: ≥12 years old		Persons (%)		Person Time of Exposure (Months) (1)		
Cohort NTRK						
Race	Male N = 4	Female N = 4	Total N = 8	Male N = 4	Female N = 4	Total N = 8
Caucasian	3 (75.0)	3 (75.0)	6 (75.0)	24.41	20.04	44.45
Asian	1 (25.0)	1 (25.0)	2 (25.0)	0.89	12.12	13.01
Black or African American	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Other	0	0	0	0	0	0
Multiple	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Not Reported	0	0	0	0	0	0
TOTAL	4 (100)	4 (100)	8 (100)	25.30	32.16	57.46

Table 2.3-14: Clinical Exposure in Person Time by Race Origin and Gender and Age Group - Full Analysis Set (CARE Study)

Cohort Other						
Race	Male N = 7	Female N = 1	Total N = 8	Male N = 7	Female N = 1	Total N = 8
Caucasian	3 (42.9)	0	3 (37.5)	11.96	0	11.96
Asian	3 (42.9)	0	3 (37.5)	15.31	0	15.31
Black or African American	0	1 (100)	1 (12.5)	0	0.85	0.85
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Other	0	0	0	0	0	0
Multiple	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Not Reported	1 (14.3)	0	1 (12.5)	17.87	0	17.87
TOTAL	7 (100)	1 (100)	8 (100)	45.14	0.85	46.00
Cohort Overall						
Race	Male N = 11	Female N = 5	Total N = 16	Male N = 11	Female N = 5	Total N = 16
Caucasian	6 (54.5)	3 (60.0)	9 (56.3)	36.37	20.04	56.41
Asian	4 (36.4)	1 (20.0)	5 (31.3)	16.20	12.12	28.32
Black or African American	0	1 (20.0)	1 (6.3)	0	0.85	0.85
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Other	0	0	0	0	0	0
Multiple	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Not Reported	1 (9.1)	0	1 (6.3)	17.87	0	17.87
TOTAL	11 (100)	5 (100)	16 (100)	70.44	33.02	103.46

(1) Sum of subject's exposure time. Subject's exposure time in months is defined as (end of treatment date - treatment start date + 1)/30.4375. Subjects still on treatment at the time of the interim database lock will have their exposure end date imputed to the database cutoff date.

Data Cutoff Date: 15-Oct-2023

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Women who are pregnant or planning to conceive a child	Based on literature reports in humans with congenital mutations leading to changes in TRK signaling, ^{54,55} findings from animal studies, and its mechanism of action, repotrectinib may cause foetal harm. There are no available data on repotrectinib use in pregnant women.	No	Fertility and pregnancy are detailed in the product information for repotrectinib. Repotrectinib should not be used unless clinical condition of the woman requires treatment with repotrectinib. Women of childbearing potential must use effective contraception.
Women who are breastfeeding	No studies have been conducted to assess the effects of repotrectinib on milk production or its presence in breast milk. For this reason, repotrectinib should not be used in women who are breastfeeding as the potential for harm to the nursing infant is unknown.	No	Breast-feeding is detailed in the product information for repotrectinib. Lactating women are advised to discontinue breastfeeding during treatment and for 10 days after the final dose.
Age < 12 years-old ^a	These subjects were excluded from TRIDENT-1 as a precaution to prevent the exposure of patients to an investigational drug for which there was insufficient safety information at the time of the conduct of the studies.	No	The availability of a suspension formulation for repotrectinib allows for testing in the paediatric population in the ongoing CARE study. ^b

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Symptomatic brain metastases or leptomeningeal involvement	These subjects were excluded from clinical trials because these conditions could confound the assessments of safety or efficacy or could impact the subjects' ability to comply with protocol requirements. Such patients often have a very short life expectancy and frequently an inadequate performance status to be eligible for clinical trials.	No	Not applicable to post marketing setting. The exclusion criterion was implemented for the purpose of the clinical trials, and not for a specific safety concern. There is no biological or mechanistic reason to suspect a safety issue in this patient population. The safety and efficacy profile for such patients is not expected to be different.
Subjects with neuroblastoma with only bone marrow disease evaluable by bone marrow aspiration only ^b	These subjects were excluded to ensure that the primary or metastatic soft tissue lesions could be evaluated per the tumour response assessment criteria specified in the protocol.	No	Not applicable to post marketing setting. The exclusion criterion was implemented for the purpose of the clinical trial, and not for a specific safety concern. The safety and efficacy profile for such patients is not expected to be different.
Any of the following cardiac criteria: • Mean resting corrected QTcF > 470 msec and > 480 msecb • Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (eg, complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec). • Any factors that increase the risk of QTc prolongation or	These subjects were excluded as a precaution to prevent the exposure of patients with severe pre-existing medical conditions to an investigational drug for which there was insufficient safety information at the time of the conduct of the studies.	No	Not applicable to post marketing setting. The exclusion criterion was implemented for the purpose of the clinical trials, and not for a specific safety concern. Based on the totality of data to date repotrectinib does not demonstrate clinically meaningful cardiac effects in this patient population. The safety and efficacy profile for such patients is not expected to be different.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or any concomitant medication known to prolong the QT interval.			
Peripheral neuropathy, paresthesia, dizziness, dysgeusia, muscle weakness, ataxia Grade ≥ 2 .	These events were a known effect for the class of ROS1 TKI agents. It was important to understand the baseline effect of repotrectinib on patients without these preexisting conditions, to better understand its potential to exacerbate these conditions on treatment.	No	CNS effects (including ataxia, cognitive disorders, and dizziness) are included as ADRs and well characterized in the product information.
History of extensive, disseminated, bilateral, or presence of CTCAE Grade 3 or 4 interstitial fibrosis or ILD including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, ILD, obliterative bronchiolitis, and pulmonary fibrosis.	TKI as a class is known to cause ILD. These patients were excluded to protect patients at risk for ILD.	No	ILD/ pneumonitis is included as an ADR in the product information.
Current use or anticipated need for drugs that are known to be strong CYP3A inhibitors or inducers.	An in vitro metabolism study suggested that repotrectinib is metabolized mainly by CYP3A4. Results from the drug interaction study TPX-0005-10 showed that administration of repeated doses of itraconazole (a strong CYP3A4 inhibitor) resulted in a significant increase in the single dose exposure of repotrectinib ($AUC_{inf} \sim 589\%$ and $C_{max} \sim 167\%$), and	No	Information regarding the use of repotrectinib with strong CYP3A inhibitors and inducers and the potential impacts (ie, a potential for an increase in toxicities when administered with CYP3A inhibitor

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
	administration of repeated doses of rifampin (a strong CYP3A4 inducer) resulted in a significant decrease in single dose exposure of repotrectinib (AUC_{inf} ~92% and C_{max} ~79%). ⁵⁶ Therefore, these patients were excluded to avoid interference with interpretation of study results. Inhibition of CYP3A isoenzymes may increase repotrectinib exposure leading to a potential increase in toxicities. Repotrectinib metabolism may be induced when taking strong CYP3A inducers resulting in reduced plasma concentrations of repotrectinib.		and a potential for decreased efficacy when administered with CYP3A inducer) are detailed in the product information for repotrectinib, including statements that co-administration of repotrectinib with strong or moderate CYP3A4 inhibitors and with strong CYP3A4 inducers is to be avoided.

^a TRIDENT-1 (Study TPX-0005-01, CA127-1024)

^b CARE (Study TPX-0005-07, CA127-1029)

2.4.2 **Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes**

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with long latency, or those caused by prolonged or cumulative exposure.

2.4.3 **Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes**

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Repotrectinib has not been studied in patients with moderate or severe hepatic impairment.
Patients with renal impairment	Repotrectinib has not been studied in patients with severe renal impairment.
Patients with cardiovascular impairment	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Included in the clinical development program (Refer to Section 2.3).
Subpopulations carrying relevant genetic polymorphisms	
• Drug metabolizing enzymes/transporters	Repotrectinib is primarily metabolized by CYP3A4; the impact of polymorphisms of CYP enzymes or transporters have not been main evaluated in the clinical development program.
Other:	
Paediatric patients	Included in the clinical development program (Refer to Section 2.3).
Elderly patients ≥ 65 years old	Included in the clinical development program (Refer to Section 2.3).

2.5 **Post-Authorisation Experience**

AUGTYRO (repotrectinib, TPX-0005, BMS-986472) was first approved in the US on 15-Nov-2023 for the treatment of adult patients with *ROS1*-positive locally advanced or metastatic

NSCLC. Repotrectinib is currently authorised for marketing in 3 countries (China, Macau, and US).

2.5.1 Post-authorisation Exposure

2.5.1.1 Method Used to Calculate Exposure

There is no readily available information on the number of patients treated with marketed repotrectinib. However, an estimate of the number of treated patients can be derived from available sales figures.

Third-party vendors provide sales figures to the Company for repotrectinib on a quarterly basis that are generally available 3 months after the close of a calendar quarter. Although these data represent the bulk (80% - 85%) of the Company's worldwide sales of repotrectinib, they are only an estimation of the total quantity of product sold based on the total amount of product distributed in all countries worldwide. Additionally, the sales data from third-party vendors may vary from one reporting period to another because of changes in subscription agreements and changes to the number of data channels available within a given country (eg, direct-to-consumer sales, hospital sales, and home care sales).

The estimated sales and average dose and duration of treatment, based on the prescribing information for repotrectinib, are used to calculate the estimated number of patients treated.⁵⁷

2.5.1.2 Exposure

The cumulative postmarketing patient exposure to repotrectinib is available to 14-May-2024.⁵⁷

Based on sales data from third-party vendors, the total cumulative post-marketing patient exposure to repotrectinib was estimated to be 5,025 patients. The estimated patient-month exposure to repotrectinib was estimated to be 13.77 patient-years.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Based on the known mechanism of action, repotrectinib is not considered a controlled substance and it has no known potential for drug abuse or dependence. Therefore, there is not expected to be a potential for misuse for illegal purposes.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP are summarized in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial Risk Management Plan

<i>Important Identified Risks</i>	Skeletal fractures
<i>Important Potential Risks</i>	None

Table 2.7.1-1: Safety Concerns in the Initial Risk Management Plan

<i>Missing Information</i>	Safety in long-term use
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2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

<i>Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)</i>	None
<i>Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated</i>	None
<i>Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised)</i>	Muscular weakness CNS effects (including ataxia, cognitive disorders, and dizziness)
<i>Known risks that do not impact the risk-benefit profile</i>	None
<i>Other reasons for considering the risks not important</i>	None

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Risks considered important for inclusion in the list of safety concerns in the RMP

Risk Type	Risk-Benefit Impact
Important Identified Risks	
Skeletal fractures	Skeletal fractures have been reported at a higher frequency in paediatric patients than in adult patients treated with repotrectinib across clinical trials. Skeletal fractures were generally localised in the lower extremity (eg. ankle, fibula, foot). While severe and serious TEAEs of skeletal fractures were observed, most of the TEAEs of skeletal fractures were Grade 1-2. In adult and paediatric patients, some fractures were reported in the setting of a fall or other trauma to the affected area; in paediatric patients some fractures occurred with no trauma. Radiologic abnormalities possibly indicative of tumour involvement were reported in some patients. Prompt evaluation of patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures is expected to ensure timely treatment to prevent more serious outcome and prompt recovery. Overall, the risk-benefit balance is positive considering the severity of the disease treated and potential efficacy for patients treated with repotrectinib.
Important Potential Risks	
None	
Missing Information	
Safety in long-term use	Treatment with repotrectinib has been well tolerated for periods beyond 12 months in a limited number of adult and paediatric subjects.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not Applicable.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Repotrectinib clinical studies supporting safety analyses in the RMP are summarized in [Table 2.3-1](#).

2.7.3.1 Presentation of Important Identified and Important Potential Risks

Table 2.7.3.1-1 Important Identified Risk: Skeletal fractures

Important Identified Risk Skeletal fractures	
Potential mechanisms	The mechanism for repotrectinib-associated fractures is unknown. TRK inhibitors are known to cause neurologic adverse effects including dizziness and ataxia ⁵⁸ , which could result in falls causing fractures.
Evidence source and strength of evidence	Fractures have been reported for another drug in the same class. ⁵⁹ Skeletal fractures have been reported in 3.5% of adults and 18.4% of paediatric patients treated with repotrectinib across clinical trials. In adult and paediatric patients, some fractures were reported in the

Table 2.7.3.1-1 Important Identified Risk: Skeletal fractures**Important Identified Risk Skeletal fractures**

setting of a fall or other trauma to the affected area; in paediatric patients some fractures were reported with no trauma. Radiologic abnormalities possibly indicative of tumour involvement were reported in some patients. In both adult and paediatric patients, most fractures were lower extremity fractures (eg, fibula, tibia, or foot).

The median time to first onset of skeletal fractures was 171.5 days, ranging from 10 to 921 days. Most of the skeletal fractures TEAEs were Grade 1-2 with a median time to resolution of 40.00 weeks, ranging from 0.1 to 220.9 weeks. One fatal case (PT femur fracture) was reported in an adult patient with *ROS1*-positive NSCLC.

For the paediatric population, the median time to first onset was 127.0 days, ranging from 25 to 514 days. Time to resolution was between 10+ to 205 days.

Characterization of risk

TRIDENT-1^a - Safety Analysis Set

	ROS1+ NSCLC Subjects (N=367)	NTRK+ Solid Tumor Subjects (N=144)	Other Treated Subjects (N=54)	Total (N=565)
Subjects with skeletal fractures TEAE, n (%)				
All Subjects with TEAE	14 (3.8)	4 (2.8)	2 (3.7)	20 (3.5)
Serious TEAEs	5 (1.4)	1 (0.7)	0	6 (1.1)
Grade $\geq$ 3 TEAEs	3 (0.8)	0	0	3 (0.5)
Fatal TEAEs	1 (0.3)	0	0	1 (0.2)

CARE^b - Safety Analysis Set

	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Subjects with skeletal fractures TEAE, n (%)			
All Subjects with TEAE	3 (15.8)	4 (21.1)	7 (18.4)
Serious TEAEs	1 (5.3)	0	1 (2.6)
Grade $\geq$ 3 TEAEs	0	0	0
Fatal TEAEs	0	0	0

Risk factors and risk groups

TRK inhibitors are known to cause neurologic adverse effects including dizziness and ataxia,⁶⁰ which could result in falls causing fractures. Skeletal fractures have been reported in 3.5% of adults and 18.4% of paediatric patients treated with repotrectinib across clinical trials. In adult and paediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area; in paediatric patients some fractures occurred with no trauma. Among subjects with baseline brain metastases, skeletal fractures were reported in 5/193 subjects. Among subjects without baseline brain metastases, skeletal fractures were reported in 15/372 subjects. For the paediatric population, among subjects with baseline brain metastases, skeletal fractures were reported in 2/7 subjects. Among subjects without baseline brain metastases, skeletal fractures were reported in 5/31 subjects.

Preventability

Although the development of skeletal fractures cannot be completely prevented, patients with signs and symptoms of fractures should be promptly evaluated and provided with timely treatment to prevent more serious outcome and ensure prompt recovery.

Table 2.7.3.1-1 Important Identified Risk: Skeletal fractures

Important Identified Risk Skeletal fractures	
Impact on the risk-benefit balance of the product	Most of skeletal fractures reported with repotrectinib treatment were Grade 1-2. Considering the severity of the disease treated and potential efficacy for patients treated with repotrectinib, the risk of skeletal fractures is outweighed by the potential benefit of repotrectinib treatment.
Public health impact	This risk has minimal public health impact outside its effect on individual patients.
MedDRA terms	See Annex 7

^a CARE (Study TPX-0005-07, CA127-1029)^b TRIDENT-1 (Study TPX-0005-01, CA127-1024)

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information

Missing Information	Evidence Source
Population in need of further characterisation:	
Patients treated with repotrectinib for long-term	Treatment with repotrectinib has been well tolerated for periods beyond 12 months in a limited number of adult and paediatric subjects.

2.8 Summary of the Safety Concerns

Table 2.8-1: Summary of Safety Concerns

Important Identified Risks	Skeletal fractures
Important Potential Risks	None
Missing Information	Safety in long-term use

3 PART III: PHARMACOVIGILANCE PLAN

3.1 Routine Pharmacovigilance Activities

There are no routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

3.2 Additional Pharmacovigilance Activities

There are no planned or ongoing post-authorization safety studies in the PV plan.

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Protocols for imposed post-authorisation efficacy studies are provided in [Annex 5](#).

Table 4-1: Planned and On-going Post-authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study / Status	Summary of objectives	Efficacy concerns addressed	Milestone(s)	Due Date(s)
Efficacy studies which are conditions of the marketing authorisation				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
CARE ^a – Phase 1/2, open-label, safety, tolerability, PK, and anti-tumor activity study of repotrectinib in pediatric and young adult subjects with advanced or metastatic malignancies harboring <i>ALK</i> , <i>ROS1</i> , or <i>NTRK1-3</i> alterations. Ongoing	To further investigate the efficacy and long-term safety in paediatric patients with solid tumours expressing a NTRK gene fusion, the MAH should submit the results of the final safety and efficacy analysis of the ongoing Phase 1/2, Open-label, Safety, Tolerability, Pharmacokinetics, and Anti-tumour Activity Study of repotrectinib in Paediatric and Young Adult Subjects with Advanced or Metastatic Malignancies Harboring <i>ALK</i> , <i>ROS1</i> , or <i>NTRK1-3</i> Alterations.	Efficacy and long-term safety.	Final Report	Q4 2030
TRIDENT-1 ^b – Phase 1/2, open-label study of safety, tolerability, PK, and anti-tumor activity of repotrectinib in patients with advanced solid tumors harboring <i>ALK</i> , <i>ROS1</i> , or <i>NTRK1-3</i> rearrangements. Ongoing	To further confirm histology-independent efficacy, efficacy despite resistance mutations, and IC responses of repotrectinib in adults, the MAH should submit the final CSR of the ongoing phase 1/2 trial TRIDENT-1 (all cohorts).	Efficacy	Final CSR	Q1 2029

^a CARE (Study TPX-0005-07, CA127-1029)

^b TRIDENT-1 (Study TPX-0005-01, CA127-1024)

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Routine Risk Minimisation Measures

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Skeletal fractures	Routine risk communication: - The SmPC warns of skeletal fractures in Section 4.4 and includes skeletal fractures as adverse reactions in Section 4.8. - The PIL includes skeletal fractures as serious side effects in Section 4. Routine risk minimization activities recommending specific clinical measures to address the risk: - Recommendation that patients with signs or symptoms (eg, pain, changes in mobility, deformity) of fractures should be promptly evaluated is included in the SmPC Section 4.4. - In the PIL Section 2, patients are advised to inform their doctor, pharmacist or nurse of a history of fractured bones, or condition which may increase the risk of breaking bones before taking repotrectinib. - In the PIL Section 4, patients are advised to inform their doctor right away if they notice any joint pain, bone pain, deformities or changes in your ability to move, as this may be a sign of fractures. Other routine risk minimization measures beyond the Product Information: - None.
Safety in long-term use	Routine risk communication: - SmPC Section 4.4, Paediatric Population includes relevant information. Routine risk minimization activities recommending specific clinical measures to address the risk: - None. Other routine risk minimization measures beyond the Product Information: - None.

5.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part 5.1 are sufficient to manage the safety concerns of the medicinal product.

5.3 Summary of Risk Minimisation Measures

A summary of risk minimisation measures and pharmacovigilance activities by safety concern is provided in Table 5.3-1.

Table 5.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk Minimization Measures	Pharmacovigilance Activities
Skeletal fractures	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8. • PIL Section 2 advising patients to inform their doctor, pharmacist or nurse of a history of fractured bones, or condition which may increase the risk of breaking bones before taking repotrectinib. • In the PIL Section 4, patients are advised to inform their doctor right away if they notice any joint pain, bone pain, deformities or changes in your ability to move, as this may be a sign of fractures. • Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None
Safety in long-term use	Routine risk minimization measures: • SmPC Section 4.4 (Paediatric Population). Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Augtyro (repotrectinib)

This is a summary of the risk management plan (RMP) for Augtyro. The RMP details important risks of Augtyro, how these risks can be minimised, and how more information will be obtained about Augtyro's risks and uncertainties (missing information).

Augtyro's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Augtyro should be used.

This summary of the RMP for Augtyro should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Augtyro's RMP.

I. The medicine and what it is used for

Augtyro is authorised as monotherapy for the treatment of adult patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) and for the treatment of adult and paediatric patients 12 years of age and older with locally advanced, metastatic solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion (see SmPC for the full indication). It contains repotrectinib as the active substance and it is given by hard gelatin capsules for oral administration.

Further information about the evaluation of Augtyro's benefits can be found in Augtyro's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: <https://www.ema.europa.eu/en/medicines/what-we-publish/when/european-public-assessment-reports-background-context>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Augtyro, together with measures to minimise such risks and the proposed studies for learning more about Augtyro's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of Augtyro is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Augtyro are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Augtyro. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

<i>Important identified risks</i>	Skeletal fractures
<i>Important potential risks</i>	None
<i>Missing information</i>	Safety in long-term use

II.B Summary of important risks

Important identified risks

Skeletal fractures

Evidence for linking the risk to the medicine	Fractures have been reported for another drug in the same class. Skeletal fractures have been reported in 3.5% of adults and 18.4% of paediatric patients treated with repotrectinib across clinical trials. In adult and paediatric patients, some fractures were reported in the setting of a fall or other trauma to the affected area; in paediatric patients some fractures were reported with no trauma. Radiologic abnormalities possibly indicative of tumour involvement were reported in some patients. In both adult and paediatric patients, most fractures were lower extremity fractures (eg, fibula, tibia, or foot).
Risk factors and risk groups	TRK inhibitors are known to cause neurologic adverse effects including dizziness and ataxia, which could result in falls causing fractures. Skeletal fractures have been reported in 3.5% of adults and 18.4% of paediatric patients treated with repotrectinib across clinical trials. In adult and paediatric patients, some fractures occurred in the setting of a fall or other trauma to the affected area; in paediatric patients some fractures occurred with no trauma. Among subjects with baseline brain metastases, skeletal fractures were reported in 5/193 subjects. Among subjects without baseline brain metastases, skeletal fractures were reported in 15/372 subjects. For the paediatric population, among subjects with baseline brain metastases, skeletal fractures were reported in 2/7 subjects. Among subjects without baseline brain metastases, skeletal fractures were reported in 5/31 subjects.
Risk minimisation measures	• SmPC Sections 4.4 and 4.8.

Important identified risks

Additional pharmacovigilance activities	- PIL Section 2 advising patients to inform their doctor, pharmacist or nurse of a history of fractured bones, or condition which may increase the risk of breaking bones before taking repotrectinib. - In the PIL Section 4, patients are advised to inform their doctor right away if they notice any joint pain, bone pain, deformities or changes in your ability to move, as this may be a sign of fractures. - None
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Important potential risk(s)

None

Missing information

Safety in long-term use

Risk minimisation measures	SmPC Section 4.4 (Paediatric Population)
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

CARE (Study TPX-0005-07, CA127-1029)

Purpose of Study: To further investigate the efficacy and long-term safety in paediatric patients with solid tumours expressing a NTRK gene fusion, the MAH should submit the results of the final safety and efficacy analysis of the ongoing Phase 1/2, Open-label, Safety, Tolerability, Pharmacokinetics, and Anti-tumour Activity Study of repotrectinib in Paediatric and Young Adult Subjects with Advanced or Metastatic Malignancies Harboring ALK, ROS1, or NTRK1 3 Alterations.

TRIDENT-1 (Study TPX-0005-01, CA127-1024)

Purpose of Study: To further confirm histology-independent efficacy, efficacy despite resistance mutations, and IC responses of repotrectinib in adults, the MAH should submit the final CSR of the ongoing phase 1/2 trial TRIDENT-1 (all cohorts).

II.C.2 Other studies in post-authorisation development plan

There are no studies required for repotrectinib.

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not Applicable