14 November 2024
EMA/567599/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Augtyro

International non-proprietary name: repotrectinib

Procedure No. EMEA/H/C/006005/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ADME	absorption distribution metabolism excretion
ADR	adverse drug reaction
AED	adult equivalent dose
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AMP	anchored multiplex PCR
AMS	accelerator mass spectrometry
ATP	adenosine triphosphate
AUC	area under the concentration -time curve
AUCinf	area under the plasma concentration time curve from dosing to infinity
AUClast	area under the concentration -time curve from dosing to last measured concentration
BCS	Biopharmaceutics Classification System
BICR	Blinded Independent Central Review
BID	twice a day
BOR	best overall response
BRAF	v-raf murine sarcoma viral oncogene homolog B1
Cavg	average concentration
CBR	clinical benefit rate
CD	cluster of differentiation
CDx	companion diagnostic
CE	Conformité Européenne
CE-IVD	CE Marking - in vitro diagnostic
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CLIA	Clinical Laboratory Improvement Act
CL/F	apparent oral clearance
CLMAX	maximum clearance
Cmax	peak drug concentration
Cmin	minimum concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CSR	Clinical Study Report
CT	computerized tomography
CTA	clinical trial assay
CTCAE	Common Terminology Criteria for Adverse Events
D	day
DCO	data cut off
DDI	drug-drug interaction
DILI	drug-induced liver injury
DL	dose level
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
DRDI	dose reduction/interruption
EBE	Empirical Bayesian estimate
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
EML	Echinoderm microtubule-associated protein like
Emax	maximum effect
EORTC	European Organization for Research and Treatment of Cancer

E-R	exposure-response
ESMO	European Society for Medical Oncology
F1	bioavailability
F1CDx	Foundation one CDx
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridisation
FMI	Foundation medicine incorporated
Gr	grade
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQOL	health-related quality of life
IC	intracranial
ICF	informed consent form
ID	identification
IDE	investigational device exemption
IFS	infantile fibrosarcoma
ILD	interstitial lung disease
IRB	Institutional Review Board
IUO	investigational use only
KA	first-order rate of absorption constant
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homologue
LoD	limit of detection
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MAIC	matching adjusted indirect comparison
MASC	mammary analogue secretory carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal epithelial transition factor
MRI	magnetic resonance imaging
MSI	micro satellite instability
MTD	maximum tolerated dose
NATA	National Association of Testing Authorities
NEAE	neurological adverse event
ND	not determined
NDA	New Drug Application
NE	not estimable
NGS	next generation sequencing
NPA	negative percent agreement
NPV	negative predictive value
NR	not reached
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
OPA	overall percent agreement
OR	objective response
ORR	objective response rate
OS	overall survival
PBPK	physiological based pharmacokinetic
PD	pharmacodynamics *or* progressive disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PopPK	population pharmacokinetics
PPA	positive percent agreement
PPV	positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PR	partial response
PRO	Patient Reported Outcome
PS	performance status
PT	preferred term

QCF	quality control failure
QD	once a day
QOL	Quality of Life
qPCR	quantitative polymerase chain reaction
QRS	ventricular depolarization
QTc	QT interval corrected
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumours
RET	rearranged during transfection
RNA	ribonucleic acid
ROS	c-ros oncogene
ROS1	receptor tyrosine kinase encoded by the ROS1 gene
RP2D	recommended Phase 2 dosing
RTK	receptor tyrosine kinases
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	standard deviation *or* stable disease
SFM	solvent front mutation
SLC	solute carrier
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TK	tyrosine kinase
TKI	tyrosine kinase inhibitor
Tlag	lag time
Tmax	time of the maximum observed concentration
TMP	tropomyosin
TRAE	treatment-related adverse events
TRK	tropomyosin receptor kinase
TTP	time to progression
TTR	time to response
ULN	upper limit of normal
V2	central volume of distribution
V3	peripheral volume of distribution
Vdss	steady state volume of distribution
Vz/F	volume of distribution
WT	wildtype

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 22 November 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Augtyro, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Augtyro as monotherapy is indicated for the treatment of adult patients with ROS1-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 solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and

- have received a prior TRK inhibitor, or
- have not received a prior TRK inhibitor and have no satisfactory treatment options (see sections 4.4 and 5.1)

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0150/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002635-PIP02-21-M01 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP EMEA-C1-002636-PIP02-21-M01.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4.2. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.4.3. New active substance status

The applicant requested the active substance repotrectinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
27 February 2020	EMEA/H/SA/4343/1/2019/III	*Dr Kristian Wennmalm, Dr Rune Kjeken*

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- In 2019 the applicant sought feedback on the proposed development and registration plans in the sought indication, envisioning a Conditional Marketing Authorisation based on the Phase 1/2 study TRIDENT-1 and clinical pharmacology studies.
- In that procedure, the suitability of the proposed quality program to support marketing authorization was discussed, including starting materials, specifications, registration plan, and stability protocols for DS and DP. CHMP considered that the development was generally in line with applicable guidelines, yet with several points in need of further justification.
- The adequacy of the completed non-clinical program, with regards to pharmacology, pharmacokinetic and toxicology studies was also put forward. This was also considered as generally in line with the relevant ICH S9 guideline.
- As part of the clinical part of the advice, the relevance of TRIDENT-1 study design and proposed analyses to support registration in adults with ROS1+ advanced NSCLC and advanced solid tumours harbouring ALK. ROS1 or NRTK1-3 rearrangements, was also considered. The discussion revolved around: a) the study population, with the CHMP accepting the estimated global distribution and noting that the eligibility criteria should ensure that patients in the second line and beyond, should have exhausted their previous first line treatment; b) the endpoints, where it was considered that ORR and DoR would be appropriate primary endpoints for a single arm trial; c) the analysis plan, where it was considered that the proposed ORR thresholds for most expansion cohorts were insufficient to allow conclusion of clinical benefit.
- The proposed strategy was to apply for a CMA based on supportive data from approximately 50 subjects from EXP2 cohort of the Trident-1 study (ROS1+ NSCLC subjects with one prior ROS1 TKI) followed by subsequent submission of a full MAA based on the full 100 subjects of cohort EXP2 and 40 subjects from cohort EXP3 (2 prior TKIs). CMA would also be sought on TKI-naive ROS1+ NSCLC (supported by data from EXP1, n=55) and TKI naive NTRK+ advanced solid tumours (EXP5, n=55).
- The CHMP expressed a disagreement with the proposal, noting preference for an RCT and refuting

all arguments against conducting a controlled study (including feasibility, rarity of the target conditions, availability of comparators and heterogeneity). Moreover, the proposed thresholds of ORR for most cohorts were not considered acceptable to justify clinical benefit.

- Finally, the acceptability of the proposed clinical pharmacology studies to support a CMA was discussed. In that context, a deferral was sought for conducting organ impairment studies and transporter and UGT1A1 drug interaction studies after initial registration, which was provisionally agreed.

- Having regards to the above and with reference to module 2.7.3. of the working documents of the validated MAA application, the applicant has not followed the preference for an RCT and submitted its application based on data from the ongoing phase 1/2 TRIDENT-1 as well as the ongoing CARE study, (the latter in 12 years or older with locally advanced or metastatic malignancies with ALK, ROS1, or NTRK1-3).

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Eva Skovlund Co-Rapporteur: Boje Kvorning Pires Ehmsen

The application was received by the EMA on	22 November 2023
The procedure started on	28 December 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 March 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 March 2024
The CHMP Co-Rapporteur's Critique Assessment Report was circulated to all CHMP and PRAC members on	01 April 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 April 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 July 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 August 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	19 September 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 October 2024

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Augtyro on	14 November 2024
The CHMP adopted a report on similarity of repotrectinib with dinutuximab beta, tebentafusp, lutetium (^{177}Lu), avapritinib, cabozantinib, sorafenib tosylate, irinotecan hydrochloride trihydrate, pemigatinib, ripretinib, ivosidenib, dabrafenib, trametinib, telotristat, niraparib, zolbetuximab, mirvetuximab soravtansine and serplulimab on (see Appendix on similarity)>	14 November 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	14 November 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is seeking approval of two separate therapeutic indications for repotrectinib:

ROS1-positive NSCLC

Repotrectinib as monotherapy for the treatment of adult patients with ROS1-positive locally advanced or metastatic NSCLC.

NTRK-positive solid tumours

Repotrectinib as monotherapy for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a NTRK gene fusion who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and have received a prior TRK inhibitor, or have not received a prior TRK inhibitor and have no satisfactory treatment options.

2.1.2. Epidemiology

ROS1-positive advanced NSCLC

Lung cancer is the most commonly diagnosed cancer (22.4% of the total cases) and the leading cause of cancer death (18% of the total cancer deaths) worldwide[1].

NSCLC accounts for more than 80%-90% of all lung cancer cases, that include non-squamous (i.e., adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell carcinoma. Nearly half of all lung cancers are adenocarcinomas. Over the last decades, in Europe squamous NSCLC decreased

[1] World Cancer Research Fund International, 2020

while adenocarcinoma has increased in men, while in women both squamous NSCLC and adenocarcinoma are still increasing[2].

In the last decade, a number of molecular alterations have been identified in NSCLC, leading to the development and approval of targeted therapies with specific tyrosine kinase inhibitor (TKI) activity, such as erlotinib, afatinib, gefitinib, osimertinib and dacomitinib for epidermal growth factor receptor (EGFR) mutations; crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib for ALK gene fusions, crizotinib for ROS1 gene fusions, and dabrafenib in combination with trametinib for BRAF V600 mutation. In general, the prevalence of oncogenic driver mutations is higher in an Asian population of adenocarcinomas than in a Caucasian population.

ROS1 rearranged NSCLC has been described as a distinct molecular type in approximately 1–2% of patients with NSCLC.

In general, the mutations/alterations are seen in a non-overlapping fashion, although between 1-3% harbour concurrent alterations[3]. According to current European guidelines, EGFR, ALK, ROS1 and BRAF V600 should be tested in advanced non-squamous NSCLC.

NTRK fusion positive solid tumours

In later years, with increasing adoption of comprehensive genomic profiling, NTRK gene fusions have been identified in a wide range of commonly occurring tumours, such as lung cancer, breast cancer, colorectal cancer, thyroid cancer, sarcoma and others, though at low frequencies.

Though commonly cited at a prevalence of 'up to 1% of all cancers', epidemiological data is limited due to only recent interest in NTRK fusions and limited large scale genomic studies using next generation sequencing (NGS) technologies. Specific NTRK fusions have been found at a high prevalence in a handful of rare cancer types, but otherwise are widely dispersed and uncommon across other cancer types. Estimation of population prevalence is further confounded by the use of multiple molecular diagnostic tests for identification, with varying diagnostic accuracy, accessibility and cost.

NTRK fusions are rare events in common adult cancers, e.g. frequency of <1% in NSCLC and 1-2% in CRC, and more frequently observed in some rare cancers, e.g. 90-100% in mammary analogue secretory carcinoma (MASC), a rare form of salivary gland cancer (representing < 1% of all cancer malignancies), and secretory breast cancer (SBC), for which NTRK fusion expression is a pathognomonic hallmark for both diseases[4]. NTRK fusions have also been described in several paediatric tumours including infantile fibrosarcoma (IFS) or the related congenital mesoblastic nephroma and have a high frequency (~40%) in high grade glioma (HGG) in patients <3 years of age[5]. Importantly, NTRK fusions are also found in primary CNS malignancies in adults, however at lower frequencies.

2.1.3. Biologic features and pathogenesis

ROS1-positive advanced NSCLC

The ROS proto-oncogene 1 (ROS1), located on chromosome 6, encodes an orphan receptor tyrosine kinase without a known ligand, whose physiological function is still unclear. Chromosomal translocations can result in ROS1 gene rearrangements, firstly reported in NSCLC in 2007,

[2] Planchard D. et al. Metastatic non-small lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol, 2018.
[3] NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines) Non-small Cell lung cancer Version 2.2021- 02 March 2021
[4] Khender ES et al. Emerging targeted therapy for tumours with NTRK fusion proteins. Clin Cancer Res, 2018
[5] Wu G et al. The genomic landscape of diffuse intrinsic pontine glioma and paediatric non-brainstem high grade glioma. Nature Gent, 2014

characterised by fusions with other genes. So far, at least 25 different fusion partner genes have been identified in lung cancer patients, with CD74-ROS1 fusion being the most common rearrangement[6]. These fusion events lead to constitutive activation of the ROS1 kinase that drives cellular transformation and promotes survival and proliferation through downstream signalling via SHP-1/SHP-2, JAK/STAT, PI3K/AKT/MTOR and MAPK/ERK pathways. The prognostic role of fusion partners is still being debated.

NTRK fusion positive tumours

The neurotrophic receptor tyrosine kinase family of genes NTRK1, NTRK2, and NTRK3 encode the tropomyosin receptor kinases A, B and C (TRKA, TRKB and TRKC), respectively. TRK family members are transmembrane proteins serving as high affinity signal transducing receptors for neurotrophins. They are expressed in neuronal tissue and play an essential physiological role in the development and function of the central and peripheral nervous systems. TRKA binds nerve growth factor (NGF), TRKB binds brain-derived growth factor (BDNF) and neurotrophin-4 (NT4, also known as NTF5) with high affinity. Binding of neurotrophins to their cognate TRK receptors results in activation of downstream signal transduction pathways involved in cell proliferation, apoptosis, and survival of neurons and other cell types.

NTRK fusions occur when the NTRK 1, 2 or 3 genes form a chromosomal rearrangement with one of many different genes (fusion partner). NTRK gene fusions lead to overexpression and constitutive activation of the tropomycin receptor kinases TRKA, TRKB and TRKC. The transcribed chimeric TRK proteins have been shown to be oncogenic, promoting tumourigenesis by constitutive ligand-independent kinase activation leading to tumour cell proliferation, differentiation, and/or apoptosis.

At least 80 different oncogenic NTRK1/2/3 gene fusions have been reported across at least 20 specific solid tumour types, most of those identified occurred in NTRK1 and NTRK3[7].

2.1.4. Clinical presentation, diagnosis and stage/prognosis

ROS1-positive advanced NSCLC

Similar to ALK rearranged tumours, patients with ROS1 positive NSCLC are more commonly of younger age, have a history of never or light smoking, and have adenocarcinoma histology[8]. The prevalence of ROS1 positive NSCLC is higher in an Asian population of adenocarcinomas than in a Caucasian population.

Overall, the incidence of brain metastases is higher in NSCLC patients with oncogenic driver mutations than in those without[9]. Data from prospective trials of ROS1 TKIs ranged approximately from 20% to 40% in TKI-naïve patients and from 30% to 50% in TKI-pretreated patients[10] It is established that brain metastasis is a negative prognostic factor for cancer patients in general. Patients with advanced ROS1 positive NSCLC, regardless of brain metastases, have a life-threatening condition.

Commonly used methods for ROS1 fusion detection have included fluorescence in situ hybridisation (FISH), immunohistochemistry (IHC), reverse-transcription polymerase chain reaction (RT-PCR) and next generation sequencing (NGS). According to ESMO guidelines, IHC may be used as a screening approach, although it is currently not recommended as the primary treatment determining test. FISH has been the standard approach to detecting ROS1 rearrangements. NGS is an emerging technology.

[6] Sai-Hong Ignatius Ou et al. Fusion partners in OS1-positive NSCLC circa 2020. JTO Clin Res Rep, 2020
[7] Christina A. Manea et al. A review of NTRK fusions in cancer. Ann Med Surg, 2020
[8] Bergethon K. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol, 2012
[9] Aaron C. Tan et al. Brain metastases in lung cancer with emerging targetable fusion drivers. Int J Mol Sci, 2020
[10] Ou et al. CNS metastasis in ROS1+ NSCLC: An urgent call to action, to understand, and to overcome. Lung Cancer, 2019

Whatever testing modality is used, it is mandatory that adequate internal validation and quality control measures are in place and that laboratories participate in, and perform adequately in, external quality assurance schemes for each biomarker test. RT-PCR assays may lead to under-detection of ROS1 fusion events as they miss the detection of previously unknown fusion partners. Whilst NGS allows for the detection of known as well as novel fusions.

ESMO clinical guideline recommends that testing for ROS1 rearrangement should be systematically carried out in non-squamous NSCLC, in addition to routinely testing for EGFR, ALK and BRAF V600 mutations.

NTRK fusion positive solid tumours

The sought indication concerns a disease setting of locally advanced or metastatic malignant solid tumours regardless of treatment line and when there is no appropriate available therapy. In this setting symptoms of disease will likely be present and the disease is incurable, probably leading to death. The purpose of treatment in this disease setting is to reduce symptoms of disease, and to prolong survival. However, the natural course of the disease will differ from tumour type to tumour type depending on histology, tumour localisation and patient characteristics. Importantly, the spectrum of tumour types in paediatric patients differ from the adult population.

The additional indication "or where surgical resection is likely to result in severe morbidity" concern patients who have a life-threatening malignant disease although presently in a potentially curable stage, however not eligible to surgery.

NTRK fusions are seen in tumour types with a high frequency of brain metastases such as NSCLC and breast cancers[11]. The incidence of brain metastases in each of the rare *NTRK* fusion-positive solid tumours is unknown. Brain metastases is an established negative prognostic factor, regardless of tumour type and mutation[12].

The prognostic significance of NTRK fusion and its influence on a tumour's sensitivity to classical treatments is not known for the time being[13]. It is assumed that tumour responses to NTRK-targeted therapy is similar regardless of age when NTRK fusions are documented within the same histology.

Several *molecular tools are currently available for the detection of NTRK fusions in tumour specimens:*

- Fluorescence in situ hybridisation (FISH)
- Next generation sequencing (NGS)
- Reverse-transcription PCR (RT-PCR)
- Immunohistochemistry (IHC)

2.1.5. Management

ROS1 positive NSCLC

According ESMO clinical practice guidelines for treatment of metastatic NSCLC, a ROS1-targeted TKI is the preferred 1st line treatment in this population. Furthermore, pemetrexed-based chemotherapy is still standard of care in 2nd line after ROS1 inhibitor. Several studies have found that ROS1-positive NSCLC patients appeared to be sensitive to pemetrexed-based treatment. No direct comparison between chemotherapy is available, neither in 1st line or 2nd line setting. In 1st line retrospective data

[11] Aaron C. Tan et al. Brain metastases in lung cancer with emerging targetable fusion drivers. Int J Mol Sci, 2020
[12] Paul W. Sperduto et al. Survival in patients with brain metastases…J Clin Oncol, 2020
[13] Ulrik Larssen et al. Prognostic value of NTRK gene fusions in solid tumours for overall survival: a systematic review and meta-analysis. J Clin Onc, 2023

comparing pemetrexed/platinum-based chemotherapy with crizotinib, indicate that crizotinib is superior to chemotherapy (ChT) in term of ORR; PFS and OS. Pemetrexed-based chemotherapy achieve response rates > 50%[14]. Progression free survival (PFS) is, however, shown to be longer in crizotinib compared to pemetrexed-based ChT (mPFS 8 months vs 12-14 months). In the 2nd line setting, data on pemetrexed-based chemotherapy is even more limited. A retrospective study in Chinese patients, indicate an ORR of 24%[15].

No direct comparison between the first and next generation TKIs has been performed, however, it is established that crizotinib has limited intracranial efficacy compared to the second and third generation TKIs. Currently, no ROS1 inhibitor are approved for use in the setting of resistance mutations and treatment failure to prior ROS1-TKI.

Unlike other oncogenic-driven NSCLC, there are no evidence to support the use of combination immunotherapy and chemotherapy in ROS1 rearranged tumours.[16]

Crizotinib, a first generation ALK-TKI, was granted an extension of indication for ROS1 positive NSCLC in 2016. The approval was bases on a single arm trial with 53 patients, mainly pretreated, NSCLC patients with known ROS1 mutation. ORR was 72% and median DoR ~24 months (SmPC Xalkori). The intracranial efficacy of crizotinib is not well characterised in patients with ROS1-rearranged disease; crizotinib has limited blood-brain-barrier (BBB) penetration and CSF concentrations are low. Intracranial efficacy is inferior to second-generation and third-generation TKIs. Accordingly, CNS is a critical and frequent site of progression in patients positive for ALK and ROS1 treated with crizotinib.

Secondary point mutations within the ROS1 kinase domain have been identified in both clinical and preclinical studies, occurring approximately in 50−60% of crizotinib resistant tumours[17].

Entrectinib, a multikinase inhibitor, targeting TRK ALK and ROS1 inhibitor, was granted a full marketing authorisation in ROS1 positive NSCLC not previously treated with ROS1 inhibitor in 2020. The approval was based on pooling of three singled arm trial including 161 patients with no prior treatment with ROS1 inhibitor. ORR was 67% and median DoR was reached at 16.5 months. 24 participants had measurable CNS metastases at baseline; 19 out of 24 (79.2%) patients had intracranial responses. Entrectinib can cross the blood-brain barrier (SmPC Rozlytrek). However, efficacy of entrectinib in the setting of crizotinib resistant ROS1 positive NSCLC is not demonstrated. Acquired resistance to entrectinib in ROS1 positive NSCLC is demonstrated, however, the mechanisms of resistance are not fully understood.

Despite effective TKI therapy, nearly in all ROS1+ NSCLC develop treatment resistance and disease progression occurs. Acquired mechanisms of resistance to ROS1 TKIs include ROS1-dependent mechanisms, such as ROS1 kinase domain mutations, or ROS1-independent mechanisms. Currently, no ROS1-TKI- product is approved for use in the setting of resistance and treatment failure to prior ROS1-TKIs.

NTRK positive solid tumours

The proposed indication for the use of repotrectinib in this application is for patients with NTRK fusion-positive locally advanced or metastatic solid tumours who have progressed following prior therapies or as initial therapy when there are no acceptable standard therapies. The prognosis for these patients is

[14] Haiyan Xu et al. Crizotinib vs platinum-based chemotherapy as first-line treatment for advanced NSCLC with different ROS1 fusion variants. Cancer Medicine, 2020
[15] Limin Zhang et al. Efficacy of crizotinib and pemetrexed-based chemotherapy in Chinese NSCLC patients with ROS1 rearrangement. Oncotarget, 2016
[16] Laura Moliner et al. ROS1 NSCLC patients treatment approach. Prec Cancer Medicine, 2021
[17] Bo Mi Ku et al. Entrectinib resistance mechanisms in ROS1-rearranged NSCLC. Invest New Drugs, 2020

poor, particularly when there is CNS involvement. The treatment goal is prolonged tumour control and survival as well as stable quality of life.

There are no common European guidelines for treatment in patients with solid tumours with NTRK fusions. Common international expert consensus recommendations, across Europe, US, Japan and Taiwan, were outlined in 2020 It states that "all patients with advanced solid tumours without actionable driver gene mutations/fusions/amplifications should be tested for NTRK fusion. TRK inhibitors are strongly recommended as treatment when no other satisfactory treatment options exist, depending on the clinical context"[18].

In 2019, the TRK inhibitor larotrectinib was granted a conditional marketing authorisation (CMA) in the EU for the treatment of adult and paediatric patients with solid tumours that display a NTRK gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options. Larotrectinib was the first pan-TRK selective inhibitor. The approval was based on a pooled primary analysis set for efficacy including 93 patients with TRK fusion-positive cancer enrolled across 3 ongoing open-label single arm studies (SAT) (of those, 28 patients were paediatric), The ORR in the pooled efficacy dataset was 72% (95%CI 62, 81). Median DOR was NR (range 1.6+, 38.7+) with 88% with duration more than 12 months. CNS activity was not categorised in the larotrectinib-studies (SmPC Vitrakvi). Data on efficacy after treatment failure on prior TRK-TKI treatment e.g. crizotinib, is limited.

In 2020, the TRK inhibitor entrectinib was conditionally approved in the EU for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a NTRK gene fusion who have not received a prior NTRK inhibitor. The approval was based on pooling of data from three SATs including 150 patients (of those, 5 patients were paediatric). ORR was 61.3% (95% Ci: 53.0, 69.2), mDoR 20 months (13.2, 31.1). 22 patients had brain metastases at baseline, 13 had measurable CNS lesions by BICR. 9 out of 13 (69.2%) had intracranial responses (SmPC Rozlytrek). Data on efficacy across resistance mutations and after treatment failure to e.g. crizotinib is limited.

Acquired resistance to first generation TRK inhibitors is a clinical challenge as treatment failure leads to progression of the disease. Retrospective data (post-progression) of secondary resistance to entrectinib and larotrectinib are limited and resistance mechanism to TRK TKIs remains to be fully understood or mapped. Currently, no TRK-TKI- product is approved for use in the setting of resistance and treatment failure to prior TRK-TKIs.

2.2. About the product

Mode of action

Repotrectinib is an oral, next-generation, ATP-competitive small-molecule inhibitor of the tyrosine kinases ROS1 (encoded by the gene ROS1), TRK (encoded by genes NTRK1, NTRK2 and NTRK3), and ALK (encoded by the gene ALK) with IC50 values of 0.05 to 1.04 nM.

Fusion proteins that include ROS1 or TRK domains can drive tumourigenic potential through hyperactivation of downstream signalling pathways leading to unconstrained cell proliferation. Repotrectinib has demonstrated in vitro and in vivo inhibition of cell lines expressing the targeted fusion oncogenes ROS1, TRKA, TRKB, TRKC, and corresponding mutations (ROS1G2032R, ROS1D2033N, TRKAG595R, TRKBG639R, TRKCG623R). Repotrectinib binds inside the boundary of the ATP-binding pocket and avoids steric interference from both solvent front and gatekeeper mutations.

[18] T. Yoshino et al. JSCO-ESMO-ASCO-JSMO-TOS: international expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or NTRK fusions. Ann Oncol, 2020

Pharmaceutical presentations:

Hard capsules 40 mg and 160 mg

The final indication is:

Augtyro as monotherapy is indicated for the treatment of adult patients with *ROS1*-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 *NTRK* 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 sections 4.4 and 5.1)

Treatment with Augtyro should be initiated and supervised by physicians experienced in the use of anticancer medicinal products.

Patient selection for treatment with Augtyro based on the ROS-1 or NTRK gene fusion expression should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see sections 4.1, 4.4 and 5.1).

Posology

ROS1-positive non-small cell lung cancer

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.

NTRK gene fusion-positive solid tumours

The recommended dose in adults and paediatric patients 12 year and older is 160 mg repotrectinib once daily for 14 days, followed by 160 mg repotrectinib twice daily until disease progression or unacceptable toxicity.

Missed dose

If a dose is missed or if a patient vomits at any time after taking a dose, subsequent doses should be resumed as prescribed. Two doses should not be taken at the same time.

Dose modifications for adverse reactions

The recommended dose reductions for adverse reactions are provided in Table 1:

Table 1: Recommended dose reductions for adverse reactions

Prescribed dose	**Dose reduction**	
	First occurrence	**Second occurrence**
160 mg once daily	120 mg once daily	80 mg once daily
160 mg twice daily	120 mg twice daily	80 mg twice daily

Recommended dose modifications for specific adverse reactions are provided in Table 2.

Table 2: Recommended dose modifications for specific adverse reactions

Adverse reactions	**Severity***	**Dosage modification**
Central nervous system effects	Intolerable Grade 2	• Withhold until less than or equal to Grade 1 or baseline. • Resume at same or reduced dose, as clinically appropriate.
	Grade 3	• Withhold until less than or equal to Grade 1 or baseline. • Resume at reduced dose.
	Grade 4	• Permanently discontinue.
Interstitial lung disease (ILD)/Pneumonitis	Any Grade	• Withhold if ILD/pneumonitis is suspected. • Permanently discontinue if ILD/pneumonitis is confirmed.
Other clinically relevant adverse reactions	Intolerable Grade 2	• Withhold until less than or equal to Grade 1 or baseline. • Resume at the same or reduced dose if resolution occurs within 4 weeks.
	Grade 3 or 4	• Withhold until adverse reaction resolves or improves to recovery or improvement to Grade 1 or baseline. • Resume at the same or reduced dose if resolution occurs within 4 weeks. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Permanently discontinue for recurrent Grade 4 events.

*Graded per NCI Common Terminology Criteria for Adverse Events 4.0

Method of administration

Augtyro is for oral use. The capsules should be swallowed whole at the same time every day. The capsules must not be opened, crushed, chewed, and the contents of the capsule must not be dissolved.

Augtyro may be taken with or without food (see section 5.2) but should not be taken with grapefruit, grapefruit juice or Seville oranges .

Proposed dose and administration

The recommended dose is 160 mg QD orally for 14 days, followed by 160 mg orally BID, until disease progression or unacceptable toxicity.

2.3. Type of application and aspects on development

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

  The applicant claims that the benefit-risk balance of repotrectinib is positive based on compelling results from studies TRIDENT-1 and CARE. TRIDENT-1 is a global Phase 1/2, open-label, multi-centre, multiple-dose study evaluating dose escalation, safety, PK, PD, and anticancer effects of repotrectinib as a single agent in subjects with ALK+, ROS1+, NTRK1+, NTRK2+, or NTRK3+ advanced solid malignancies, which, according to the applicant, showed compelling results in the indications sought. According to the applicant, these results appear to extend to paediatric patients with NTRK fusions based on the initial results from CARE: a Phase 1/2, open-label, single-arm, multicentre, multicohort study to evaluate the safety, tolerability, PK, and efficacy of repotrectinib, in paediatric and young adult patients with advanced or metastatic solid tumours with ALK, ROS1, or NTRK alterations. Based on the totality of efficacy data and the manageable safety profile repotrectinib demonstrates a positive benefit-risk balance for the population of patients with ROS1-positive NSCLC or NTRK-positive solid tumours.

- It is likely that the applicant will be able to provide comprehensive data.

  The applicant plans to report efficacy on approximately 230 adult and paediatric subjects with NTRK-positive solid tumours (from TRIDENT-1 and CARE). Safety results are planned to be reported from all treated subjects (N > 600) across the repotrectinib program, including those with NTRK alterations, on TRIDENT-1 and CARE. According to the applicant, this will allow for characterisation of the safety and efficacy in a larger sample of subjects, as well as confirm the histology-agnostic effect across specific tumour types. Enrolment is ongoing with an estimated study completion of December 2030.

- Unmet medical needs will be addressed.

  The applicant claims that based on the results in TRIDENT-1 and CARE, there is a high level of confidence that repotrectinib can address these unmet needs by providing better clinical outcomes for these patients and doing so with a manageable safety profile. In addition, an unmet medical need will be addressed as current approved NTRK TKIs are subject to resistance mechanisms, most commonly solvent-front mutations. No available therapies have shown activity following disease progression on an initial NTRK TKI and patients have very limited options. Overall, advanced malignancies are life-threatening and represent an area of unmet medical need in adult and paediatric patients.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  The applicant claims there is less acquired resistance mutations (such as SFMs that can sterically block drug binding) compared to other kinase inhibitors and that there are advantages based on the clinical meaningful ORR, durable responses and intra-cranial activity in TKI-naive and pretreated patients and differentiated safety profile compared to available treatment options. Additionally, the applicant claims that the durable improvements in PFS, OS, and DOR at 18 months and the consistent efficacy observed across prespecified subgroups further highlight the benefits of treatment with repotrectinib. The applicant states that current data have the potential to outweigh the risk that further data are still required.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard capsules containing 40 mg and 160 mg of repotrectinib as active substance.

Other ingredients are:

Capsule content: microcrystalline cellulose, sodium lauryl sulphate, croscarmellose sodium, silica colloidal anhydrous, and magnesium stearate (for 160 mg hard capsule only).

Capsule shell: gelatin, titanium dioxide (E171), and brilliant blue (E133 - for 160 mg hard capsule only);

Printing ink (40 mg hard capsule): shellac (E904), and indigo carmine aluminium lake (E132);

Printing ink (160 mg hard capsule): shellac (E904), and titanium dioxide (E171).

Augtyro 40 mg hard capsules is available in high-density polyethylene (HDPE) bottles with 2-piece child-resistant continuous thread (CRCT) polypropylene (PP) closures as described in section 6.5 of the SmPC.

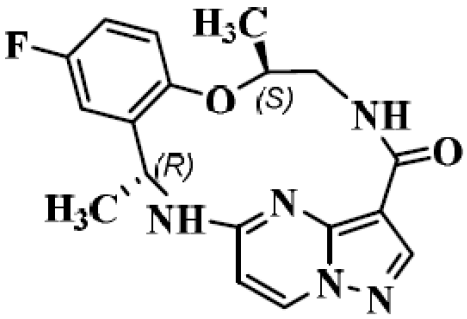
Augtyro 160 mg hard capsules is available in PVC/Aclar clear blister with push through aluminium foil lidding. Aclar refers to polychlorotrifluoroethylene (PCTFE) as described in section 6.5 of the SmPC.

2.4.2. Active substance

General information

The chemical name of the active substance is (3R,11S)-6-Fluoro-3,11-dimethyl-10-oxa-2,13,17,18,21-pentaazatetracyclo[13.5.2.04,9.018,22]docosa-1(21),4,6,8,15(22),16,19-heptaen-14-one or (7S,13R)-11-Fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one corresponding to the molecular formula C18H18FN5O2. It has a relative molecular weight of 355.37 and the following structure:

Figure 1 Active substance structure



The chemical structure of the active substance was elucidated by a combination of UV-Vis, IR, NMR, MS, elemental analysis; the solid state properties of the active substance were measured by a single crystal X-ray diffraction.

The active substance is a non-hygroscopic white to off-white solid. Repotrectinib exhibits pH-independent aqueous solubility of 0.006 to 0.008 mg/mL across the pH range of 1.2 to 7.4 at 37 °C.

The active substance exhibits stereoisomerism due to the presence of 2 chiral centres.

Polymorphism has been observed for the active substance

Manufacture, characterisation and process controls

The active substance is manufactured at one manufacturing site.

The active substance is synthesized in 4 main steps.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Specification

The active substance specification includes tests for appearance (visual), colour (visual), identification (IR, LC), assay (RP-UPLC), related substances (RP-UPLC), stereoisomers (NP-HPLC), residual solvents (GC) and particle size (Ph. Eur.)

The proposed specifications are in accordance with the ICH Q6A and are acceptable.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package under long term conditions (25 ºC / 60% RH) and under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance and colour, assay, impurities-related substances, and chiral impurities, water content, and particle size distribution. The analytical methods used were the same as for release and were stability indicating. In addition, process related reagent by-product impurities and microbial limits (by the Ph. Eur. method) were tested in the stability samples.

The results from 5 ºC, long-term and accelerated stability studies show no trends for any of the tested parameters, demonstrating that repotrectinib is a stable substance.

Photostability testing following the ICH guideline Q1B was performed on one batch, no degradation is observed. The photostability results show that the active substance is not sensitive to exposure to light.

Stress studies were conducted on repotrectinib in solid state and in solution. No degradation is observed in solid state. Repotrectinib in solution showed minor degradation when stressed under acidic conditions, moderate degradation under oxidative stress and significant degradation under light. None of the impurities observed during the stress studies were detected during long-term/accelerated stability studies.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The 40 mg strength is presented as size 0 (21.7 mm in length), hard gelatin capsule with white opaque body and cap, and "REP 40" printed in blue ink on the cap.

The 160 mg strength is presented as size 0 (21.7 mm in length), hard gelatin capsule with blue opaque body and cap, and "REP 160" printed in white ink on the cap.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Two immediate-release hard gelatin capsule formulations have been developed for the finished product.

An overall risk assessment of the formulation components was performed for the finished product to determine the impact of formulation components on the finished products critical quality attributes (CQAs). However, design space was not requested by the applicant.

A process risk assessment for the manufacturing process development of both strengths was performed to evaluate the impact of manufacturing process parameters on the critical quality attributes (CQAs) of the finished product. The risk assessment further guided the development of the commercial manufacturing processes to establish the acceptable ranges for process parameters and appropriate in-process controls (IPCs). The development of both manufacturing processes is acceptably described.

The primary packaging for the 40 mg is high-density polyethylene (HDPE) bottles with 2-piece child-resistant continuous thread (CRCT) polypropylene (PP) closures.

The primary packaging for the 160 mg is PVC/Aclar clear blister with push through aluminium foil lidding. Aclar refers to polychlorotrifluoroethylene (PCTFE).

The primary packaging materials for both strengths comply with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Both 40 mg and 160 mg capsules are manufactured by one manufacturing site. Satisfactory GMP documentation has been provided.

The 40 mg capsules are manufactured by a standard process comprising of blending, screening and encapsulation followed by packaging.

The 160 mg capsules are manufactured by a standard process comprising of blending, screening, roller compaction, lubrication and encapsulation followed by packaging.

The applicant committed to performing prospective performance qualification (PPQ)/process validation (PV) for both strengths at the commercial site prior to launch of the commercial product. The PPQ/PV batches will be processed according to approved manufacturing process/batch records and an approved PPQ/PV Protocol. During the PPQ /PV study, process steps will be monitored and the results

will be covered in a PPQ/PV Report. This is acceptable as both manufacturing process are standard process.

Critical steps and process controls for the manufacture of repotrectinib capsules have been presented. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), identification (RP-HPLC, UV), assay (RP-HPLC), impurities (RP-HPLC), uniformity of dosage (RP-HPLC), dissolution (RP-HPLC), and microbial limits (Ph. Eur.).

The finished product specifications include relevant tests to ensure the quality of the capsules and the proposed limits are acceptably justified.

No organic solvents are used in the finished product manufacturing process. Residual solvents in the finished product are controlled and they are well below their respective permitted daily exposure (PDE).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale of 40 mg strength batches and 3 commercial scale of 160 mg of finished product stored for up to 36 months (40 mg strength) and 24 months (160 mg strength) under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, dissolution, and microbiology. The analytical methods used in the stability testing are the same as those for release testing with the additional compendial method water content by Karl Fischer. The analytical procedures used are stability indicating.

All results comply with the specifications at all time points and storage conditions (long term and accelerated). No significant change in any of the studied parameters was observed. Degradation products remained below the reporting limit.

In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photostability studies performed indicate that the finished product is not photosensitive and does not need to be protected from light.

Open dish studies (6 months at 25°C/60%RH) are presented and no changes were observed. In addition, the 40 mg strength was also tested after storage at 5 °C and 50 °C for 1 month to support shipping excursions.

Based on available stability data, the proposed shelf-life of 3 years without any special storage conditions as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design space was claimed for the manufacturing process of the finished product.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Repotrectinib was evaluated in cell lines expressing the targeted oncogenes to determine its ability to suppress phosphorylation of the targeted oncogenic fusion proteins and their downstream signalling effectors as well as its ability to inhibit cell proliferation. In vivo studies were performed in allograft and xenograft tumour models in mouse to determine repotrectinib efficacy toward inhibition of tumour

growth, the corresponding suppression of target autophosphorylation, phosphorylation of downstream effectors, and the respective repotrectinib plasma exposure relationship.

The nonclinical toxicology program was conducted in line with ICH S9 Guideline and the ICH S9 Q&A document. The programme comprises single- and repeat-dose toxicology studies in rats and monkeys dosed once daily for up to 91 days, a phototoxicity study in pigmented rats, a dose range-finding embryo-foetal development (EFD) study in pregnant rats, and repeat-dose toxicology studies in juvenile rats. In addition, in vitro and in vivo assessments of genotoxicity were performed. Pivotal studies were conducted in accordance with Good Laboratory Practices (GLP) regulations. Selection of the rat and cynomolgus monkey as the toxicological species was supported by in vivo pharmacokinetics and metabolism studies. The micronized crystalline form of repotrectinib was used in all toxicology and safety pharmacology studies.

2.5.2. Pharmacology

Repotrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1), the anaplastic lymphoma kinase ALK, and the tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC. Repotrectinib binds inside the boundary of the ATP-binding pocket and may therefore avoid steric interference from both solvent front and gatekeeper mutations.

2.5.2.1. Primary pharmacodynamic studies

In vitro studies assessing cellular activity of TPX-0005 were addressed in murine NIH3T3 or BA/F3 cells engineered to express wt ROS1, ALK and TRK and selected mutations. In vivo studies were further conducted to address antitumour activity and PK/PD effects in mouse allograft models implanted with these engineered murine NIH3T3 or BA/F3 cells, and in xenograft models implanted with human KM12 cells expressing TPM3-TRKA or Karpas299 cells expressing NPM-ALK. Overall, the results indicate that TPX-0005 a potent inhibitor of fusion proteins of ROS1, ALK and TRK and clinically relevant solvent front mutations in vitro and has effect in corresponding tumour models in vivo.

In vitro/in silico

Structural modelling studies of the binding to ROS1, TRKA-C, and ALK kinases with solvent-front mutations indicates that repotrectinib binds within the ATP binding site, independent of the solvent-front area of the kinases.

TPX-0005 inhibits recombinant human wt ROS1, ALK and TRK kinases in a HotSpot kinase assay, with IC50 in low to sub-nM range. Similar inhibitory effect was also seen on one solvent-front mutation of ROS1 and numerous mutations of ALK.

Table 3 Inhibitory Activity (IC50) of TPX-0005 against ALK, ROS1 and TRK Family Kinases and their Mutants

Target (mutation)	TPX-0005 IC_{50} (nM) at 10 µM ATP
ROS1	0.0706
ROS1 (G2032R)	0.456
TPM3-ROS1	0.113
ALK	1.04
ALK (L1196M)	1.08
ALK (G1202R)	1.21
ALK (F1174L)	1.46

Target (mutation)	TPX-0005 IC_{50} (nM) at 10 µM ATP
ALK (F1174S)	1.02
ALK (C1156Y)	0.932
ALK (S1206R)	0.525
ALK (L1152R)	1.23
ALK (R1275Q)	2.79
ALK (1151T Ins)	2.16
ALK (T1151M)	0.491
ALK (G1269A)	5.50
ALK (G1269S)	14.1
ALK-NPM1	1.23
TRKA	0.826
TRKB	0.0517
TRKC	0.0956

ALK = anaplastic lymphoma kinase; ATP = adenosine triphosphate; IC50 = half maximal inhibitory concentration; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TRK = tropomyosin receptor kinase; TRKA = tropomyosin receptor kinase A; TRKB = tropomyosin receptor kinase B; TRKC = tropomyosin receptor kinase C.

Antiproliferative activity was confirmed in murine cell lines engineered to express wt and relevant solvent front and gatekeeper mutations of ROS1, ALK and TRK, and in two human cell lines expressing wt ALK and TRKA. IC50 for cell proliferation and autophosphorylation was within low nM-range for cells expressing the wt kinases and all but one ALK mutant (G1269S; IC50 430 nM).

The effect on cell proliferation and autophosphorylation was further compared to other clinically relevant kinase inhibitors, including crizotinib (targeting ROS1 and ALK) and entrectinib (targeting ROS1 and TRK). Similar low nM inhibitory effect was seen for TPX-0005, crizotinib and entrectinib on cells expressing the wt kinases. In general, the inhibitory effect of crizotinib and entrectinib was significantly lower than TPX-0005 in cells engineered to express clinically relevant solvent front and gatekeeper mutations of ROS1, ALK or TRK, with IC50 levels >600 nM, supporting a potential benefit of entrectinib in treatment of tumours developing resistance to crizotinib and entrectinib.

In vivo

In vivo studies were conducted in mouse models to address effect on tumour growth, autophosphorylation, phosphorylation of downstream effectors, and the respective TPX-0005 plasma exposure relationship following oral dosing. In allograft models, female athymic or SCID mice were inoculated subcutaneously with murine NIH3T3 and BaF3 cells engineered to express wild type and solvent front mutated fusion proteins of ROS1 (wt and mutation G2032R), ALK (wt and mutation G1202R) or TRKA (wt and mutation G595R). The anti-proliferative effect was also evaluated in xenograft models with the human Karpas299 T-cell lymphoma human cancer cell line expressing the NPM-ALK fusion protein and the human KM12 colorectal cancer cell line expressing the TPM3-NTRKA fusion protein.

In all tumour models, including models expressing solvent front mutations, repeated oral dosing of TPX-0005 for up to 26 days was well tolerated, and resulted in robust and dose-related inhibition of tumour growth at all doses tested (3 to 75 mg/kg/dose, BID). The TGI was statistically significant at doses ≥15 mg/kg/dose BID, ranging from 56% to 200% (complete regression).

At 15 mg/kg, PK/PD data indicate >90% inhibition of autophosphorylation of solvent front mutated ROS1 and TRKA at Cmax (3 hours post dose), and ≥74% inhibition at Ctrough (12 hours post dose).

The anti-tumour effect of TPX-0005 was compared to entrectinib in NIH3T3 allograft models expressing wt LMNA-TRKA and LMNA-TRKA with solvent front mutation G595R tumours, a mutation seen in

entrectinib-resistant patients. In the wt-model, both TPX-0005 and entrectinib resulted in TGIs of 128% and 98%, respectively. In the G595R model, TPX-0005 at 60 mg/kg/dose resulted in a TGI of 123%, resulting in a tumour regression of approximately 20%. In contrast, the TGI was 78% with entrectinib, leading to a 5-fold tumour growth.

2.5.2.2. Secondary pharmacodynamic studies

Based on a competition binding assay against 456 human kinases and mutants, repotrectinib demonstrated substantial kinase inhibition on a number of non-target kinases in vitro.

In a panel of 44 receptors, enzymes and ion channels, TPX 0005 inhibited ligand binding of adenosine A2A receptor and L-type Ca2+ channel at IC50 87-fold and 48-fold multiples to unbound human mean Cmax (0.072 µM) at 160 mg BID, indicating low clinical relevance. TPX-0005 further inhibited LCK activity with an IC50 value 1.5-fold multiple to unbound human mean Cmax.

Table 4: Secondary kinase targets for TPX-0005

Kinase	IC_{50} (nM)	Selectivity[a]
TRKA[b]	0.826	-
JAK2	1.04	1.25
TXK	3.17	3.84
ARK5	4.46	5.41
SRC	5.29	6.40
DDR1	5.73	6.94
FAK	6.96	8.43
SNARK	13	15.74
HCK	16.4	19.86
LCK	18.6	22.52
JAK1	18.8	22.76
TYK2	21.6	26.15
TYK1	21.8	26.39
DDR2	23	27.85
ACK1	24.1	29.18
EPHA1	25	30.27
BLK	32.3	39.10
GRK7	35.2	42.62
PYK2	39.9	48.30
RET	47.1	57.02
JAK3	49.9	60.41
EPHA8	50.2	60.78
PLK4	126	152.54
AXL	149	180.39
MARK3	512	619.86
[a]Selectivity calculated by dividing IC50 with IC50 for TRKA; [b]From study 00111		

2.5.2.3. Safety pharmacology programme

Safety pharmacology endpoints (CNS, cardiovascular and respiratory) were incorporated into study designs for the pivotal repeat-dose toxicity studies in rat and monkey. In addition, an in vitro ion channels assay (hERG, hNav1.5, and hCav1.2) was performed. Signs of CNS toxicity (tremors and ataxia) were seen in sexually mature and juvenile rats with low to non-existing safety margins. No cardiovascular- or respiratory effects were observed. In a non-GLP compliant study on ion channels, repotrectinib had minimal effects on hERG (IC50 = 18 µM, CHO cells), hNav1.5 (IC50 > 30 µM, HEK293 cells) and human L-type Cav1.2 (IC50 > 30 µM, HEK293 cells). The hERG patch clamp data indicate a potential for QT prolongation at a 249-fold multiple to unbound human mean C_{max} (0.072 µM) at the clinical dose of 160 mg BID.

2.5.2.4. Pharmacodynamic drug interactions

No studies on pharmacodynamic drug interactions have been conducted with repotrectinib, which is acceptable given the intended use as a monotherapy.

2.5.3. Pharmacokinetics

Analytical methods

In vitro and in vivo studies were conducted to evaluate the pharmacokinetics/toxicokinetics, absorption, distribution, metabolism, and excretion properties of repotrectinib in mouse, rat, dog and monkey. Concentrations of TPX-0005 were quantified in plasma and brain homogenates using LC-MS/MS. Radioactivity in biological samples was measured by liquid scintillation analysis.

The LC-MS/MS methods used to determine levels of TPX-0005 in plasma and brain homogenates in PK and non-GLP toxicity studies were not formally validated but were referred to as either research grade or qualified.

The LC-MS/MS methods used for determining TPX-0005 in rat and monkey plasma in the pivotal repeat-dose toxicity studies and in the in vivo rat micronucleus assay are considered adequately validated and GLP-compliant.

Absorption

PK studies with single IV and PO doses were conducted in rats and monkeys, species used for toxicity studies. In addition, single dose mouse and dog data were provided. PK/TK data following repeated dosing were collected from repeat-dose toxicity studies in rats and monkeys dosed for up to 91 days.

IV TPX-0005 was eliminated with low-to-moderate plasma clearance, and with an elimination half-life of 7-12h in rat, dog and monkey. In general, TPX-0005 is rapidly absorbed in all species following oral dosing (2-4 hours), with low to moderate bioavailability, and mean half-lives ranging from 3.4h in mouse to 29h in monkey.

In rats, dose-proportional exposure was seen at oral doses up to 40 mg/kg, while less than dose-proportional exposure was seen at doses above 40 mg/kg. Females were generally higher exposed than males. Increased exposure (Cmax and AUC) was seen in both male and female rats following repeated dosing, with accumulation ratios up to 4 at lower dose levels, and up to 2.8 at higher dose levels.

In juvenile rats, exposures were lower at PND40 and PND70 compared to PND 12, indicating an age-dependent reduction in exposure. As the maturation of the cytochrome P450s (CYPs) metabolic system reach adult levels at ~PND21, the observed decrease in exposure with age could possibly be due to

effects of drug-metabolising enzyme ontogeny. There was a sex-related difference in exposure in line with what is seen in adult rats, although less marked.

In monkeys, less than dose-proportional exposure was seen at all dose levels, with no sex-related differences in the TK data, and no significant accumulation (AR 0.9-2.0) following repeated dosing.

Distribution

At a test concentration of 2 µM, similar and high levels of protein binding were observed in plasma from mouse, rat, dog, monkey and human, with free fraction ranging from 4.2% to 7.9%. Only a single test concentration was applied. In a follow-up study to further address human protein binding, TPX-0005 was predominantly bound to albumin (95-96%), and in a concentration-independent manner when tested at 0.3 and 2 µM. TPX-0005 had limited distribution to RBCs.

Following oral administration of [14C]-TPX-0005 to pigmented rats, radioactivity was widely distributed with quantifiable levels in most tissues. Highest levels were detected in pigmented skin, uveal tract, liver, renal cortex and kidneys. Overall, the pattern of distribution was comparable between male and female rats, but tissue exposures in females were generally 2-fold male exposure. At 168h post-dose, quantifiable levels were only detected in male liver and female preputial gland, and no radioactivity was detected in pigmented tissues. Potential distribution across placenta is not known.

In male rats, radioactivity was not detected in any tissues of the non-circumventricular CNS, suggesting that [14C]-TPX-0005-related radioactivity did not cross the blood:brain barrier at levels above 331 ng eq/g. In females, radioactivity was quantifiable in the brain cerebrum and cerebellum (but not other tissues of the CNS protected by the blood:brain barrier) at 4 hours post dose only, with concentrations of 343 and 376 ng eq/g, respectively, indicating that [14C]-TPX-0005-related radioactivity crossed the blood:brain barrier at very low levels. Low CNS distribution is further confirmed in juvenile rats and adult mice administered oral TPX-0005, where brain:plasma ratios ranged from 0.35 % in rats (PND45) to 5% in mice. In addition, P-gp and BCRP efflux ratios of 7.3 (study 00106) indicate that repotrectinib is a substrate for both transporters, limiting brain distribution.

Metabolism

Overall, the in vitro and in vivo metabolism data suggested that absorbed TPX-0005 was extensively metabolised in humans, rats and monkeys. In vitro metabolism was low across species, and unchanged TPX-0005 was the predominant circulating component in plasma in all species following oral dosing of [14C]TPX-0005.

In humans, the oxidative metabolism of TPX-0005 was mainly catalysed by CYP3A4. Biotransformation pathways in all species included oxidation or hydration followed by glucuronidation. No individual human plasma metabolite represented > 10%. Although human metabolites M1, M2 and M3 (together representing ~6% of total AUC) were below the limit of quantification in rat and monkey plasma, all 3 metabolites were present in monkey urine and M2 was present in rat bile. In addition, M5 (a potential precursor to M1, M2, and M3), was common to human, monkey and rat plasma, M9 was common to human and rat plasma, and M11 (glucuronide of a mono-oxidation product) was unique to monkey plasma.

Excretion

In rats, excretion is rapid in rats following oral administration with majority excreted within 24-48h, and essentially complete within 72h. Total recovery in bile-duct canulated rats was 95 and 96% in males and females, respectively, at 72h post-dose. Excretion primarily via faeces (≥81%) and bile (10 and 6% in males and females, respectively), with low levels in urine (1-3%). Based on the extent of radioactivity excreted in bile and urine, total absorption in rat was estimated to 14 and 9% in males

and females, respectively, indicating poor absorption. In monkeys, total recovery at 168h was 82% and 84% in males and females, respectively, indicating incomplete excretion. Radioactivity was predominantly in faeces and cage debris (80-81%), with low levels in urine (≤0.82%). Excretion in milk has not been studied.

PK drug interaction

See Clinical aspects.

2.5.4. Toxicology

A comprehensive toxicology programme was conducted in line with ICH S9 recommendations. Toxicology studies submitted included single- and exploratory/definitive repeat-dose toxicity studies in rats and monkeys (up to 3 months duration), in vitro and in vivo genotoxicity, a dose rage-finding EFD study in rats, dose range-finding/definitive juvenile toxicity studies in rats and evaluation of phototoxic potential. All pivotal studies were conducted in compliance with GLP regulations and administration was by oral gavage which is the intended route clinical route of administration.

Type of Study (Study No)	**Species/Strain**	**Dosing**	**Doses (mg/kg) Concentrations**	**GLP**
Single and repeat-dose toxicity				
Single-Dose Toxicity[a]	Rat, Sprague Dawley	Once	400, 600, 800, 1000	No
	Monkey, cynomolgus	Once	30, 100, 300, 1000	No
7-Day exploratory	Rat, Sprague Dawley	Once daily	0, 100, 300, 1000	No
28-Day pivotal & 28-Day recovery period	Rat, Sprague Dawley	Once daily	M: 0, **30**, 100/50[b], 300[c,d] F: 0, 6, **20**, 60[d]	Yes
91-Day pivotal & 28-Day recovery period	Rat, Sprague Dawley	Once daily	M: 0, 5, **15**, 50/40[e] F: 0, 5, **15**, 40/30[f]	Yes
7-Day exploratory	Monkey, cynomolgus	Once daily	0, 100, 300, 1000	No
28-Day pivotal	Monkey, cynomolgus	Once daily	0, 10, **30**, 100	Yes
91-Day pivotal	Monkey, cynomolgus	Once daily	0, **5**, 15, 50	Yes
Genotoxicity				
In vitro: Bacterial reverse mutation assay	*S. typhimurium*/ TA98, TA100, TA1535, TA1537 *E. Coli*/ WP2 *uvr*A	NA	15,50,150,500, 1500, 5000 µg per plate	Yes
In vitro: Mammalian cell micronucleus assay	TK6 lymphocytic cell line	NA	4 hour exposure: 0.1 to 15 µg/mL 27 hour exposure: 0.1 to 2 µg/mL	Yes
In vivo: Mammalian erythrocyte micronucleus assay	Rat, Sprague-Dawley	Once	0, 500, 1000, 2000	Yes
In vivo: Mammalian erythrocyte micronucleus assay	Rat, Sprague-Dawley	Once	0, 20, 50, 100	Yes
Developmental and reproductive toxicity				
Dose-range-finding on embryo/fetal development	Rat, Sprague Dawley	Once daily GD 6-17	0, 2, **6**, 12, 20	No
Dose-finding juvenile animal study	Rat, Sprague Dawley	Once daily PND 12-40	0, 0.1, 0.3, 1, 3, 10, 30	No
Pivotal juvenile animal study	Rat, Sprague Dawley	Once daily PND 12-70	0, 0.3, **1**, 3	Yes
Other studies				
Multiple dose phototoxicity study	Rat, Long-Evans	Once daily 3 Days	0, 100, 300, 1000	Yes

Type of Study (Study No)	Species/Strain	Dosing	Doses (mg/kg) Concentrations	GLP
Single and repeat-dose toxicity				

a: Formal single-dose toxicity studies with TPX-0005 have not been conducted. Instead, the tolerability of acute TPX-0005 administration was investigated within the context of oral dose range-finding studies conducted in both rats and monkeys.
b: Due to mortality, animals were placed on a dosing holiday beginning on Day 20; dosing resumed on Day 22 at 50 mg/kg/day.
c: Animals were dosed up to 14 consecutive days before a dosing holiday was implemented on Day 15
d: Due to mortality at 100 mg/kg/day (M) and 60 mg/kg/day (F), animals in the terminal necropsy groups were sacrificed on Day 20. Animals in the recovery groups began the recovery period on Day 20.
e: Beginning on Day 21, all males at 50 mg/kg/day were placed a dose holiday. Dosing resumed on Day 25 at 40 mg/kg/day.
f: Beginning on Day 18, all females at 40 mg/kg/day were placed on a dose holiday. Dosing resumed on Day 25 at 30 mg/kg/day.

2.5.4.1. Single dose toxicity

Following single doses, repotrectinib was well tolerated up to 1000 mg/kg (MTD) in rats and monkeys.

2.5.4.2. Repeat dose toxicity

The toxicological profile of repotrectinib was assessed in repeat-dose oral 7-day, 28-day and 91-day toxicity studies in SD rats and cynomolgus monkeys.

In the 7-day non-GLP RD-toxicity studies, the main findings in rats were body weight loss, suppression of haematopoiesis indicated by decreased RCM and reticulocytes in addition to suggested effects on the lymphatic system. The RCM and reticulocyte effects were adverse at all dose levels in females and at 1000 mg/kg in males**,** in accordance with TK data demonstrating higher plasma levels in female rats. In monkeys, repotrectinib was well tolerated up the highest dose of 1000 mg/kg. Findings consisted of dose-related emesis and faecal changes, erythropoiesis suppression and increased platelets.

In the pivotal GLP-compliant RD-toxicity studies, the major target organs across species were the skin (rat), CNS (rat), bone marrow (rat and monkey), and GI (monkey). These findings were generally dose-dependent and were reversible or showed a trend towards reversibility.

Mortalities: In rats, treatment-related mortality/moribundity occurred in 28-day and 91-day toxicity studies, with a total of 19 rats found dead. In the 91-day study, death/euthanasia occurred between D14-87 at 50 and 40 mg/kg in males and females respectively, at exposure levels ~0.96-1.88-fold human exposure based on AUC. Clinical signs of toxicity in dead/terminated animals included decreased body weight, decreased appetite, ataxia, piloerection, tremors, thin/unkempt appearance, decreased activity, hypersensitivity to touch, weakness, low carriage, leaning, penis extended, loss of skin elasticity, and/or skin abrasion/scab. The exact cause of death/moribundity was uncertain, however the deaths appear to be attributed to the severe clinical sign of toxicity.

In monkeys, two animals were euthanised in moribund condition. In the 28-day study, one high-dose male was euthanised on D28 due to adverse clinical signs (reduced body weight, dehydration, emesis, watery faeces). The animal had increased platelets, decreased thymic cortical and GALT lymphocytes, severely depleted body fat (decreased lymphocytes in the mesenteric and mandibular lymph nodes and splenic white pulp; hepatocellular glycogen depletion; pancreatic acinar atrophy; and increased thyroid colloid). The morbidity seemed treatment-related, although the applicant claimed that no definitive cause was determined. In the 91-day study, one mid-dose female was euthanized on D72 due to clinical signs of severe dehydration, soft and/or watery faeces, and lateral recumbency. The cause of death was unknown but could be related to dehydration secondary to enteritis/bacterial infection.

Skin effects: In rats, reversible treatment-related skin scab and/or abrasions were seen at all dose levels, and occurred mainly in the cervical, cranial, face, ear, shoulder, jaw, and/or thoracic regions. Microscopic erosion/ulceration included surface serocellular crusts, dermal granulation tissue with

subacute inflammation, and epidermal hyperplasia and hyperkeratosis adjacent to the erosion/ulceration. An inflammatory response was evident by increases in monocytes and/or neutrophils, increases in fibrinogen and globulin concentrations, and/or decreases in serum albumin concentrations which correlated to the microscopic erosion/ulceration and skin inflammation.

CNS effects: In rats, CNS toxicity (ataxia and tremors) was observed RD toxicity studies in sexually mature and juvenile rats, with juvenile rats being more sensitive. Several of these animals had to be euthanised early due to clinical decline, whereas those that survived to terminal necropsy had complete recovery.

Bone marrow effects: In rats and monkeys, reversible decreased RCM and reticulocytes were seen at all doses, with bone marrow hypocellularity (sternal and femoral) in rats observed correlating with the decreased RCM and reticulocytes.

GI effects: In monkeys, non-adverse GI tract findings (emesis and watery faeces) were observed at all dose levels. These effects correlated with microscopic changes of minimal subacute/chronic inflammation and/or minimal to mild mucosal gland hyperplasia in the large intestine in the 91-day study. Subacute/chronic inflammation was also seen within the jejunum. Inflammatory changes in the intestines correlated with the clinical pathology parameters (increased fibrinogen, globulin, inflammatory immune cells, and decreased albumin). GI symptoms are often associated with TKIs, and GI effects (constipation, nausea, vomiting, and diarrhoea), were observed with repotrectinib in the clinical trials, and are generally considered manageable.

Lymphoid organ effects: In rats, non-adverse decreased lymphocytes in circulation and in multiple lymphoid organs were observed at ≥15 mg/kg (M) and at ≥5 mg/kg (F). In monkeys, non-adverse decreased lymphocytes in multiple lymphoid organs were observed at ≥15 mg/kg which may have been related to stress.

Body weight changes: In rats, increased body weights were observed in the 28-day study at 30 mg/kg (M) and 20 mg/kg (F), with exposures ~2-fold higher than the human exposures based on AUC and were according to the applicant related to increased food consumption. These effects on body weight and food consumption in treated rats could be associated with TRKB inhibition and addressed by the applicant with reference to published literature. In the clinic, weight increase has been reported after administration with repotrectinib.

2.5.4.3. Genotoxicity

The genotoxic potential of repotrectinib was evaluated in an in vitro bacterial reverse mutation assay (Ames), an in vitro micronucleus assay in TK6 cells, and two in vivo mammalian micronucleus tests in SD male rats.

The Ames test did not reveal any evidence for a genotoxic potential. In the mammalian cell micronucleus assay in TK6 cells, repotrectinib was positive with and without S9. In a follow-up CREST staining, repotrectinib induced a high frequency of micronuclei in the presence of kinetochore staining (82-87%), indicating an aneugenic mechanism of action.

Repotrectinib was positive in the first in vivo micronucleus assay performed on bone marrow cells from male rats at doses of ≥500 mg/kg, with significant and dose-related increases MnPCE were observed at all dose levels after 24-hour, and at high-dose after 48-hour relative to vehicle control. In the second in vivo rat micronucleus assay, repotrectinib was negative at all dose levels tested, with exposure levels at the highest nominal dose of 100 mg/kg 3.4-fold above the anticipated human exposure based on AUC.

Overall, repotrectinib was not mutagenic or clastogenic, but aneugenic with a demonstrated threshold for induction of micronuclei at >100 mg/kg (nominal dose).

2.5.4.4. Carcinogenicity

In line with ICH S9 guideline, no carcinogenicity studies with repotrectinib were performed.

2.5.4.5. Reproductive and developmental toxicity

Three DART studies are included in the toxicological program: one non-GLP DRF study on embryo-foetal development (EFD) in pregnant SD rats and two juvenile toxicity studies in SD rats (one non-GLP DRF and one definitive GLP RD-toxicity). The extent of the DART program is in line with ICH S9 guideline recommendations plus the intended use in adolescent patients.

Embryo-foetal development (EFD): Repotrectinib-related maternal effects included clinical observations of skin scabbing/abrasions in the cervical and thoracic regions, which correlated with macroscopic observations of scabbing/abrasions at ≥12 mg/kg. Increased food consumption was observed at ≥6 mg/kg. Foetal effects included significant decreased body weights for females and combined sexes at 20 mg/kg, in addition to external malformation of malrotated hindlimbs in 2 foetuses at 12 mg/kg and 1 foetus at 20 mg/kg. NOAEL was 6 mg/kg, based on foetal effects (external malformation of malrotated hindlimbs and decreased mean body weight) and maternal effects (skin scabbing and abrasions). The foetal effects indicated potentially teratogenic effects.

Juvenile toxicity studies: In the DRF study (dosed from PND 12 to 40), adverse CNS toxicity was observed at D2-3 of dosing (≥10 mg/kg, exposure levels ≥1.5-fold clinical exposure), resulting in mortality/euthanasia of all animals in the two highest dose groups on PND 13-15. These animals had clinical findings including ataxia, hypoactivity, laboured respiration, decreased respiration rate, cool body or extremities, and/or splayed hindlimbs.

New dose groups of 0.1 and 0.3 mg/kg were added to the study after completion of evaluation of 0, 1, 3, 10, and 30 mg/kg, due to the early termination of animals in the two highest dose groups. Also, low-dose animals (0.1 and 0.3 mg/kg) were found dead/euthanised during PND 22–40. These animals had significantly lower body weights, and clinical findings that included thin, unkempt appearance, pale or cool extremities, hypoactivity, splayed hindlimbs, lying on side, and/or laboured respiration on day of death/euthanasia. These deaths were not considered treatment related.

In the GLP definitive RD juvenile toxicity study (dosed from PND 12 to 70), only one male in the 1 mg/kg group was found dead on PND 71. The death was considered by the applicant as an accidental death associated with blood collection and not related to repotrectinib, which is supported. At 3 mg/kg, repotrectinib-related adverse effects on growth (decreased body weight, body weight gain, food consumption and femur length), were seen in both sexes without any microscopic correlates. In addition, reversible minimal increase in platelets and decreased urine volume and increased urine specific gravity were observed. The changes in urinalysis parameters may be considered secondary to decreased food consumption. At ≥1 mg/kg, body weight at the age of attainment of vaginal patency was lower. In contrast to sexually mature rats, no skin findings were observed in juvenile rats.

In summary, CNS related mortality was observed in a DRF study juvenile rats at doses ≥10 mg/kg. NOAEL was 1 mg/kg in the pivotal study, based on adverse effects on growth (decreased body weight, food consumption and femur length) at 3 mg/kg. No effects were seen on neuro-behavioural parameters, including learning and memory at doses up to 3 mg/kg, with exposure levels 0.1-fold adolescent exposure levels based on AUC.

2.5.4.6. Toxicokinetic data

For summary of data see section 2.5.3.

Interspecies comparison

Major target organs for toxicity in rats comprises CNS, skin and bone marrow, with low to non-existing safety margins based on systemic exposure at NOAEL and expected human exposure at clinical intended dosing of 160 mg BID. Major target organs for toxicity in monkeys were limited to the gastrointestinal tract and haematopoiesis/bone marrow. Due to dose-limiting gastrointestinal findings and limited bioavailability, exposure levels achieved in the pivotal repeat-dose toxicity studies were below clinical exposure.

2.5.4.7. Local Tolerance

Local tolerance studies have not been performed since the clinical route of administration is oral.

2.5.4.8. Other toxicity studies

Repotrectinib had no phototoxic potential on the eyes and skin in an GLP in vivo phototoxicity study in female pigmented Long-Evans rats.

2.5.5. Ecotoxicity/environmental risk assessment

The Phase I assessment was based on a proposed maximum daily dose of 320 mg/day. The Phase I PEC_{SW} was determined after calculating a refined prevalence Fpen for both ROS1-positive NSCLC and solid tumours expressing an NTRK gene fusion. Taking into account both proposed indications, the overall refined PEC_{SW} was calculated to be 0.0045 µg/L, which is below the action threshold for Phase II assessment (0.01 µg/L). Further, repotrectinib is not considered a PBT substance with log Kow of 3.52 at pH 7. Considering the above data, repotrectinib is not expected to pose a risk to the environment.

Table 5 Summary of main study results

Substance (INN/Invented Name): repotrectinib				
CAS-number: 1802220-02-5				
PBT screening		Result		**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.52 (pH 7)		Potential PBT: N
Phase I				
Calculation	**Value**		**Unit**	**Conclusion**
PEC_{sw}, refined (prevalence)	0.0045		µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)				N

2.5.6. Discussion on non-clinical aspects

Primary pharmacodynamics

The human cell line data provided is limited to in vitro studies with human cell lines expressing wild type ALK and TRKA, and a single in vivo xenograft model with a human cell line expressing wild type TRKA.

Structural modelling studies indicate that repotrectinib fits completely inside the ATP-binding pocket with no solvent front exposure, thereby circumventing the steric interference that results in resistance to bulkier kinase inhibitors, especially the solvent-front and gatekeeper mutations of ROS1, TRK, and ALK kinases. This is also supported by PD data showing beneficial effects of repotrectinib on mutated kinases less sensitive to crizotinib and entrectinib.

While in vitro data confirms nM inhibitory activity against human wt ROS1, ALK and TRK and their corresponding mutants, PD data confirming activity against target kinases in rat or monkey, species used in the toxicity studies is not available. In view of 100% sequence homology for the ATP binding pockets between human, rat and monkey proteins however, both rat and monkey are considered relevant species for safety assessment.

Taken together, in vitro and in vivo data do support a rationale for potential effect of TPX-0005 in patients developing resistance to crizotinib and entrectinib due to solvent front mutations, likely due to TPX-0005 binding inside the ATP-binding pocket with no solvent front exposure.

The sought indication comprises ROS1-positive locally advanced or metastatic NSLC, and solid tumours expressing a NTRK fusion protein. It is acknowledged that a substantial amount of data has been submitted indicating PD effects on murine cells engineered to express wt and solvent front mutated ROS1 and TRK. The in vivo human cell line data is limited to the KM12 human colorectal carcinoma cell line expressing wt TPM3-TRKA, while no data have been provided on human cell lines expressing wt or mutated ROS1, TRKB or TRKC. It is acknowledged that there are limited human cell lines available with ROS1 or NTRK fusions. Although not ideal, the approach to use engineered murine cells may therefore be considered acceptable under these circumstances.

Repotrectinib demonstrated substantial kinase inhibition on a number of non-target kinases in vitro, with IC50 values for 21 kinases within expected free fraction C_{max} in plasma following intended dosing, indicating a number of potential safety concerns. Via off-target inhibition of FAK, DDR1, JAK3 and EPHA8, the developing brain is a potential target organ of concern, and adverse CNS findings were reported in the juvenile animal studies. Most potential off-target effects, including skeletal fractures and CNS findings, are already included as known adverse reactions based on existing clinical safety data or are adequately addressed in routine pharmacovigilance activities. In view of the intended patient population (adults and adolescents ≥12 years), no further safety measures are considered needed.

One of the targets of potential concern for the paediatric population is DDR2, a kinase required for normal bone development. DDR2 loss-of-function mutations in humans and mice cause severe defects in skeletal growth and development, with DDR2 loss of function mutations in humans causing the rare autosomal recessive growth disorder, spondylo-meta-epiphyseal dysplasia (SMED) with short limbs (see discussion on toxicity in juvenile rats).

Safety pharmacology

No CNS effects were seen in sexually mature rats following initial dosing at levels up to 1000 mg/kg/day. Following repeated dosing, however, CNS effects (tremors and ataxia without any histopathologic findings) were observed in RD-toxicity studies at doses from 40 mg/kg in adult rats and from 10 mg/kg in juvenile rats at doses, with low to non-existing safety margins. A plausible cause for the delay in CNS effects in adult rats could be slow accumulation in the brain until threshold concentration was reached and maintained. The earlier onset of CNS signs in juvenile rats can be associated with the lower level of brain efflux transporters during early postnatal development resulting in higher brain-to-plasma concentrations in juvenile rats compared with adult rats.

No effect of repotrectinib on CNS or ECG parameters (RR, PR, QT intervals, QRS duration, and heart rate) were observed in monkeys. Of note, the lack of findings in monkeys seem of less value

considering TK data demonstrated that the monkeys were not sufficiently exposed compared to clinical exposure.

Cases of QT prolongation have been reported in the CARE study with repotrectinib. Although, the hERG assay was not GLP-compliant, no additional study is required as no dedicated safety studies are warranted according to ICH S9 guideline, and appropriate and ECG measurements in non-rodents are generally considered sufficient.

No treatment-related respiratory effects were observed in single-dose or RD-toxicity studies in rats and monkeys. A few high-dose rats had increased respiratory rate/effort in both pivotal RD-toxicity studies; however, these animals were of moribund state and the findings had no lung histopathologic correlates.

Pharmacokinetics

PK and TK data indicate substantial inter-individual variability in all species (no information regarding variability is available for mice) following both IV and PO administration, with higher variation following PO administration. Both poor solubility and timing of food consumption are plausible contributing factors.

In a repeat dose PK study in male monkeys (study 00212) the PK data following the first dose of 20 mg/kg to fasted individuals is strikingly different from the single dose PK data from female fasted monkeys in study 00208, with a long Tmax (up to 12h) and a corresponding Cmax 16-fold less than in study 00208, indicating a potential sex-related difference. The provided plasma concentration plots from PK studies 00212 (male monkeys) and 00208 (female monkeys) do reveal striking differences in initial plasma levels, with similar and remarkable peaks in all three females at 2h post-dose. No further clarification for these striking peaks at 2h has been provided. However, following the applicant's review of exposure-time profiles in male and female monkeys in the GLP-compliant repeat-dose toxicity studies at dosing day 1, it is agreed that there is not a notable difference in the absorption or exposure between male and female monkeys.

According to the applicant, there are beneficial effects of repotrectinib in patients with brain metastasis in the TRIDENT-1 study. Non-clinical data from rats and mice do, however, indicate very low distribution across the BBB, with blood:brain ratios ranging from 0.35% in rats to 5% in mice. Further, repotrectinib is a substrate for both P-gp and BCRP, limiting brain distribution. There is generally a poor correlation between free fraction in plasma and brain. While plasma has twice as much protein as the brain, the brain has 20-fold more lipids than plasma. In the brain tissue, phospholipids drive the non-specific binding. The brain concentrations measured in homogenates from mouse and rat are total concentrations, and the level of unspecified binding is not known. However, by considering total brain:free plasma ratio of 0.5 to 1 in humans (range measured in rodents 0.2-1) and the applicant's conservative scenario of 99% binding, a free brain concentration of 0.22 to 0.45 nM could be estimated. It is agreed that the free brain concentrations may reach/exceed the IC50 values for most targets (ROS1, ROS1 (G2032R), TRKB and TRKC). The IC50 for TRKA is 2- to 4-fold above estimated free levels at the very low free fraction estimate of 1%. However, considering available data for a number of substances all having a free brain fraction above 1% (e.g., Gustafsson et al 2019; Ma et al 2024), and that the BBB may be compromised in patients with brain metastases, free brain concentrations likely exceed the IC50 for TRKA as well.

Metabolism data from animals and humans have not shown any major or disproportionate human metabolites in the circulation, and all human metabolites were also formed in rat and/or monkey, confirming the suitability of these species for nonclinical safety testing based on metabolism. Potential pharmacological activity of metabolites has not been tested; however, the minor circulating

metabolites are not expected to contribute to the pharmacology of TPX-0005 due to their low abundance and/or significant structural changes.

Toxicology

Rats (Sprague-Dawley) and monkeys (cynomolgus) are considered relevant toxicological species based on 100% sequence homology for the target binding sites and similar metabolism. In rats, reversible treatment-related skin scab and/or abrasions were seen at all dose levels. By referring to literature on TRK-deficient mice, the lesions are related to sensory and sympathetic neuropathies. Peripheral neuropathy is considered a common adverse event with repotrectinib, but skin effects have thus far not been reported in clinical studies

In the 28-day RD toxicity study, rambunctious play interactions were reported as a potential cause for the lesions. These behavioural changes did not occur during the 91-day study despite similar skin effects. Due to the abrasions and/or scabbing, measures were applied in both studies comprising additional environmental enrichment, suggesting that treatment-related altered behaviour may have contributed to the lesions. It is agreed that while no repotrectinib-related CNS findings were observed in either pivotal RD rat toxicity study's macroscopic or microscopic evaluations, the possibility that treatment-related CNS effects could contribute to altered behaviour and subsequent skin lesions cannot be excluded. Further, it is acknowledged that repotrectinib is unlikely to inhibit TrkA alone in the absence of an initiating inflammatory signal, although it cannot be ruled out that the abrasions and/or scabbing that correlated with erosion/ulceration of the skin occurred as a direct effect of repotrectinib on skin keratinocytes in rat. It is noted, however, that increased markers of inflammation was observed in the repeat dose studies and thus an initiating inflammatory signal to cause these skin effects may theoretically have been present at site.

At all dose levels in the 28-day and 91-day RD rat toxicity studies, clinical signs of skin lesions correlated with macroscopic and microscopic findings of skin erosion/ulceration. The severity of the skin effects resulted in additional environmental enrichment, and higher sensitivity in female rats (based on biochemical parameters, higher mortality rate combined with 2-fold increase in systemic exposure compared to male rats) was observed. However the NOAEL values can be maintained without modification as the environmental enrichment was only administered as needed and that the skin lesions did not affect the normal physiological function of the animals.

The underlying mechanism for the change in bone marrow cellularity observed in rats and monkeys is unknown. TKIs are, however, associated with haematologic toxicities (Sunder et al. 2023), and anaemia and other cytopenias have been reported in clinical trials with repotrectinib.

Marked thrombocytosis was observed in both species and the increased platelet count was statistically significant in monkey. Thrombocytosis was however only accompanied by an increase in bone marrow megakaryocytes in rat. A possible explanation to this discrepancy could be the differences in platelet lifespan between the two species (shorter in rats) and therefore the megakaryocytes would be more active (increased cellularity) in this species upon inflammatory stimulation. However, it should be noted that the general cellularity in the bone marrow of rats was decreased and that these cellularity changes were considered possibly related to repotrectinib and to occur by an unknown mechanism.

Dedicated local tolerance studies have not been conducted. Repotrectinib was administered once daily by oral gavage in repeat-dose studies in rats and monkeys with no related gross or microscopic findings in the oesophagus or the stomach in either species. Gastrointestinal tract events were observed in monkeys and consisted of emesis and watery faeces at ≥ 5 mg/kg/day that correlated with microscopic changes of minimal subacute/chronic inflammation and/or minimal to mild mucosal gland hyperplasia in the large intestine (cecum, colon, and rectum) in the 91-day study only. Subacute/chronic inflammation was also seen within the jejunum. Inflammatory changes in the

intestines correlated with markers of inflammation in the clinical pathology assessment. In monkeys, the LOEL for GI findings occurred at exposures of 0.17-fold for Cmax and 0.11-fold for AUC compared to adult human exposures at 160 mg BID.

Single-dose oral excretion and mass balance studies demonstrated that the majority of the radioactivity was detected mainly in faeces of both species, suggesting that the entire GI tract likely is exposed to repotrectinib and/or its metabolites. It is important to note, however, that the mechanism of the GI effects is not known; findings could be due to direct contact of repotrectinib with the large intestinal epithelium (a local tolerance effect), and/or secondary to systemic mechanism(s) or other local effects such as alterations in the microbiome (Secombe KR, et al. 2020).

A non-GLP DRF embryo/foetal development (EFD) toxicity study in time-mated female SD rats was conducted to determine appropriate repotrectinib dose levels for a definitive EFD study. In summary, NOAEL was 6 mg/kg, based on foetal effects and maternal effects. The foetal effects indicated potentially teratogenic effects, hence no definitive EFD studies were conducted, which is supported and consistent with relevant guidelines (ICH S9 Q&A document 2018 and ICH S5 (R3) 2020).

Carcinogenicity studies with repotrectinib were not conducted in line with ICH S9.

Genotoxicity studies have shown that repotrectinib is not mutagenic or clastogenic but has aneugenic properties. According to SWP/NcWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug (EMA/CHMP/SWP/74077/20/rev.1), the recommended duration of contraception in male and female patients should be until the end of relevant systemic exposure to an aneugenic compound (i.e. five half-lives after the last dose) plus 90 days or plus 1 months, respectively. Based on the population PK data, the single dose mean (SD) terminal half-life was estimated to be 60.7 (27.4) hours, and the steady state terminal t1/2 was estimated to be 40.3 (16.8) hours in cancer patients. Thus, WOCBP must use highly effective birth control methods during study treatment and until 2 months after end of study treatment. Male patients with female partners of childbearing potential must use condoms during treatment and for 4 months following the final dose. This is adequately reflected in the SmPC.

No dedicated fertility or early embryonic studies have been conducted. There were no effects on male and female reproductive organs observed in general toxicology studies conducted in rats and monkeys at any dose level tested, which equated to exposures in rats of up to 2-fold and 2.6-fold in males and females, respectively, and at exposures in monkeys that were below the human exposure at recommended clinical dose. Although no concerns were raised in the repeated dose studies with respect to reproductive organs, repotrectinib is aneugenic, and literature data do suggest involvement of the ROS1 gene in male fertility. The possible impact of repotrectinib on human fertility was discussed with references to scientific literature. No studies of ROS1 on female fertility were identified. However, the reviewed literature showed that the absence of ROS1 is linked to infertility in male knockout mice due to defects in sperm maturation and function in the epididymis. The provided information suggests that in the epididymis, ROS1 is a receptor for testicular lumicrine factors mediating differentiation of epididymal epithelial cells, a process critical for male fertility in mice. Although similar mechanisms may exist in humans, it is supported that ROS1's role in human fertility remains uncertain. It is acknowledged that the potential aneugenic effects of repotrectinib on fertility could not be assessed in the pivotal RD toxicity studies because the doses used were below those expected to have an aneugenic effects.

The CNS toxicity findings observed in the DRF juvenile toxicity study indicated increased sensitivity of the developing rodent nervous system. Repotrectinib is considered a substrate for both P-gp and BCRP, likely limiting CNS distribution in rats from PND21. At younger ages, however, a higher CNS distribution cannot be excluded, potentially causing higher sensitivity at ages below PND 21. The

severe CNS findings at PND13-15 is considered of low clinical relevance for the intended patient population (adults and adolescents ≥12 years of age) with functionally mature BBB.

In the DRF juvenile toxicity study, low-dose animals (0.1 and 0.3 mg/kg) were also found dead/euthanised during PND 22–40. These deaths could be due to the lower body weights and the animals' failure to thrive following weaning. Given that no effects on growth nor mortality were observed at 1 and 3 mg/kg in the DRF study, nor at doses up to 1 mg/mg in the pivotal RD juvenile toxicity study, these deaths were not considered treatment related.

In general, similar toxicities were observed in juvenile and adult rats. PD data indicate nM inhibitory activity on TRKB, a receptor for brain-derived neurotrophic factor (BDNF). The binding of BDNF to TRKB receptor causes many intracellular cascades to be activated, which regulate neuronal development and plasticity, long-term potentiation, and apoptosis. Thus, a potential concern of repotrectinib is adverse effects on neuro-development in paediatric patients. No effects were, however seen on auditory startle response, motor activity, and learning and memory (water-filled Biel maze) in juvenile rats following dosing from PND12-70 in the GLP definitive RD juvenile toxicity study.

Decreased femur lengths were observed in juvenile animals at 3 mg/kg/day, at approximately 0.1 times the human exposure (adult and adolescent) based on AUC at the recommended clinical dose of 160 mg BID. In the absence of any other macroscopic or microscopic effects on bone, the shortened femur lengths at 3 mg/kg/day were attributed to the reduced body weights in this group. The lower mean body weight gains correlated with lower mean food consumption. By referring to relevant published literature, it seems plausible to assume that reduced femur lengths may be related to the lower body weights. Although effects of other TKIs on bone in the form of skeletal fractures has been reported clinically in both adult and paediatric patients and appears more pronounced in the latter, affecting close to 1 in 5 paediatric patients (7 out of 38). A direct effect of repotrectinib on bone due to a pharmacological on target or off-target effect of DDR2 inhibition cannot be entirely ruled out (see discussion on primary pharmacodynamics above). No additional safety measures are warranted for the intended paediatric population as bone growth will be monitored through routine pharmacovigilance activities.

Environment risk assessment :

For repotrectinib PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

Therefore, repotrectinib is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies results indicate that TPX-0005 a potent inhibitor of fusion proteins of ROS1, ALK and TRK and clinically relevant solvent front mutations in engineered cells in vitro at nM levels, and prevents downstream phosphorylation, cellular proliferation and tumour growth in allograft models effect in corresponding tumour models in vivo. Data on human cell lines are limited to wt ALK and TRKA expressing cells in vitro, and one xenograft model in vivo expressing on wt TRKA. Due to inhibitory effects on a number of non-target kinases at low concentrations, off-target side effects are expected. There were no safety pharmacology findings of concern following single doses.

From the pharmacokinetic point of view, the analytical methods were generally GLP-compliant or considered fit for purpose. PK and TK data from rats and monkeys indicate low to moderate oral bioavailability. Distribution data have shown low distribution to CNS. Based on metabolism, rat and

monkey are considered suitable species for toxicity testing. Supportive data indicating activity against target kinases in rat and monkey is, however, missing which is considered acceptable.

With regard to the toxicological aspects, the major target organs across species were the skin (rat), CNS (rat), bone marrow (rat and monkey), and GI (monkey), with low to non-existing safety margins. Repotrectinib was not mutagenic or clastogenic but had aneugenic properties, and teratogenic effects were seen in rats. In juvenile rats, adverse effects were seen on growth. No effects were seen on neuro-behavioural parameters.

The nonclinical part of the dossier is considered approvable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 6. Overview of repotrectinib clinical pharmacology studies

Study	Main objectives	Study design	Dose, formulation and regimen	Prandial state
Healthy subjects – repotrectinib single dose				
TPX-0005-08	Relative bioavailability	Randomised, 2-treatment, 2-period, crossover study	160 mg (Gen.1 capsules), 32 mg/mL suspension (paediatric formulation)	Fasted
TPX-0005-09	PK characteristics	Open-label, non-randomised, 2-part (A and B), fixed-sequence crossover study		Fasted
- Part A	- Absolute bioavailability		100 µg IV [14C]-repotrectinib	Fasted
			160 mg (Gen.1 capsule)	
- Part B	- Mass balance		160 mg oral [14C]-repotrectinib	
TPX-0005-10	DDI victim study	Open-label, fixed-sequence study		
- Part 1	- Itraconazole DDI		Repotrectinib: 80 mg (Gen.1 capsules) and itraconazole 200 mg oral solution QD for 11 days	Fasted
- Part 2	- Rifampicin DDI		160 mg (Gen.1 capsules) and multiple dose rifampicin 600 mg capsules QD for 14 days	Fasted
TPX-0005-11	Food effect	Open label, randomised, two-period, two-treatment crossover study.	160 mg (Gen.1 capsules)	Fasted, fed
TPX-0005-12	Formulation development: Relative bioavailability	Randomised, 3 treatment, 3 period, crossover study	160 mg (Gen.1 vs two prototype Gen.2 formulations)	Fasted
TPX-0005-14	Formulations intended for marketing: Food effect and relative bioavailability	Open label, randomised, 3 period, 4 treatment crossover study	160 mg (Gen.1 capsules vs. Gen.2 capsules)	Fasted, fed (high and low fat)
Planned, not submitted	Hepatic impairment	ND	ND	ND
Patients with advanced solid tumours - repotrectinib single and multiple doses				
TPX-0005-01 (TRIDENT-01)		Phase 1/2, open-label, single-arm, multi-centre, first-in-human study		
- Phase 1a	- Determine DLTs, MTD and or RP2D	Standard 3 + 3 design	40, 80, 160, and 240 mg QD, 160 and 200 mg BID (Gen.1 capsules)	Modified fasted[e]
- Phase 1b	- Food impact pilot study	Three dose level, cross-over study	40, 80, 120 mg single dose	Modified fasted[e], Fed
- Phase 1c	- Dose escalation	Standard 3 + 3 design	120, 160 mg QD and 160 mg QD/BID[a] (Gen.1 capsules)	Fed
- Phase 1 midazolam	- Perpetrator DDI	Two-period study	160 mg QD/BID[b] (Gen.1 capsules) and midazolam 5 mg single dose	Unknown
- Phase 2	- Pivotal efficacy and safety - (Japanese/Chinese comparison)	Expansion cohorts 1-6	160 mg QD/BID[b] (Gen.1 capsules)	Unknown
TPX-0005-07 (CARE)		Phase 1/2, open-label, single-arm, multi-centre, multicohort study		
- Phase 1	Safety, MTD or MAD, paediatric RP2D		160 mg AED QD or 160 mg AED QD/BID	Unknown
- Phase 2	Anti-tumour activity in paediatric and young adult subjects		160 mg AED QD/BID (Suspension or Gen.1 capsules)[d]	Unknown
TPX-0005-16[c], not submitted	Cocktail study: (OATP1B1, P-gp, BCRP and MATE2-K)	ND	160 mg QD/BID	ND

a. Titration regimen: 7 days of QD treatment followed by BID treatment starting on Day 8.
b. RP2D titration regimen: 14 days of QD treatment, if tolerated, followed by BID treatment starting on Day 15.
c. Ongoing, no results submitted.
d. Capsules 10 mg were also used in the CARE-study; 2 of the 13 adolescents included received both 40 mg and 10 mg Gen.1 capsules (dose of 140 mg).
e. Modified fasted *i.e.* no food 1 hour before and 2 hours after dosing
Abbreviations: AED=adult equivalent dose; DL=dose level; Gen.1=generation 1 40 mg capsules; Gen.2/F1=generation 2 formulation 1 160 mg capsules; ND=not described.

Table 7. Key clinical studies supporting the efficacy and safety of repotrectinib in ROS1 positive NSCLC and NTRK positive solid tumours

Study	Primary Objective	Population	Regimen and Dose	Treated Subjects (N)	Study Status
TRIDENT-1 Phase 1/2, open-label, multi-center, first in human study of the safety, tolerability, PK, and anti-tumour activity of TPX-0005 in patients harbouring ALK, ROS1, or NTRK1-3 rearrangements	**Phase 1:** Phase 1a: determine DLTs, MTD and/or RP2D Phase 1b: food effect Phase 1c: dose escalation Midazolam DDI sub study: evaluate CYP3A induction	Adult subjects (≥ 18 years old) with histologically or cytologically confirmed locally advanced or metastatic solid tumour that harbors an *ALK, ROS1, NTRK1, NTRK2*, or *NTRK3* gene rearrangement	Phase 1a: 40, 80, 160, or 240 mg QD up to 160 or 200 mg BID Phase 1b: 40, 80, or 120 mg QD with food Phase 1c: 120 or 160 mg QD with food, or 160 mg BID with food Midazolam DDI sub study:5 mg fasted on Day -2 and C1D22, 160 mg QD/BID	Phase 1a: 44 Phase 1b: 28 Phase 1c: 21 Midazolam DDI sub-study: 10	Completed CSR DCO: 20-Jun-2022 Addendum to the CSR DCO: 19-Dec-2022
	Phase 2: ORR by BICR EXP-1: (TKI-naive, *ROS1*+ NSCLC) EXP-2: (TKI-pretreated, *ROS1*+ NSCLC with 1 prior TKI and 1 prior line of platinum-based chemotherapy) EXP-3: (TKI-pretreated, *ROS1*+ NSCLC with 2 prior TKIs and no prior platinum-based chemotherapy) EXP-4: (TKI-pretreated, *ROS1*+ NSCLC with 1 prior TKI and no prior platinum-based chemotherapy) EXP-5: (*TRK* TKI- naive, *NTRK*+ solid tumours) EXP-6: (*TRK* TKI-pretreated, *NTRK*+ solid tumours)[a]	Adult and adolescent subjects (≥ 12 years old) with histologically or cytologically confirmed locally advanced or metastatic solid tumour that harbors a *ROS1, NTRK1, NTRK2,* or *NTRK3* gene rearrangement	160 mg QD for 14 days with option to increase to 160 mg BID based on subject's tolerability assessment at Cycle 1 Day 15 in repeated 4-week cycles.	EXP-1: 107 EXP-2: 46 EXP-3: 38 EXP-4: 102 EXP-5: 43 EXP-6: 61 EXP-Other: 19	Ongoing CSR DCO: 20-Jun-2022 Addendum to the CSR DCO: 19-Dec-2022
CARE Phase 1/2, open-label, safety, tolerability, PK, anti-tumour activity in paediatric/young adult subjects with advanced/metastatic malignancies	**Phase 1** Evaluate the safety and tolerability at different dose levels; determine the MTD or MAD, select the paediatric RP2D	< 12 years old Harboring *ALK*, *ROS1*, or *NTRK1-3* Alterations	160 mg QD AED for first 14 days, followed by up to 160 mg BID AED.	10 (Enrollment completed)	Ongoing, ad hoc report DCO: 19-Dec-2022
	Phase 2 Determine anti-tumour activity in paediatric and young adult subjects	≤ 25 years old Harboring *ALK*, *ROS1*, or *NTRK1-3* Alterations	RP2D (160 mg QD AED for first 14 days, followed by up to 160 mg BID AED)	16 (28 at DCO: 15.Oct.2023)	Ongoing, ad hoc report DCO: 19-Dec-2022

a. To align with inclusion criteria updates in the protocol, subjects enrolled in previous protocol amendments who no longer fit in the EXP-1 to EXP-6 definitions were categorised into a new EXP-Other group (e.g. subjects with two prior TKI and one prior chemotherapy).
Each Cycle = 28 days. Source: TRIDENT-1 Phase 1 CSR Addendum, TRIDENT-1 Phase 2 CSR Addendum, and CARE Ad hoc Report.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The recommended dosing regimen of repotrectinib is 160 mg orally QD for 14 days, followed by an increase to 160 mg BID, with or without food, in both adults and adolescents. Generation 1 oral capsule (40 mg strength), and Generation 2 oral capsule (160 mg strength), are the intended to-be-marketed formulations. Clinical pharmacokinetic data were retrieved from the clinical studies described in Table 6. The repotrectinib clinical pharmacology program included assessments of ADME characteristics, relative and absolute bioavailability, food effect, bioequivalence across formulations, effect of intrinsic factors, DDI potential, concentration-QTc and exposure-response (ER) analyses. Repotrectinib PK was studied in healthy adult volunteers (single dose), and in adult and paediatric patients (single and multiple dose) with solid tumours harbouring ALK, ROS1, or NTRK1-3 molecular mutations. Twenty studies characterising *in vitro* metabolism, transporters, protein binding as well as potential to inhibit or induce enzymes or transporters are also provided.

Population pharmacokinetic (popPK) modelling has been used to characterise repotrectinib PK across clinical studies, identify sources of variability, and to support posology recommendations in adolescents. The DDI potential was further evaluated using a PBPK model approach. Repotrectinib effect on cardiac repolarisation has been investigated by concentration-QTc modelling, and E-R efficacy and safety analyses are used to support 160 mg QD/BID as the recommended dose.

Methods

Bioanalytical methods

A high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method is used for the analysis of repotrectinib in human plasma. The method is fully validated and applicable for measuring concentrations of TPX-0005 ranging from 1.00 to 1,000 ng/mL. Three sites (BioAgilytix, LabCorp and PPD Laboratories) use similar versions of this method for sample analysis. Interference studies have been performed and concluded that detection of TPX-0005 in human plasma using the MN16112 method is not interfered by midazolam, 1-Hydroxy-midazolam, rifampicin, 25-desacetyl rifampicin, itraconazole, hydroxy itraconazole, trametinib, sotorasib, metformin, digoxin and rosuvastatin.

To confirm that no *in vivo* conversion of repotrectinib to its enantiomer or diastereomers a chiral HPLC method with MS/MS detection was qualified by BioAgilytix. The method is applicable for measuring concentrations ranging from 10.0 to 2,500 ng/mL for TPX-0005 and 1.00 to 500 ng/mL for TPX-0009, TPX-0015 and TPX-0016.

A method to quantify TPX-0005 in human urine using LC-MS/MS was validated at PPD Laboratories, and is applicable to quantify TPX-0005 within a nominal range of 0.500 to 500 ng/mL.

For the absolute bioavailability study an HPLC + AMS method for the analysis of [^{14}C]-repotrectinib in human plasma was validated by Pharmaron.

Non-compartmental analysis

Standard non-compartment analysis was performed in all studies with rich PK sampling.

Physiologically based pharmacokinetic analysis

A physiologically based pharmacokinetic (PBPK) model, integrating available *in vitro* and clinical data (SimCYP vs 21), was used to predict repotrectinib DDI potential as victim of CYP3A4- and P-gp-mediated interactions and as perpetrator on the exposure of CYP2B6, CYP2C8, and CYP2C19 substrates. PBPK model simulations of DDI scenarios were used to inform the SmPC sections 4.5 and 5.2. Evaluation of the predictive performance of the model was used by comparison of observed data in study TPX-0005-10 (healthy, single dose with/without strong CYP3A4 inducer/inhibitor) and in TPX-005-08 (healthy, single dose) and TPX-0005-01 phase 1 (patients, single and multiple dose) with those predicted by the model.

Population pharmacokinetic (popPK) analysis

A repotrectinib popPK model was developed based on patient data from 502 adult subjects included in TRIDENT-1 and 24 paediatric subjects ≥4 years (14.6-76.7 kg) included in CARE. The model described repotrectinib PK with a 2-compartment model structure with first-order absorption with a Tlag, non-linear elimination with autoinduction modelled through a time-dependent Emax function driven by trough concentration, and an allometrically scaled baseline body weight effect on CL and V with fixed exponents of 0.75 and 1, respectively. Significant covariate effects in the final model were sex and race on CL. Age, tumour type, mutation, hepatic impairment (normal, mild), renal impairment (normal, mild, moderate), performance status, previous TKI use, and food effect were not significant covariates in the final model.

Absorption

BCS/solubility

Repotrectinib is a neutral compound and exhibits pH-independent aqueous solubility of 0.006 to 0.008 mg/mL across the physiological pH-range (pH 1.2-7.4, at 37°C). *In vitro* investigations suggests that repotrectinib is a class II (low solubility, high permeability) substance in accordance with the Biopharmaceutics Classification System (BCS).

Bioavailability

The geometric mean absolute bioavailability of repotrectinib following a single oral dose of 160 mg repotrectinib administered as capsule formulation was 45.7% (19.6%CV) under fasted condition in healthy subjects (TPX-0005-09 part A). Tmax was 2h (range 1-4h).

Bioequivalence

Two immediate-release capsule formulations are intended for marketing; Generation 1 40 mg capsules which was used in the pivotal study, TRIDENT-1, and Generation 2 160 mg capsules. Bioequivalence between the capsules was demonstrated in healthy volunteers in study TPX-0005-14, with 90% CIs of the geometric mean ratios for Cmax, AUClast, and AUCinf within 80% to 125% (n=26). The paediatric patients included in the CARE study received the oral suspension (32 mg/mL) or Generation 1 capsules (40 mg or 10 mg). The ratios of geometric means (90% CI) between the test oral suspension formulation and the reference Generation 1 capsule formulation for Cmax, AUClast, and AUCinf were 93.9% (78.4% to 112.3%), 96.5% (90.0% to 103.4%), and 97.2% (91.1% to 103.6%) (TPX-0005-08).

Food interaction

In the pilot food effect study in TRIDENT-1 comparing a high-fat meal to modified fasted conditions (no food and beverage 1 hour before and 2 hours after dosing), dose normalised geometric mean Cmax

and AUCinf increased by 15% and 23%, respectively (n=28) across all investigated dose levels, and by 43% and 34%, respectively for the 160 mg dose (N=15). Food effects were also investigated in healthy subjects where an overnight fast of at least 10 hours was implemented. Following administration of repotrectinib Generation 1 40 mg capsules, the Cmax increased by 149%, and the AUCinf increased by 56% with a high-fat meal compared to fasted conditions (TPX-0005-11, n=14). Following administration of repotrectinib Generation 2 160 mg capsule, the Cmax increased by 110%, and AUCinf increased by 42% with a high-fat meal (n=15), and the Cmax increased by 124%, and AUCinf increased by 36% with a low-fat meal (n=13), compared to fasted conditions (TPX-0005-14).Repotrectinib peak concentration occurred at approximately 4 to 6 hours post a single oral dose of 40 mg to 160 mg under fed conditions (high-fat meal).

Distribution

Repotrectinib was 95.4% bound to plasma proteins. The blood to plasma ratio was 0.56 *in vitro*. The geometric mean (CV%) Vdss was 264 L (22.3%) following a single intravenous dose. The geometric mean (CV%) apparent Vz/F was 432 L (55.9 %) in subjects with cancer following a single 160 mg oral dose (TPX-0005-01 phase 1a).

In the final popPK model, the estimated volume of distribution (Vc+Vp) for a typical adult patient of 70 kg was 221.9 L.

Elimination

Excretion via faeces accounted for the major elimination pathway of the administered dose. Renal excretion is a minor elimination pathway.

Following an IV administration in healthy subjects, repotrectinib exhibited low CL with a geometric mean (CV%) of 7.04 L/h (14.0%). The geometric mean (CV%) apparent oral clearance (CL/F) was 15.9 L/h (45.5%) in subjects with cancer following a single 160 mg oral dose. Based on the final popPK analysis, the single dose terminal t1/2 was estimated to be 62.9 hours for adult healthy subjects and 68.6 (SD 29.6) hours for adult cancer subjects. The steady-state terminal t1/2 was estimated to be 44.5 (20.8) hours for adult cancer subjects.

Mass balance

Study TPX-0005-09 part B was a mass balance study conducted in seven healthy male subjects receiving a 160 mg oral dose of [14C]-radiolabelled repotrectinib (~100 uCi) in the fasted state. The [14C]-repotrectinib was administered as a 30 mL oral suspension. The overall mean interpolated total recovery was 93.7% (n=6) over the 672-hour study. On average, 88.8% of the dose was excreted in faeces and 4.84% of dose was recovered in the urine through the last collection interval.

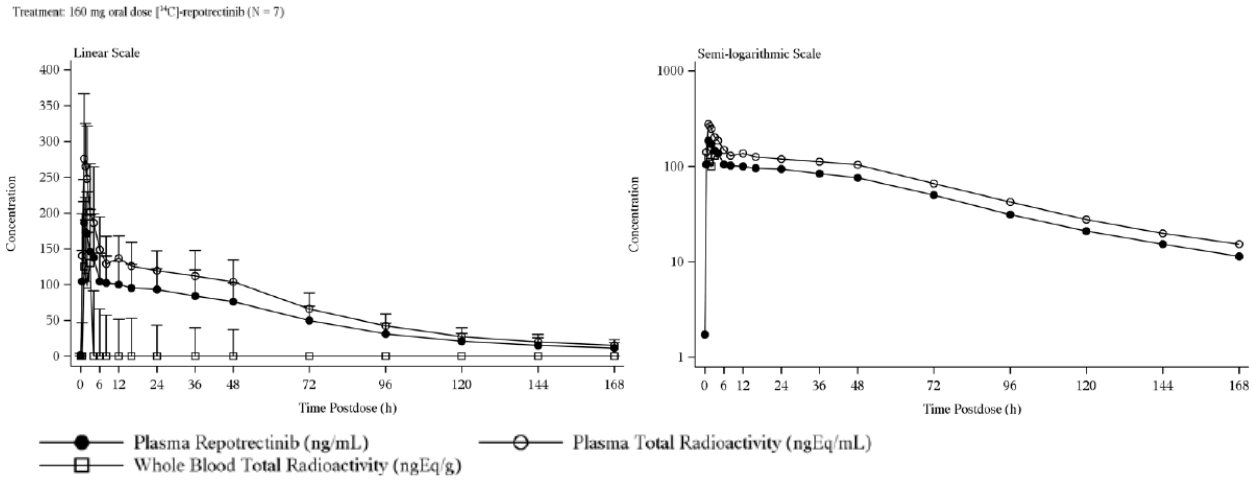
The geometric mean percent of repotrectinib recovered in urine up to 168h post-dose was 0.686% (36.7 %CV). The geometric mean CLR of repotrectinib was 0.141 L/h.

One subject exhibited atypical, low radioactivity recovery of 27.7% (faecal recovery 19.83%) of repotrectinib-related material through 44 days of the study period. Thus, data from this subject were excluded from summary statistics. The clinical records did not show any dosing error, unusual activity or missing faecal sample collection. The total radioactivity measurements in plasma and urine were comparable to the other subjects. The cause of the low recovery is unknown.

Mean blood to plasma concentration ratios (0.55-0.80, up to 48h) indicated limited distribution of repotrectinib related radioactivity into blood cells. The geometric mean AUCinf ratio of plasma repotrectinib to plasma total radioactivity suggested that repotrectinib was the predominant drug-related

component in the circulation and circulating metabolites were present (Figure 2). The respective PK profiles were parallel, suggesting that there were no long-lived metabolites.

Figure 2. Arithmetic mean (+SD) plasma repotrectinib concentration, plasma and whole blood concentrations of total radioactivity following a single 160-mg oral dose (linear and semi-logarithmic scale)

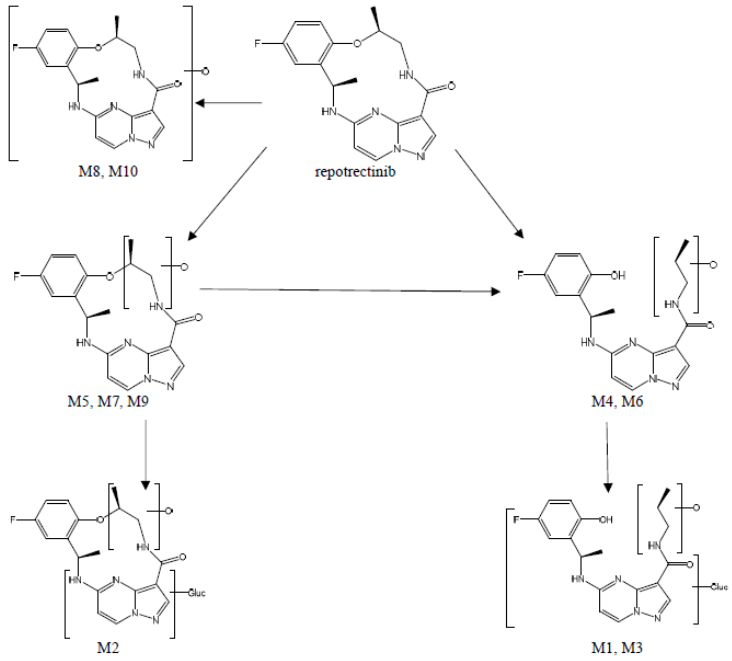


N = number of subjects
Reference: Table 14.2.1-1b
Program Location: /cvn/projects/prj/ecb/programs/000000194604/dev/figures/f_pcmean.sas
Program Status: FINAL Program Run: 26APR2021 Protocol Reference: TPX-0005-09

Metabolism

Repotrectinib is primarily metabolised by CYP3A4 to form oxidative metabolites followed by secondary glucuronidation. There were no major/disproportionate or unique human metabolites.

Figure 3. Proposed biotransformation pathway of repotrectinib following a single oral administration of [14C]-repotrectinib (160 mg) to healthy male human subjects



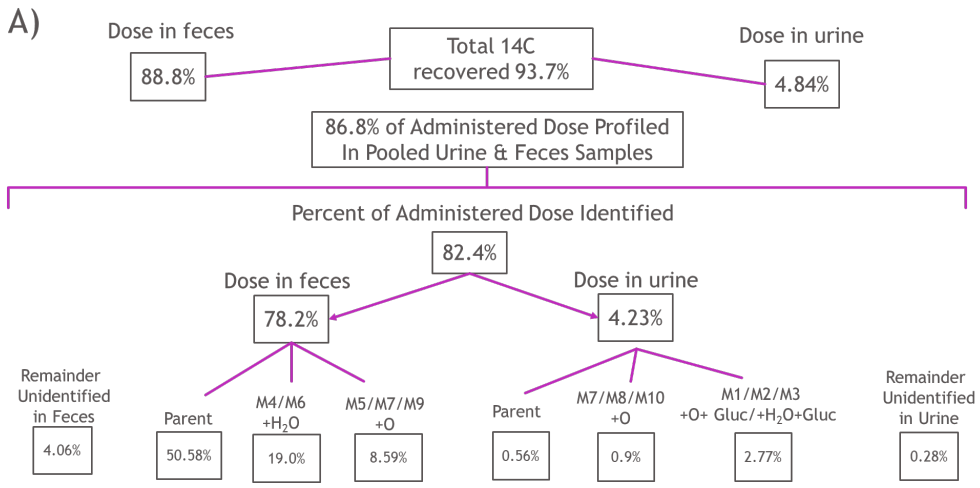
Metabolism of repotrectinib was focused on hydroxylation (on the propyl amine chain) and ring-opening (hydroxylation and hydrated [+O, +2H]) and glucuronidation of these Phase I metabolites. No direct conjugates of repotrectinib were detected.
Several of these metabolites showed isomers which had the same mass/molecular formula. In the presented structures, the chirality and stereochemistry are based on that illustrated in repotrectinib and have not been confirmed.

Unchanged repotrectinib accounted for the majority (84.3%) of systemically available radioactivity in a cross-subject pooled plasma extract from individually pooled plasma up to 72h (TPX-0005-09 part B). Circulating metabolites included M1/M3 (glucuronide conjugates of hydrated [+O, +2H] repotrectinib), M2 (glucuronide conjugate of a hydroxylated metabolite of repotrectinib) and M5 and M9 (hydroxylated metabolites of repotrectinib).

Approximately 51% of the administered dose in the mass balance study (TPX-0005-09 part B, Figure 4) was excreted via the faeces as unchanged repotrectinib, possibly representing unabsorbed dose. Metabolites detected in the faeces were predominantly hydrated metabolites M4 (+O, ~13% of dose) and M6 (+2H, ~6%) and hydroxylated metabolites M5 (~7%), M7 and M9 [each < 1%]), either following direct secretion, or by deconjugation of the corresponding glucuronide metabolites M1/M3 and M2, through the action of the gut microflora. No direct conjugates of repotrectinib were detected. Although faecal recovery was low in one subject (19.83% of dose), proportions of individual metabolites and radioactive components were not significantly different to those observed in other subjects.

Unchanged repotrectinib found in urine was 0.56% of the dose. The glucuronide conjugates metabolites (*i.e.* M1, M2 and M3) and a hydroxylated metabolite (M7) were detected in urine as major urinary metabolites (combined total of <3.5% of dose).

Figure 4. Repotrectinib Mass Balance following the 160 mg oral dose of [14C]-repotrectinib in healthy subjects (TPX-0005-09).



Metabolites

No metabolite in plasma exceeded 10% of total circulating drug related radioactivity. Approximately 84% of systemically available radioactivity in the cross-subject pooled plasma extract (based on sampling up to 72h, n=7) was identified as repotrectinib, while estimated AUC ratio repotrectinib to total radioactivity was 73% (range 61.5-88.4%) based on 168h sampling. The relative proportions of each metabolite are reported in a related study (Sponsor reference TPX-0005-09, Pharmaron study number 219-004).

Inter conversion

Repotrectinib contains two chiral centers with the potential to covert to three stereoisomers. Results indicated that in all pooled samples tested (103 samples from seven patients, TPX-0005-01 240 mg cohort), all stereoisomers were <1% of repotrectinib concentration. Thus, chiral inversion of repotrectinib is considered to be minimal.

Dose proportionality and time dependencies

Dose proportionality

Dose proportionality was assessed using PK data from TRIDENT-1 (TPX-0005-01) with single doses ranging from 40-240 mg and from TPX-0005-10 with 80 mg and 160 mg single dose in healthy subjects.

In TRIDENT-1, the dose proportionality following a single dose administration of repotrectinib at 40 mg, 80 mg, 160 mg and 240 mg was assessed using a power model. Following a single dose administration, the increases of repotrectinib exposure (Cmax and AUClast) were approximately dose proportional from 40 mg to 240 mg since the slope estimates were 0.783 and 0.803, respectively, and the 90% CI for slope included 1. However, AUCinf increase was slightly less than dose proportional (slope of 0.70) which is likely due to high variability observed.

Exposures (arithmetic means) following single 80 mg and 160 mg doses of repotrectinib administered to healthy subjects in study TPX-0005-10 were compared. The 2-fold increase in dose resulted in mean increases of 1.98, 2.03, and 1.97-fold in Cmax, AUClast and AUCinf, respectively.

Time dependency

Multiple dose repotrectinib PK was time dependent with a net autoinduction of CYP3A4 and potentially P-gp.

Time dependency of repotrectinib was assessed in subjects with advanced solid tumours. The mean steady-state accumulation ratio (based on AUC0-24) in subjects with advanced solid tumours at 40 mg, 80 mg, 160 mg and 240 mg QD were 1.19, 1.12, 0.67, and 0.54, respectively. The accumulation ratio was lower than anticipated based on half-life and dose interval especially at doses above 80 mg QD suggesting that repotrectinib PK is time dependent with a net autoinduction. Steady state appeared to be achieved after approximately one treatment cycle (4 weeks) of 160 mg QD/BID dosing based on trough concentration data from TRIDENT-1 phase 2.

Special populations

Renal impairment

Since renal excretion is a minor elimination pathway, a dedicated renal impairment study is not planned. Adult subjects with mild (n=139) and moderate (n=27) renal impairment (eGFR, CKD-EPI) had similar exposure compared to the subjects with normal renal function (based on comparison of EBE-based exposure).

Hepatic impairment

A phase 1 study to assess the effect of moderate and severe hepatic impairment on the pharmacokinetics of repotrectinib in non-cancer volunteers following a single dose is planned. Subjects with mild hepatic impairment (n=58) had similar exposure as those with normal hepatic status (based on comparison of EBE-based exposure).

Body weight

The effect of body weight (adult range 39.5 to 169 kg) on PK was modelled using allometric scaling. Compared to a 68 kg subject, steady-state Cmax and AUC was predicted to decrease 24% and 22% in a subject weighing 46 kg and increase 30% and 26% in a subject weighing 104 kg, respectively.

Children

As of the data cutoff date of Oct-2023, 30 paediatric patients from the CARE study, 17 children <12 years, 13 adolescents from 12 to <18 years (all >40 kg), provided PK data. The doses for adolescents were body weight-tiered (i.e. body weight >50 kg, 160 mg; body weight ≥40 kg and <50 kg, 140 mg; body weight ≥30 kg and <40 kg: 120 mg).

NCA analysis

Similar to adult PK, repotrectinib was absorbed with a median Tmax of 2 to 4 hours after oral administration of suspension or capsule formulation in paediatric subjects. Repotrectinib exposures decreased from Cycle 1 Day 1 to Cycle 1 Day 15 following once daily dosing, consistent with adult PK with demonstrated autoinduction.

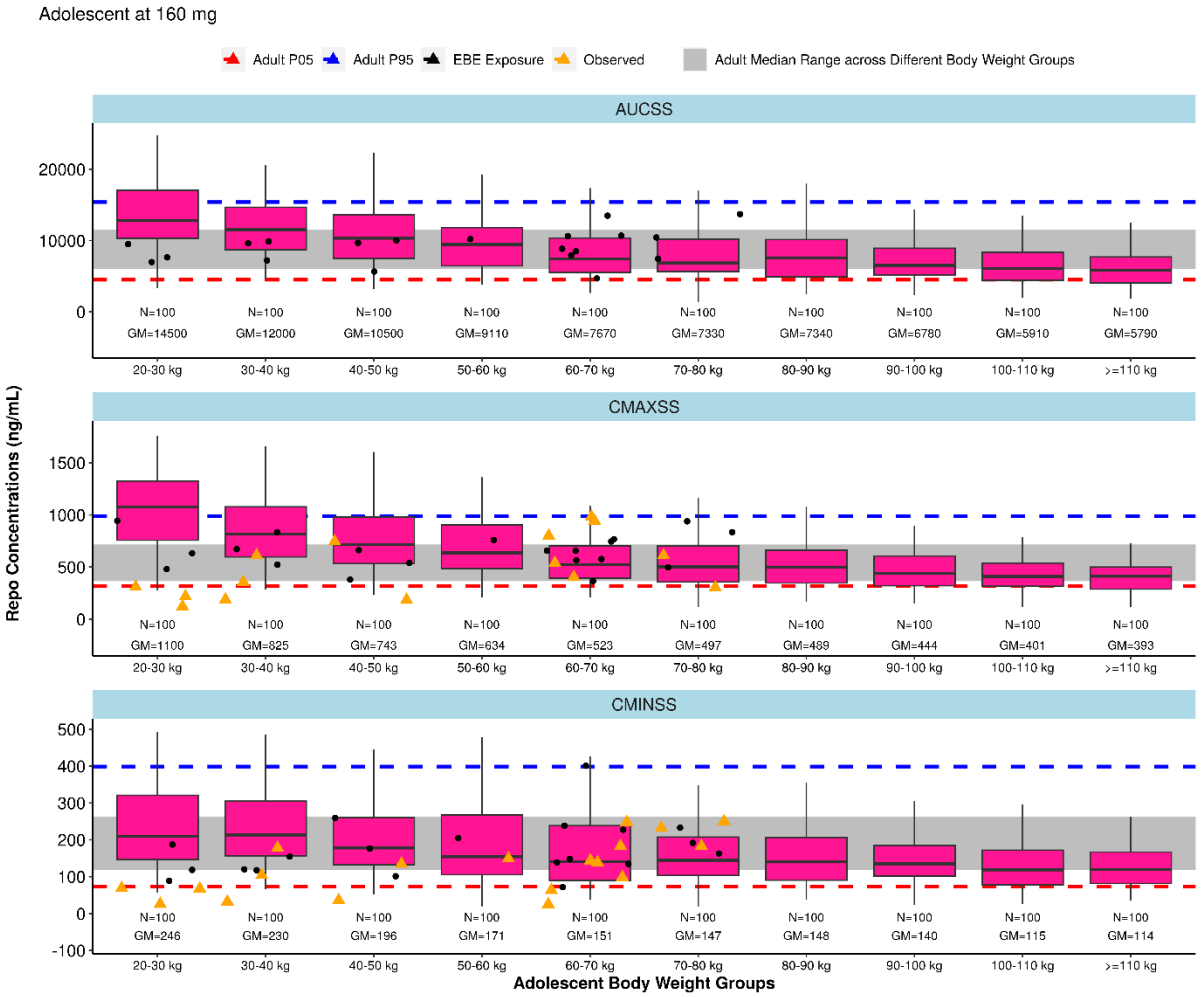
Repotrectinib exposures [Cmax and AUC(0-24)] in paediatric subjects were similar to those in adult subjects with rich PK data from the TRIDENT-1 study. Trough and 4h post-dose concentrations were similar in adolescents and in adults with sparse PK data in phase 2 of TRIDENT-1.

popPK model analysis

The EBEs of PK parameters for each subject were derived from the final popPK model. The adolescent and adult patients had comparable PK parameters.

The popPK model was used to simulate exposures (first dose, C1D15, steady-state) in adolescents across body weights following the recommended dose of 160 mg QD/BID. Stochastic simulations based on randomly sampled adolescent subjects (N=800) from National Health and Nutrition Examination Survey database (NHANES) were conducted. The ranges of AUC and Cmax in adolescents at each body weight group were largely overlapping with the 5th-95th percentiles of EBE-based exposures in adult patients in TRIDENT-1.

Figure 5. Simulated steady state exposures in paediatric and adolescent patients (>24 kg and ≥10 years old) compared to adult subjects at 160 mg QD/BID



Individual predicted (EBE) exposures (at 160 mg QD/BID, i.e. black closed circles) and observed exposures (at the appropriate body weight-tiered dose, i.e. yellow triangles) in paediatric patients (>20-39 kg) and adolescents are included for comparison.

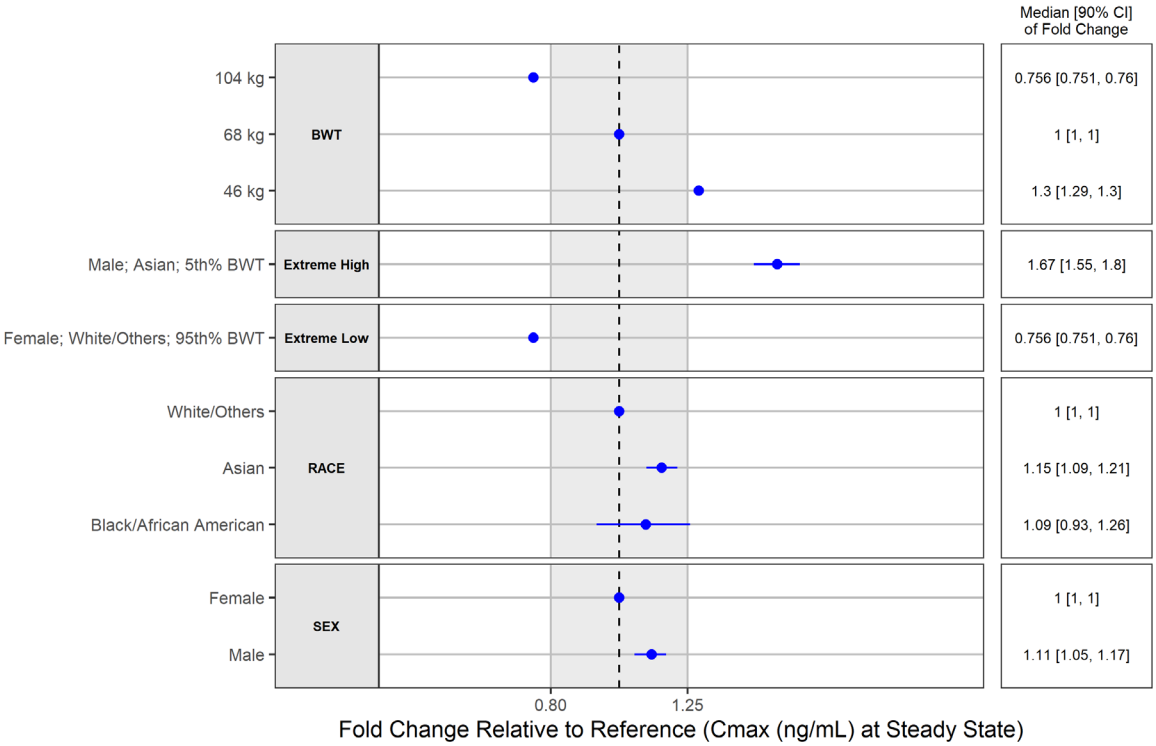
Age, sex, race

Age (range 4-93 years) was not identified as a covariate associated with repotrectinib PK exposure in adults. Of the elderly subjects providing PK data, 95 were 65-<75 years, 29 were 75-<85 years and one subject was ≥85 years old. Compared to White subjects/Other races, predicted steady-state Cmax and AUC was 15% and 19% higher in Asian subjects, and 9% and 12% higher in Black/African

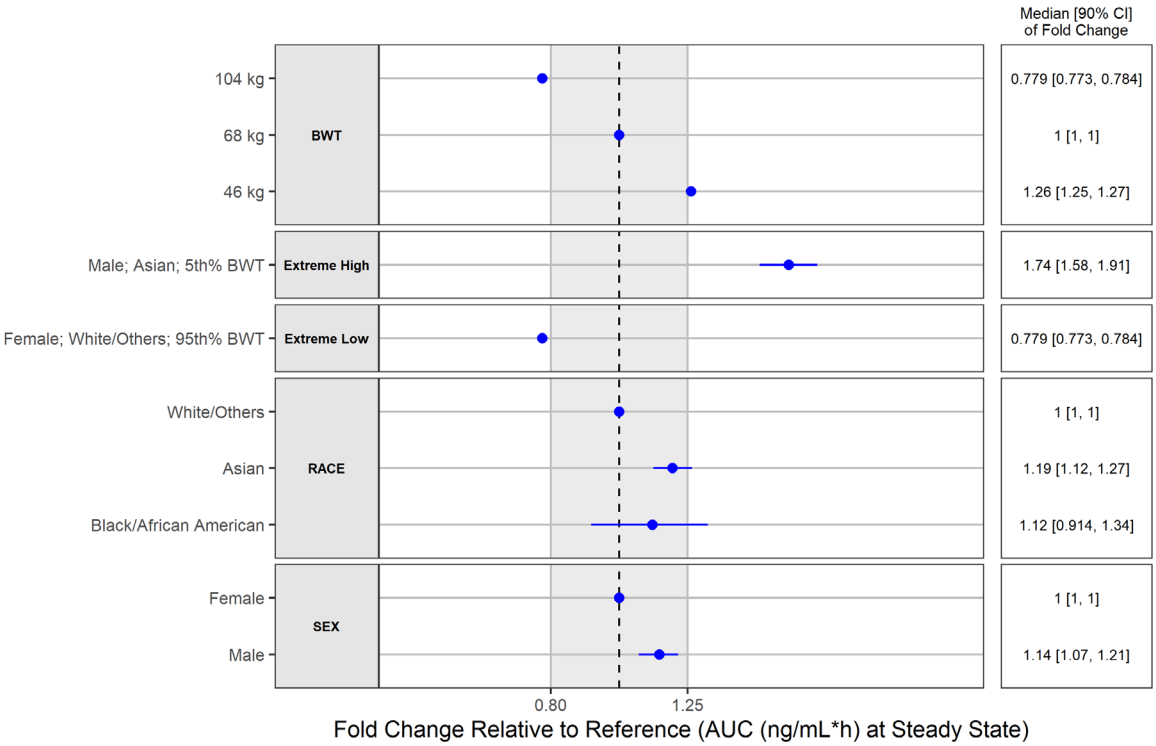
American subjects, respectively. Steady state Cmax and AUC was predicted to be 11% and 14% higher in males compared with females.

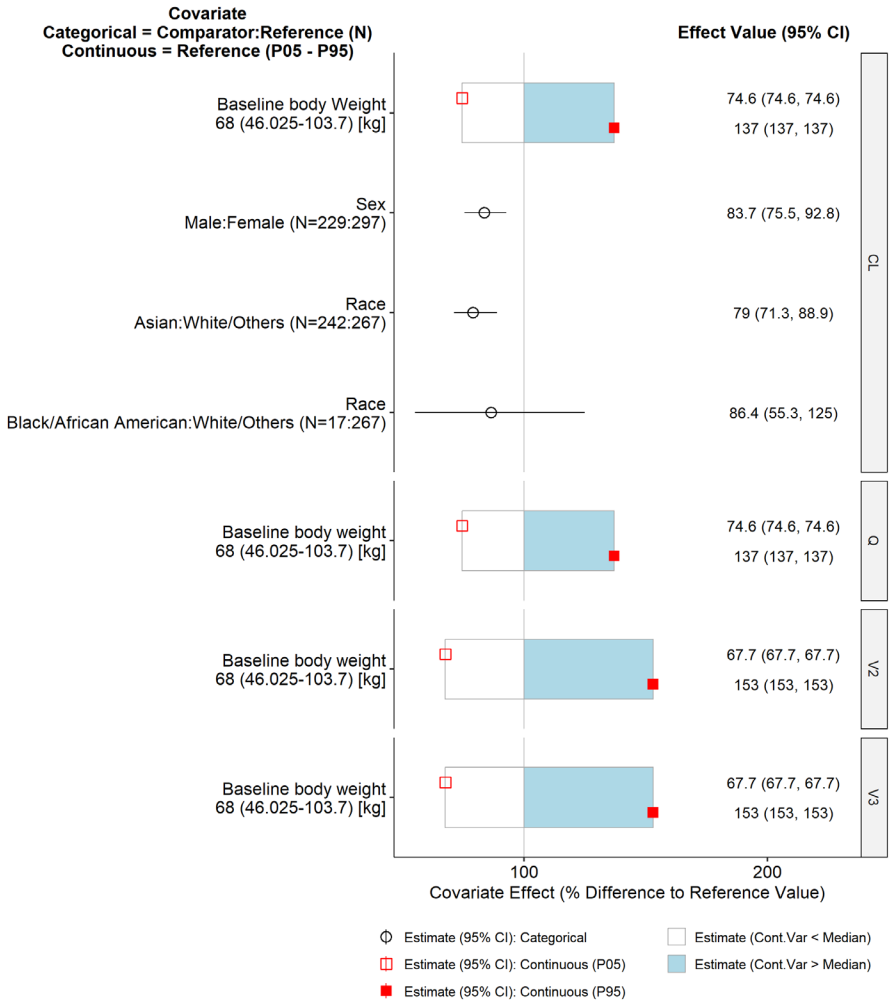
Figure 6: Forest Plot for the Effect of Significant Covariates on Steady-state Exposures

A) Cmax



B) AUC0-24





	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	95/644	29/644	1/644

Pharmacokinetic interaction studies

The assessments of repotrectinib DDI potential was based on *in vitro* IC50 and estimated Ki (*i.e.* IC50/2) values and the mean steady-state Cmax of 747 ng/mL (~2.1 µM) or unbound Cmax ($Cmax_{(u)}$) of ~0.09 µM. This mean Cmax was observed at C1D15 following daily doses of 160 mg QD (fed state) in eight patients with solid tumours in TRIDENT-1 phase 1c.

In vivo DDI potential was further investigated in studies TPX-0005-01 (midazolam sub-study), TPX-0005-10 (CYP3A4) and TPX-0005-16 (ongoing transporter cocktail study). The *in vitro* and *in vivo* drug interaction results were supplemented with prediction of drug interactions using a PBPK model approach.

In vitro – repotrectinib as perpetrator

Inhibition of enzymes

In vitro data suggests that repotrectinib is a potential inhibitor of CYP2C8, CYP2C9 and CYP2C19 systemically, and CYP3A4/5 in the intestine. Repotrectinib has a low potential to cause DDI by inhibiting the activity of CYP1A2, CYP2B6, CYP2D6, and CYP3A4/5 systemically (R1 values<1.02).

In vitro results indicate a low potential for repotrectinib to cause DDI by inhibiting the activity of UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 (R1 values <1.02), but repotrectinib may be an inhibitor of UGT1A1.

Induction of enzymes

Repotrectinib caused dose-dependent induction of CYP2B6 and CYP3A4 mRNA expression (*i.e.* >2-fold and >20% of the positive controls at the concentrations up to 30 µM), suggesting that there is a potential for repotrectinib to cause DDI via induction of these two CYP enzymes *in vivo.* Repotrectinib had little or no effects on CYP1A2.

Repotrectinib has the potential to induce CYP2C8, CYP2C9 and CYP2C19. Repotrectinib has also the potential to induce UGT1A1 as it is an inducer for CYP3A4, presumably via activation of pregnane X receptor (PXR).

Inhibition of transporters

Repotrectinib may have the potential to inhibit P-gp and BCRP (both systemically and in the GI tract), as well as OATP1B1, MATE1, and MATE2-K at clinically relevant concentrations (*i.e.* ratios of [I]1,u to IC50 of >0.02-0.1), but have a low potential to cause DDI by inhibiting OATP1B3, OAT1, OAT3, and OCT2.

Induction of transporters

No *in vitro* studies investigating the potential of repotrectinib to induce transporters have been performed. Repotrectinib has the potential to induce OATP1B1 and P-gp as it is an inducer for CYP3A4, presumably via activation of nuclear receptor PXR.

In silico

The PBPK model predicted weak to moderate interactions with moderate CYP3A4 inhibitors (erythromycin and fluconazole). Simulations with a moderate CYP3A4 inducer predicted moderate interaction with single dose repotrectinib. However, upon multiple dose administration of repotrectinib, the moderate interaction reduced to weak interaction which is within the inter-subject variability observed in TPX-0005-01.

Concomitant use of repotrectinib was predicted to decrease the concentration of sensitive CYP2B6 substrates, which may reduce the efficacy of these substrates. The predicted effects of repotrectinib on exposures of repaglinide (CYP2C8) and omeprazole (CYP2C19) were considered not clinically relevant. Since repotrectinib showed similar *in vitro* inhibition and induction potency towards CYP2C9 and CYP2C8, DDI with CYP2C9 substrates are also not expected to be clinically relevant.

Clinical studies

Repotrectinib as victim

The phase 1, two-part, open-label, fixed-sequence study TPX-0005-10 investigated the effects of multiple dose itraconazole (part 1) and rifampicin (part 2) on the single dose PK of repotrectinib in healthy adult male subjects (fasted state). Thirty adult male subjects (22-53 years) were enrolled and completed the study (Part 1, n=16; Part 2, N=14). All cohorts in part 1 received 80 mg repotrectinib due to the significant increase in repotrectinib exposure in period 2. All patients in part 2 received repotrectinib 160 mg. In part 1, repotrectinib maximum (Cmax) and total (AUCinf) exposure were increased by 1.7-fold (GMR 267%) and almost 6-fold (GMR 689%) when co-administered with the strong CYP3A4/P-gp inhibitor itraconazole. In part 2, repotrectinib maximum (Cmax) and total (AUCinf) exposure were decreased by ~80% and more than 90%, respectively, when co-administered with the strong CYP3A4/P-gp inducer rifampicin. Results suggest that repotrectinib is susceptible to DDIs when co-administered with strong CYP3A4 inhibitors and inducers and concomitant use with repotrectinib should be avoided.

Repotrectinib as perpetrator

A secondary objective in the patient study TPX-0005-01 phase 1 was to evaluate the potential of repotrectinib to induce CYP3A using midazolam as a probe substrate. Six patients were given midazolam 5 mg (2 mg/mL oral syrup, fasted state) on two occasions, prior and after start of repotrectinib therapy (*i.e.* on Day -2 and Day 22). Midazolam maximum (Cmax) and total (AUCinf) exposure following a single dose of 5 mg midazolam 2 mg/mL syrup (fasted state) was reduced by 48% and 69%, respectively, when co-administrated with repotrectinib at the proposed posology (*i.e.* 160 mg QD titrated to BID dosing). Results suggest that repotrectinib is a moderate inducer of CYP3A4 and that concomitant use with certain substrates of CYP3A4, for which minimal concentration change may lead to serious therapeutic failure, should be avoided.

A Phase 1 transporter cocktail study to assess the effect of multiple doses of repotrectinib at the proposed dose at steady state on the single dose PK of metformin (MATE1 and MATE2-K substrate), digoxin (P-gp substrate), and rosuvastatin (OATP1B1 and BCRP substrate) in patients with advanced solid tumours harbouring ROS1 or NTRK1-3 rearrangements. The study results and conclusions will be submitted to EMA when the study is completed.

Total bilirubin levels in patients (n=439) in TPX-0005-01 phase 1/2 have been investigated as a marker of UGT1A1 activity. There is a decrease in total bilirubin levels at all doses within first four dosing cycles. At the clinically relevant doses (160 mg QD or 160 mg BID), the decrease of bilirubin levels from baseline at steady state ranged from approximately 25% – 46% (N = 233 to 337 across cycles). Thus, the net effect of repotrectinib on UGT1A1 is not inhibition, but possibly weak induction. The risk of a clinically relevant drug interaction between repotrectinib and UGT1A1 substrates is considered low.

There are no data available on the potential effect of repotrectinib on systemic hormonal contraceptives.

Pharmacokinetics using human biomaterials

The hepatic metabolism of repotrectinib involved oxidative reactions followed by secondary glucuronidation. All the metabolites identified in human hepatocytes were also detected in nonclinical species. CYP3A4 appeared to be the major enzyme involved in the metabolism of repotrectinib.

Repotrectinib is a substrate for P-gp, a potential substrate for BCRP and MATE2-K, but not a substrate for the hepatic uptake and efflux transporters (OATP1B1/OATP1B3/OCT1 and BSEP) and renal uptake and efflux transporters (OAT1/OAT3/OCT2 and MATE1).

2.6.2.2. Pharmacodynamics

Mechanism of action

Non-clinical in vitro studies with murine cells engineered to express wt ROS1, ALK and TRK and selected mutations indicate that repotrectinib is a potent inhibitor of fusion proteins of ROS1, ALK and TRK and clinically relevant solvent front mutations, with IC50 in low to sub-nM range. Repotrectinib inhibits autophosphorylation, phosphorylation of down-stream effectors, and cell proliferation. In general, the inhibitory effect of crizotinib and entrectinib was significantly lower than repotrectinib in cells engineered to express clinically relevant solvent front and gatekeeper mutations of ROS1, ALK or TRK, with IC50 levels >600 nM, supporting a potential benefit in treatment of tumours developing resistance to crizotinib and entrectinib.

Primary and secondary pharmacology

Primary pharmacology

No dedicated clinical PD studies were conducted, and no PD end points were included in the conducted studies.

Secondary pharmacology

Cardiac safety analysis was performed by descriptive summary statistics (see clinical safety part) and by two concentration-QTc model analyses.

Primary objective of the main model analysis was to evaluate the effect of single and multiple doses of repotrectinib on ΔQTcF in adult patients with advanced solid malignancies. Secondary objectives included by time-point evaluation of repotrectinib effect on other ECG parameters, including heart rate.

Concentration-QTc analysis was performed separately for the Phases 1a (N=43), 1c (N=21), and 2 (N=334) in study TPX-0005-01, and for the pooled dataset (n=398, data cutoff 20-Jun-2022). Baseline QTcF was defined as the non-missing values closest to and prior to first dose date and time were used. The change from baseline QTcF (ΔQTcF) was defined as the value at each post-dose sampling time minus the baseline value. Data describing the circadian rhythm for each nominal time of sample collection in each individual were not available. The repotrectinib concentration-QTc relationship was quantified using a linear mixed-effects modelling approach with ΔQTcF as the dependent variable (Garnett et al .2018 White paper).

Repotrectinib had no clinically significant effects on heart rate, PR interval, or QRS duration. The individual and pooled analyses all resulted in negative slopes for the relationship between repotrectinib and QTcF, with model predicted QTc increase predicted to be below 10 msec for the highest exposures reached in all cohorts of the study. According to the applicant, an effect on ΔQTcF exceeding 20 msec can be excluded within the full observed range of plasma concentrations of repotrectinib up to ~3750 ng/mL (> 5-fold of observed steady-state mean Cmax of 747 ng/mL at 160 mg QD.

Relationship between plasma concentration and effect and safety

Exposure-response (ER) analyses for efficacy and safety based on adult patient data from TRIDENT-1 phase 1 and phase 2 have been provided.

The ER efficacy analysis included data from 215 subjects with ROS+ or NTRK+ alterations, of which ~91% received the proposed dose and indicated a positive relationship between exposure (average concentration over the first 56 days) and ORR for ROS+ NSCLC patients, but not for patients with NTRK+ solid tumours. The ER safety analysis included data from 502 subjects with ALK, ROS+ or NTRK+ alterations of which ~82% received the proposed dose and indicated increased probability of Gr2+ dizziness and DRDI with increasing exposure (time varying cumulative half-daily Cavg from Day 1 to the event or censor or Cmax on Day 1).

Dose justification

Repotrectinib at the recommended dose demonstrated clinical activity and a tolerable and manageable safety profile in ROS1-positive NSCLC patients and in patients with NTRK1-3-positive solid tumours in the Phase 2 portion of TRIDENT-1. The proposed dose in adolescents is mainly based on an adult exposure matching approach using a popPK model based on both adult and paediatric data.

Repotrectinib AUC following 160 mg QD was reduced at steady state compared to the first dose, due to auto-induction of CYP3A4. Increasing to BID dosing after 14 days is designed to compensate for the PK exposure loss due to auto-induction.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Repotrectinib PK has been described in healthy (single dose) and in cancer patients (single and multiple dose). Two indications are sought in adult cancer patients with locally advanced/metastatic disease: ROS1-positive NSCLC and NTRK positive cancer. The latter also includes children ≥12 years, and the posology recommendations in adolescents is based on adult exposure-matching. Two formulations are applied, 40 mg and 160 mg immediate release capsules, and their development is supported by BE studies.

Bioanalytical assays

The bioanalytical methods used are adequately validated.

popPK modelling

The final popPK model developed based on patient PK data was used to support the extrapolation concept in adolescents. The model with allometric scaling using fixed theoretical exponents shows acceptable predictive ability across body weights and age. Although estimated exponents provided an improved fit to the overall data, the data set consist primarily of adult subjects and adult exponents may be affected by other factors than pure body size relations and are generally not appropriate for paediatric models, unless adequately justified (M&S Q&A EMA). Also, very limited data is available from subjects with low weight <40 kg to evaluate the predictive ability in this subgroup. The magnitude of other covariate effects, i.e. race and sex on CL, was small (<20% difference on exposure). The effect of Black/African race on CL was estimated with poor precision and the bootstrap-derived 95% CI includes the null value. Additional analyses were required to support the proposed dose in adolescents during the procedure, and upon provision of response, the model was considered adequate for supporting exposure matching and dose recommendations across the expected weight range in adolescents.

ADME

Absorption

Repotrectinib is considered to have low solubility according to BCS criteria. However high permeability is not sufficiently demonstrated in accordance with ICH M9 and the classification of repotrectinib as a low solubility, high permeability drug (BCS II) is not confirmed. As repotrectinib solubility is not pH dependent, no interaction study with acid-reducing agents is required.

Repotrectinib is a substrate of P-gp and potentially BCRP, at clinically relevant (intestinal and systemically) concentrations. The DDI potential of P-gp has been (indirectly) investigated in the clinical study TPX-0005-10 and by PBPK modelling, see below.

The large proportion of unchanged repotrectinib found in faeces (~51%), comparable to the absolute bioavailability of 45.7%, likely represents (in part) unabsorbed drug. Absorption is likely dissolution-limited given the low solubility of repotrectinib, and the observed higher Cmax (and AUC) and delayed Tmax in fed compared to fasted state which could be explained by a combination of increased solubility and delayed GI transit time when repotrectinib is administered with food. Based on data from the mass balance study (TPX-0005-09 part B), it cannot be excluded that a higher proportion of repotrectinib is absorbed compared to the proportion reaching systemic circulation. Biliary excretion was observed in other species. A high degree of first pass metabolism is not likely considering the available non-clinical and single dose clinical data which indicate low intrinsic CL/hepatic extraction. Bioavailability following multiple dose repotrectinib is not investigated.

The applied 40 mg capsule formulation (generation 1) intended for marketing was used in most of the clinical studies conducted in adults, including the pivotal efficacy and safety TRIDENT-1 Phase 2 study. Bioequivalence has been demonstrated for the Generation 1 40 mg capsule versus the applied Generation 2 160 mg capsule, providing a PK bridge to support the approval of the 160 mg capsule for marketing. The paediatric patients included in the CARE study received the oral suspension (32 mg/mL) or Generation 1 capsules (40 mg or 10 mg). Of the adolescents, only two received a starting dose of 140 mg and used both 40 mg and 10 mg capsules. A bioequivalence study for the 10 mg capsule is not needed to support the extrapolation concept in adolescents considering the limited use in the CARE study, and as this formulation is not intended for marketing at present. The relative bioavailability study for the oral suspension used in the CARE study versus capsule supports the extrapolation of efficacy and safety data to the paediatric population <12 years (and is thus not directly relevant for the current application).

Repotrectinib was administered without regards to food in both pivotal studies, and this is reflected in the proposed food recommendations in the SmPC. Food is demonstrated to impact the exposure of repotrectinib, but food effects do not differ greatly between different meal types in the healthy subject and patient studies investigating impact of prandial state on repotrectinib PK. The greatest difference was observed for fasted (i.e. overnight fast of at least 10 hours, and until 4 hours post-dose) vs a high-fat/high-calorie meal, which represents the worst-case scenario and likely not the clinical situation. Although administration without regards to food introduce increased intra-and inter-variability in repotrectinib exposure, strictly fasted state is not feasible in the clinical setting. It is acknowledged that dosing without regard to food is more convenient considering the intended target population, which also includes adolescents down to 12 years of age. Further, the pivotal study (TRIDENT-1 phase 2), providing the main body of safety data, was conducted under the proposed food recommendations. Otherwise, patients are closely monitored and also dose reductions/interruptions are proposed for AEs. The recommendation to use repotrectinib with or without food is thus acceptable.

Distribution

In vitro, protein binding was 95.4%. No clinical data are available. Repotrectinib binds primarily to human serum albumin, and in a lesser extent to human α-1-acid glycoprotein. Concentration dependency of total protein binding has not been evaluated. Repotrectinib demonstrated limited distribution to red blood cells.

The proposed repotrectinib indication includes patients with CNS tumours. No data on, or discussion of, the distribution of repotrectinib over the blood-brain-barrier (BBB) has been presented in the clinical pharmacology dossier. Non-clinical data indicate limited brain penetration (mice). Further, repotrectinib is a substrate of the human efflux transporters P-gp and possible BCRP, which could limit overall CNS permeability. For further discussion, see non-clinical and clinical efficacy and safety sections.

Biotransformation and elimination

A single dose mass balance study is questioned since repotrectinib exhibit time-dependent pharmacokinetics as observed in clinical studies and described by popPK modelling, presumably due to CYP3A4 autoinduction. Thus, a steady state design should ideally have been used for the mass balance study TPX-0005-09 part B in accordance with EMA guidance (CPMP/EWP/560/95/Rev. 1 Corr. 2**, Appendix V). However, it is acknowledged that a multiple dose study in healthy subjects or patients is not practically or ethically feasible. The applicant has estimated the expected exposures of metabolites at steady state following multiple doses of 160 mg QD based on the single dose mass balance study results (cross-subject samples over 72h). Overall, the underlying assumptions appear reasonable and enables a sufficiently conservative estimate of metabolite levels. Assuming a 1.5-fold higher loss of repotrectinib, metabolites (as percentage of total drug related material) at steady state were estimated to be below the regulatory threshold of 10% for the oxidative metabolites M5 and M9 which are the circulating metabolites of greatest interest. Extrapolation of the results to the steady state situation is thus acceptable.

The relative bioavailability of the suspension formulation (160 mL/30 mL) used to in the mass balance study compared to capsules is not known and the formulation is not described in detail. It is noted that the maximum and total exposure is lower and Tmax slightly shorter in the mass balance study (part B, N=7) compared to other studies using single dose of 160 mg as capsules administered in fasted state. The amount excreted as unchanged repotrectinib in faeces (part B) was comparable to the absolute bioavailability (part A). No consequence for the overall conclusion on main route of elimination of repotrectinib is expected, and the issue is not further pursued.

The overall total mean radioactivity found in excreta satisfies the guideline requirement of >90% recovery. Also, ~88% of the recovered radioactivity was identified as repotrectinib or metabolites in the excreta (*i.e.* 81% of the dose was characterised). One patient was excluded for summary statistics due to low overall and faecal recovery which is acceptable based on examination of individual repotrectinib and total radioactivity plasma PK profiles which indicate no dosing errors or abnormal absorption.

Ten human metabolites (M1 to M10) were identified in excreta, and these were also identified in other species. Urinary excretion is of minor importance for repotrectinib elimination, as <1% of the dose recovered in urine was unchanged repotrectinib. Less than 3% of the dose was found as glucuronide metabolites M1-3 in urine. The majority of the administered dose was found in faeces (~82%), with ~51% of the material as unchanged repotrectinib and 31% as metabolites. The most predominant metabolites in excreta, all exclusively recovered in faeces, were hydrated/with ring-opening (M4, M6) and hydroxylated (M5) metabolites of repotrectinib, representing 26% of the dose. It is stated that no direct glucuronide conjugates were identified. The stability of glucuronides in the gut has not been

examined and back conversion (from glucuronide to parent/metabolites) in the gut cannot be fully excluded.

The proposed elimination pathway seems reasonable. The primary route for metabolism of repotrectinib appears to be oxidative metabolism, likely mediated by CYP3A4, followed by glucuronidation and/or faecal elimination. Based on the *in vitro* data, the metabolic turnover of repotrectinib appears to be low.

In vivo, circulating parent accounted for most of the repotrectinib-related material (~73 or ~84%, depending on time interval examined (168h or 72h, respectively). The total and repotrectinib radioactivity PK profiles are parallel indicating that metabolites collectively have similar CL as repotrectinib. Metabolites contributing to >2% of radioactivity in the cross-subject plasma extract were identified and consisted of glucuronide conjugates (of hydrated repotrectinib [M1/2] or hydroxylated metabolite [M2]), but also hydroxylated metabolites of repotrectinib (M5/9). Based on single dose data, no single metabolite contributed to >10% of circulating radioactivity. Glucuronides accounted for 6%, while all other peaks were <3% of total radioactivity across the 72h sampling period.

Repotrectinib contains two chiral centers with the potential to covert to three stereoisomers. No indication of chiral inversion was seen *in vitro* in human plateled hepatocytes or *in vivo* in study TPX-0005-01 phase 1.

No investigation of genetic polymorphism is required as CYP3A4 seems to be the most important enzyme involved in the metabolism of repotrectinib.

Dose proportionality and time dependency

Based on the predefined criteria set by the applicant (i.e. 0.8-1.2, associated CI including 1), repotrectinib seems to be approximately dose proportional after single dose in the dose range of 40 mg to 240 mg. Based on the slope estimates of 0.78 and 0.7 for Cmax and AUC0-inf, respectively, the relationship seems to be less than linear. No formal dose proportionality assessment from multiple dosing have been performed. NCA data indicates a lack of dose proportionality and a less than linear relationship after multiple dosing. This is in line with the presumption of a net auto-induction of CYP enzymes and transporters by repotrectinib.

Repotrectinib exhibits time-dependent pharmacokinetics with increased clearance over time, presumably due to CYP3A4 autoinduction. An up-titration of the dose from 160 mg QD to BID from Day 15 compensates for exposure lost due to autoinduction.

Target population

Only single dose data is available in healthy subjects, and no NCA comparison of multiple dose/steady state PK data for healthy subjects and subjects with advanced solid tumours is therefore available. Different food recommendations across studies also complicates a direct comparison across studies and subject type, as food is shown to have an impact on repotrectinib PK.

The Cmin and C4h across expansion cohorts 1, 4, 5 and 6 in TRIDENT-1 appear comparable, suggesting similar PK exposure in subjects with ROS1 and NTRK mutations, and in TKI-naïve and TKI-pretreated subjects. The applicant has defined repotrectinib target exposures based on the 5-95th percentile range of popPK predicted (EBE) exposures (AUC0-24, Cmax, and Cmin) at steady state in TRIDENT-1 (n=503) at the proposed dose 160 mg QD/BID. The approach is considered acceptable. The therapeutic window cannot be determined with available data, and the exposures achieved in the pivotal study are therefore the best available reference ranges to be used for exposure matching in adolescents.

Children

The adolescent indication is primarily based on extrapolation of efficacy and safety from adults via PK exposure matching. The PK bridge is supported both by observed data and NCA analysis, and simulations using the popPK model. Repotrectinib PK is expected to be similar in adolescents and adults, but exposure is influenced by body weight, and the expected weight range in adolescents extends lower than in adults. In the paediatric CARE study, repotrectinib was dosed according to body weight; 160 mg QD/BID in subjects ≥50 kg, 140 mg QD/BID in subjects 40-49 kg (12.5% reduction), and 120 mg QD/BID in subjects 30-40 kg (25% reduction). The applicant proposes, however, that the 160 mg QD/BID dose is appropriate for all adolescents regardless of body weight. No PK data were available from adults or adolescents with body weight <40 kg.

The proposed dose of 160 mg QD/BID is acceptable for adolescents >12 years with body weight ≥ 40 kg as adequate adult exposure matching has been demonstrated by observed and simulated PK data. Additional analyses and data have been requested to further evaluate the proposed dose at lower body weights. The simulated exposures in adolescents with a body weight of ≥30 kg following 160 mg QD/BID dosing is similar to adult exposures, thus allowing for extrapolation of efficacy and safety. Stochastic simulations indicate that exposures in subjects weighing 24-29 kg start to exceed adult exposures. However, it is agreed that a body weight <30 kg in adolescents is expected to be rare, and further that a weight in the lower end of the 24-29 kg range is unlikely. Noteworthy, available EBEs from subjects in CARE <12 years with a weight of ~20-21 kg, indicated similar PK parameters as in older children. Based on the totality of observed and simulated PK data, the proposed dose of 160 mg QD/BID is considered acceptable for adolescents across the expected body weight range from a PK perspective.

Other special populations

There is very limited/no data available in patients with moderate and severe hepatic impairment, or severe renal impairment. A dedicated PK study (CA127-1070) in non-cancer patients with moderate to severe hepatic impairment is ongoing (**REC**). In the meantime, relevant sections of the SmPC have been updated with current knowledge. Considering the proposed posology recommendations (160 mg QD first 14 days, then increased to 160 mg BID dosing due to autoinduction) and the potential risk of AEs due to over-exposure, repotrectinib therapy should not be used in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment. In the popPK analysis, mild hepatic impairment (total bilirubin > 1.0 to 1.5 times ULN or AST >ULN, n = 59) did not influence the clearance of repotrectinib.

In the popPK analysis, mild (eGFR-CKD-EPI 60 to 90 mL/min, n = 139) or moderate (eGFR-CKD-EPI 30 to 60 mL/min, n = 27) renal impairment did not influence the clearance of repotrectinib. Repotrectinib has not been studied in patients with severe renal impairment (eGFR- CKD-EPI < 30 mL/min). The lack of a renal study could be acceptable as renal excretion constitutes a minor elimination pathway. However, severe renal impairment can impact on primarily hepatically eliminated drugs through e.g. suppression/inhibition of metabolism by uremic toxins (EMA/CHMP/83874/2014).

In the popPK analysis, no clinically relevant differences in the pharmacokinetics of repotrectinib were identified based on gender, age (18 years to 93 years), body weight (39.5 kg to 169 kg), or race (Asian and White) in adults. Of note, there are limited data in Black/African American subjects (n=16), subjects with moderate/severe renal impairment (n=27/4), and subjects with moderate hepatic impairment (n=1) and no data in subjects with severe hepatic impairment. The effect of these factors on PK can therefore not be concluded based on available data. The main identified driver of PK variability is body weight.

Interactions

The potential of repotrectinib as a substrate of transporters, and its potential to inhibit or induce the metabolism (through CYP or UGT) or transport of other drugs has been investigated *in vitro* in accordance with the EMA and ICH DDI guidelines (CPMP/EWP/560/95/Rev. 1 Corr. 2** and the current version of the draft ICH guideline M12 on drug interaction studies). Overall, positive *in vitro* findings have been, or are planned to be, investigated *in vivo*, or have been further explored by PBPK modelling.

The concentration cut-off values used by the applicant to evaluate the clinical relevance of the *in vitro* DDI results are derived from multiple dose 160 mg QD dosing (fed state) and is considered at reasonable estimate of Cmax at steady state following 160 mg BID dosing (unknown prandial state) based on the available data.

The absorption rate constant (Ka) value of 1.6/h, derived from non-clinical data, was used to calculate cut-off values for DDI assessment. Although less conservative than the worst case value recommended in the EMA DDI guideline (6/h), conclusions drawn from *in vitro* DDI investigations are not affected.

The data used to estimate concentration cut-offs for the evaluation of the interaction potential was taken from the adult program. Assuming that adolescent concentrations *in vivo* are in a similar range compared to the adult population, this is generally acceptable (see Special populations).

A PBPK model has been developed integrating available information from *in vitro* and clinical studies, and it is used to support clinical recommendations in the absence of clinical studies. Specifically, the model is used to predict DDI effects with repotrectinib 1) as a victim of moderate CYP3A4 inhibitors/inducers (with and without additional P-gp effect) and 2) as a perpetrator on the exposure of CYP2B6, CYP2C8 and CYP2C19 substrates. However, the platform qualification is not in accordance with the EMA guideline on PBPK modelling and simulation (EMA/CHMP/458101/2016), and it has not been demonstrated that the PBPK platform is qualified for simulations of the relevant/intended scenarios The PBPK model is not considered reliable for predictions, and the SmPC recommendations should instead be informed by *in vitro* and clinical study results.

<u>Repotrectinib as a victim</u>

Repotrectinib (single dose) was investigated as a victim of CYP3A4-mediated DDIs (study TPX-0005-10). Results showed that the strong CYP3A4 inhibitor itraconazole increased single dose repotrectinib AUCinf by 5.9 fold and Cmax by 1.7 fold, which could increase the frequency or severity of adverse reactions. In the presence of the strong CYP3A4 inducer rifampicin, repotrectinib AUCinf and Cmax decreased by >90% and ~80%, respectively. Considering these substantial changes in plasma levels, a clinically relevant impact on repotrectinib exposure when co-administered with moderate CYP3A4 inhibitors/inducers cannot be ruled out. The role of P-gp transport cannot be distinguished from the effect on CYP3A4. Thus, administration of repotrectinib with strong or moderate CYP3A4/P-gp inhibitors or inducers should be avoided (see section 4.5 of the SmPC). Based on the totality of data it is agreed that no warnings are required for weak CYP3A4/P-gp inhibitors/inducers.

Co-administration of repotrectinib with strong or moderate CYP3A4 or P-gp inducers (including but not limited to carbamazepine, phenytoin, rifampicin, St. John's Wort- Hypericum perforatum, apalutamide, ritonavir) decreases repotrectinib plasma concentrations and should be avoided.

Similarly, co-administration of Augtyro with strong or moderate CYP3A4 or P-gp inhibitors (including but not limited to ritonavir, saquinavir, ketoconazole, itraconazole, voriconazole, posaconazole, verapamil, nifedipine, felodipine, fluvoxamine, grapefruit, or Seville oranges) increases repotrectinib plasma concentrations and should thus be avoided.

A DDI study is planned (CA127-1072) in healthy subjects investigating the effect of multiple doses of a specific P-gp inhibitor quinidine and specific CYP3A4 inhibitor voriconazole on single-dose PK of repotrectinib. The applicant has committed to submit the CA127-1072 final CSR following study completion as a post-authorisation measure (**REC**).

Repotrectinib as a perpetrator

Repotrectinib is both an *in vitro* inhibitor and inducer of CYP2C8, -9 and -19., and an *in vitro* inducer of CYP2B6. There are no *in vivo* study investigating the clinical relevance of the induction/inhibition effects of repotrectinib on these CYP enzymes, and the PBPK model is not considered reliable for predictions. A clinical pharmacokinetic study (CA127-1027) investigating the effect of multiple dose repotrectinib on single dose of sensitive CYP2B6, CYP2C9 and -C19 substrates is planned. The PBPK model will be updated with this additional clinical data to assess the impact also on CYP2C8 substrates. The applicant has committed to submit the CA127-1027 final CSR following study completion as a post-authorisation measure (**REC**). In the meantime, the SmPC reflects current knowledge.

A cocktail DDI study has been initiated to further investigate the clinical relevance of the *in vitro* results where repotrectinib was identified as an inhibitor of P-gp, BCRP, OATP1B1, MATE1 and MATE2-K at clinically relevant concentrations. Also, repotrectinib is potentially an inducer of OATP1B1 and P-gp through the PXR pathway. A cocktail clinical DDI study is ongoing to evaluate the net effect of steady-state repotrectinib exposure on the single dose PK of metformin (MATE1/MATE2-K substrate), digoxin (P-gp substrate), and rosuvastatin (OATP1B1 and BCRP substrate) (**REC**). In the meantime, the SmPC reflects current knowledge.

Repotrectinib is an inducer of CYP3A4 *in vitro*. The clinical relevance/potential DDI effect of multiple doses of repotrectinib on the CYP3A4 substrate midazolam was investigated (TPX-0005-01), and it is agreed that repotrectinib can be considered a moderate inducer of CYP3A4 (geometric mean and corresponding 90%CI AUC reduced by ≥50% to ≤80%).

In vitro, repotrectinib is an inhibitor of UGT1A1 and may have a potential for induction of UGT1A1 through activation of the nuclear receptor PXR. The *in vivo* net effect of induction and inhibition of UGT1A1 on sensitive substrates is not known. Section 4.5 of the SmPC includes information of repotrectinib as a potential perpetrator of (sensitive) substrates of PXR-regulated/CYP2C enzymes.

Repotrectinib is a potential human teratogen. As the applied indications may include fertile women, repotrectinib needs to be studied *in vivo* for effects on contraceptive steroids (EMA DDI guideline CPMP/EWP/560/95/Rev. 1 Corr. 2**). No DDI study has however been performed to investigate the effect of repotrectinib on oral hormonal contraceptives. *In vivo* net induction of CYP3A4 (TPX-0005-01 midazolam sub-study) and *in vitro* induction of CYP2C enzymes, respectively, have been demonstrated for repotrectinib, thus there is a risk of an effect on steroid metabolism through enzyme induction mediated by the PXR pathway. The lack of data, as well as precautions to be taken, are adequately reflected in relevant sections of the SmPC.

Pharmacodynamics

Mechanism of action

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 several human cancer cell lines expressing the targeted fusion oncogenes ROS1, TRKA, TRKB, TRKC, and corresponding mutations. See section 2.5.6.

Concentration-QTc

As a class, TKIs are associated with QTc interval prolongation which increases the risk of life-threatening arrythmias. The QTc prolongation potential of repotrectinib has been investigated using concentration-QTc modelling based on PK-matched ECGs collected in healthy subjects and patients across all submitted clinical studies in adults.

The integrated nonclinical and clinical QT/QTc assessment (in accordance with E14/S7B Q&A, EMA/CHMP/ICH/415588/2020) do not indicate a high likelihood of proarrhythmic effects due to delayed repolarisation. No clear relationship between exposure levels and occurrence of QTc interval prolongation was observed in the concentration-QTc model analysis, however ΔQTc (upper bound) increases above 10 msec and sporadically above 20 msec was observed across doses and prandial states investigated. Considering the uncertainties/limitations in the concentration-QTc analysis as well as in the non-clinical investigations, interpretation of these QTc results is difficult. Importantly, the available safety data indicate that cardiac toxicity, including QT prolongation, is not of concern.

Relationship between plasma concentration and effect and safety

The exposure-response analyses suggested decreasing efficacy in ROS+ NSCLC patients at lower exposure, and increased risk of Gr2+ dizziness and DRDI at higher exposure but are hampered by several uncertainties and considered explorative and of low regulatory impact.

The exposure efficacy analyses were based on data from one dose level (160 mg QD/BID) and the repotrectinib exposure range in the analyses is therefore limited.

Dose justification/dose response studies

No formal dose-response study has been performed. The RP2D was chosen based on results from the dose escalating part in TRIDENT-1 phase 1 and explorative popPK/ER efficacy and safety investigations. Only one dose level was taken forward to phase 2, and limited efficacy and safety data is available from other dose levels (see efficacy part). Overall, the proposed adult dose was used in, and is therefore supported by, the pivotal efficacy and safety phase 2 part of the TRIDENT-1 study. The proposed dose in adolescents is based primarily on adult exposure matching.

2.6.4. Conclusions on clinical pharmacology

Repotrectinib pharmacokinetics have been adequately described in healthy subjects and in patients.

The NTRK indication in adolescents relies on extrapolation of pivotal adult data through PK exposure matching under the assumption of similarity of disease and response to treatment. Based on the totality of available data, the adult dose of 160 mg QD/BID is acceptable for adolescents across the expected body weight range.

Studies investigating the potential for repotrectinib perpetrator and victim DDIs involving CYPs and transporters, and effects of moderate and severe hepatic impairment on repotrectinib PK are ongoing/planned and will be submitted post-authorisation.

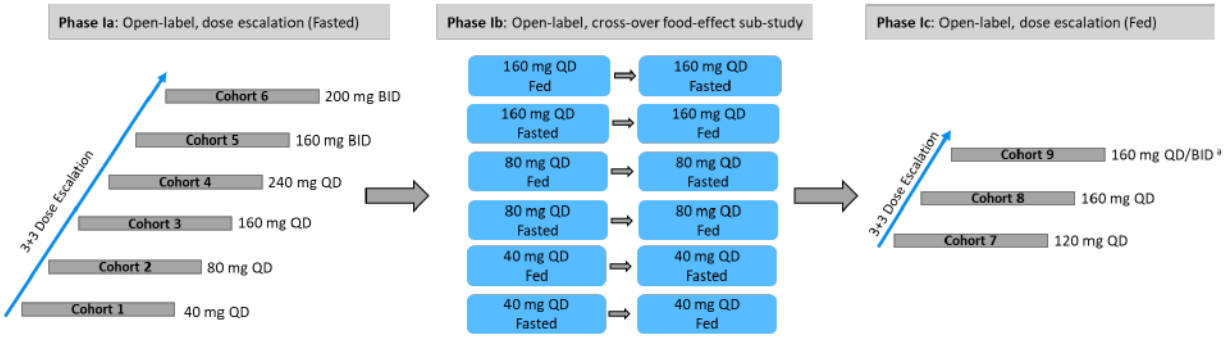
2.6.5. Clinical efficacy

2.6.5.1. Dose response study

The primary objectives of TRIDENT-1 Phase 1 were to determine the first cycle dose-limiting toxicities (DLTs), MTD and RP2D of repotrectinib given to adult subjects with advanced solid malignancies

harbouring an ALK, ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement. The overall study schematic for Phase 1a, Phase 1b, and Phase 1c is provided in Figure 7. Refer to Clinical Pharmacology for further study details.

Figure 7. Schema of Phase 1a, Phase 1b, and Phase 1c



Abbreviations: BID = twice a day; QD = once a day.
[a] 160 mg QD for 7 days followed by 160 mg BID

Overall, 93 subjects were enrolled and received at least one dose of repotrectinib across all dose cohorts in phase 1a, 1b and 1c (data cutoff 20 June 2022). There were 3 subjects with DLTs, and the MTD (based on first cycle DLTs) was not reached. The most common TEAE was dizziness that was reported in 61% of subjects. Two DLTs of dizziness as assessed by the Investigator were reported within the first 14 days of treatment: one at 240 mg QD and one at 160 mg BID dose levels. One subject at the 160 mg BID level met the DLT criteria with an event of grade 3 dyspnoea and hypoxia. The preliminary efficacy analysis (data cutoff 04-Mar-2019) demonstrated clinical activity in ROS1-positive NSCLC and NTRK1-3-positive advanced solid tumours across the studied dose range. In TKI pretreated- ROS1-positive NSCLC subjects repotrectinib doses ≥ 160 mg QD demonstrated a higher ORR (n = 6 of 11, 55%) compared with lower doses of < 160 mg QD (ORR n = 1 of 7, 14%). In TKI-naïve subjects, clinical activity was observed across all dose levels, yet at the doses of ≥ 160 mg QD the confirmed ORR was highest (n = 5 of 6, 83%). Further, the integrated PK/pharmacodynamic simulations supported dose titration from 160 mg QD to 160 mg BID to maximize PK/pharmacodynamic exposure coverage.

Taken together, based on the preliminary safety, clinical activity, available PK data, as well as the results of preliminary population PK modelling and exploratory ER analyses obtained from Phase 1 study, RP2D for Phase 2 study was selected as 160 mg QD (taken with or without food) for the first 14 days, after which the dose may be increased to 160 mg BID based on subject safety and tolerability and assuming specific criteria are met.

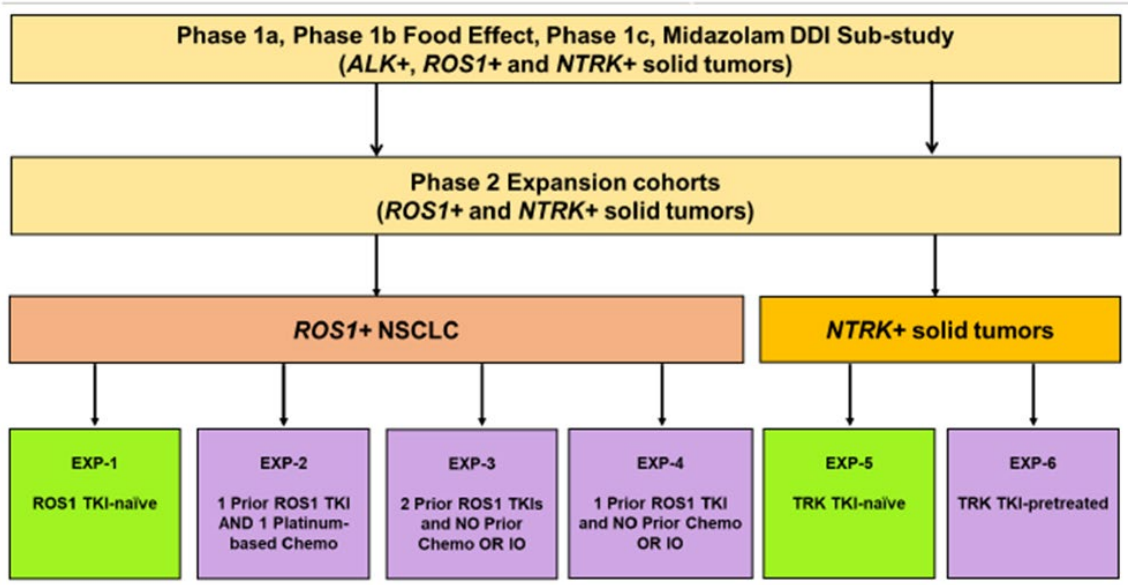
2.6.5.2. Main study

TRIDENT-1 is an ongoing Phase 1/2, open-label, single-arm, multi-centre, first-in-human study of the safety, tolerability, PK, pharmacokinetics, and anti-tumour activity of repotrectinib (TPX-0005) as a single agent in patients with advanced solid tumours harbouring ALK, ROS1 or NTRK1-3 rearrangements.

Phase 1 is further described and assessed in section 3.2 Dose response study(ies). Phase 2 includes 6 different expansion cohorts (EXP-1 to EXP-6). Phase 2 data are presented in two documents; the CSR which focuses on subjects with ROS1+ NSCLC (EXP-1 to EXP-4) and the CSR addendum which focuses on subjects with NRTK+ solid tumours (EXP-5 and EXP-6) as well as an update to the ROS1-positive NSCLC efficacy data, with an additional 6 months of follow-up since the original CSR. Integrated

analyses of efficacy, pooling the Phase 2 population with eligible patients from Phase 1, were presented in the clinical overview.

Figure 8. Study schema phase 1/2 TRIDENT-1



Abbreviations: ALK+ = anaplastic lymphoma kinase-positive; chemo = chemotherapy; DDI = drug-drug interaction; EXP = expansion cohort; IO = immunotherapy; NSCLC = non-small cell lung cancer; NTRK+ = neurotrophin receptor kinase-positive; ROS1 = receptor tyrosine kinase encoded by the *ROS1* gene; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase.

Study TPX-0005-01 (TRIDENT-1)

Methods

- ***Study Participants***

Key inclusion criteria all cohorts:

- Histologically or cytologically confirmed diagnosis of locally advanced, or metastatic solid tumour (including primary CNS tumours) that harbours a *ROS1* or *NTRK1-3* gene fusion. Locally advanced disease is defined as Stage III when subject is not a candidate for surgery, radiation, or multi-modality therapy and metastatic disease is defined as Stage IV.
- Subject must have a documented *ROS1* or *NTRK1-3* gene fusion determined by tissue based local testing using either:

  a) a next-generation sequencing (NGS) or quantitative polymerase chain reaction (qPCR) test will be accepted to determine molecular eligibility.
     - Adequate tumour tissue needs to be sent to the Sponsor designated central diagnostic laboratory for retrospective confirmation by a central diagnostic laboratory test selected by the Sponsor. In cases where archived tumour tissue is not available, a de novo biopsy should be obtained at Screening or as soon as possible after enrolment.
     - If NGS was used, the partner of the fusion target gene needs to be identified.

  b) a fluorescence in situ hybridisation (FISH) test AND prospective confirmation of fusion status by a central diagnostic laboratory test selected by the Sponsor BEFORE enrolment will be accepted to determine molecular eligibility.
- Age ≥ 12 (or age ≥ 20 as required by local regulation)

- ECOG performance status 0-1 (≥ 18 years) **or** Karnofsky score of at least 50 (16 to < 18 years) **or** Lansky score of at least 50 (< 16 years)
- At least one measurable target lesion according to RECIST v.1.1 prospectively confirmed by Blinded Independent Central radiology Review (BICR), before enrolment. Subjects with CNS-only measurable disease ≥ 10 mm as defined by RECISTv.1.1 are eligible.
- Subjects with asymptomatic CNS metastases (treated or untreated) and/or asymptomatic leptomeningeal carcinomatosis are eligible to enrol if they satisfy the following criteria:
    - Subjects requiring steroids at a stable or decreasing dose (≤ 12 mg/day dexamethasone or equivalent) for at least 14 days are eligible.
    - Subjects on stable doses of levetiracetam (same dose for 14 days).
    - A minimum of 14 days must have elapsed from the completion of whole brain radiation treatment (WBRT) before the start of treatment with repotrectinib, and all side effects (with the exception of alopecia) from WBRT are resolved to grade ≤ 1.
    - A minimum of 7 days must have elapsed from the completion of stereotactic radiosurgery before the start of treatment with repotrectinib, and all side effects (with the exception of alopecia) from stereotactic radiosurgery are resolved to grade ≤ 1.
- Normal baseline laboratory values
- Ability to swallow capsules intact without chewing, crushing or opening.

Key exclusion criteria:

- Major surgery within 4 weeks before start of repotrectinib treatment
- Radiation therapy within 2 weeks of study entry. Palliative radiation (≤ 10 fractions) must have been completed at least 48 hours before study entry.
- Clinical significant cardiovascular disease including clinically relevant abnormalities in resting EKG (e.g. prolonged QT-interval)
- Any factors that increase risk of QTc prolongation (e.g. hypokalaemia, congenital long QT syndrome, heart failure etc)

- ***Treatments***

Subjects take repotrectinib orally 160 mg QD for the first 14 days. The dose may be increased based on the treating physician's evaluation of subject tolerability on Cycle 1 Day 15. Subjects who have no grade ≥ 3 TRAEs; unmanageable grade ≥ 2 dizziness, ataxia, or paraesthesia; or grade ≥ 3 clinically significant laboratory abnormalities while on 160 mg QD may increase their dose to 160 mg BID. Subjects receive treatment until documented progression of disease or death due to any cause.

Dosing is at a consistent time each day; QD and BID dosing is separated by approximately 24 hours (± 2 hours) and 12 hours (± 1 hour), respectively. The subject keeps a daily diary to record dosing compliance. Repotrectinib can be taken with or without food.

Dose modifications may occur in 2 ways:

- Within a cycle: dosing interruption until adequate recovery followed by dose reduction, if required, during a given treatment cycle; this may persist delaying the start of a new cycle.
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle

For Phase 2 portion of the study, recommended dose reduction guidance is summarized in the Table below:

Table 8. Recommended dose reduction guidance for phase 2

Dose level	160 mg QD	160 mg BID
First dose reduction	120 mg QD	120 mg BID
Second dose reduction	80 mg QD	80 mg BID
If any further dose reduction is needed	Discuss with Medical Monitor	Discuss with Medical Monitor

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first cycle in Phase 1 but they may be used to treat treatment-emergent neutropenia or anaemia in Phase 2 as indicated by the current American Society of Clinical Oncology (ASCO) guidelines. Erythropoietin may be used at the Investigator's discretion for the supportive treatment of anaemia.

Moderate inducers of CYP3A, such as dexamethasone or other glucocorticoids, may be used at the discretion of the Investigator. Seizure prophylaxis with non–enzyme-inducing anti-epileptic drugs (non-EIAEDs) is allowed during the study for subjects with controlled asymptomatic CNS involvement. Prompt medical intervention is recommended at the first sign of appearance of cutaneous toxicity including topical or oral corticosteroids if required according to Investigator's judgment.

Objectives and endpoints

Table 9. TRIDENT-1 Efficacy Objectives and Endpoints

Objectives	Endpoints	Endpoint Description
Primary		
Determine the confirmed ORR as assessed by BICR of repotrectinib in each subject population expansion cohort of solid tumours that harbor a ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement.	ORR by BICR per RECIST v1.1 in each expansion cohort	ORR was defined as the proportion of subjects with a confirmed CR or PR. A confirmed response is a response that persists on a repeat-imaging performed at least 4 weeks after initial documentation of response. Subjects with a confirmed objective response (CR or PR) were referred to as responders. Non-responders included subjects without a confirmed objective response, stable disease, or PD.
Secondary		
Determine the duration of response (DOR), TTR, and clinical benefit rate (CBR) of repotrectinib, as assessed by BICR, in each subject population expansion cohort of advanced solid tumours that harbor a ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement.	DOR, TTR, and CBR by BICR	DOR was defined from the first date of objective response (either CR or PR) to first documentation of radiographic disease progression, as assessed by RECIST v1.1. TTR was defined as the time from the first dose of repotrectinib to the first documentation of objective response (either CR or PR), as assessed by RECIST v1.1. CBR was defined as the proportion of subjects with CR, PR, or SD. Stable disease refers to a condition where the tumour is neither increasing nor decreasing in extent or severity for at least 6 weeks after the first dose of repotrectinib, as assessed by RECIST v1.1.
Estimate the progression-free survival (PFS) and overall survival (OS) of subjects treated with repotrectinib with advanced solid tumours that harbor a ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement.	PFS and OS	PFS was defined as the time from the first dose of repotrectinib to first documentation of radiographic disease progression by BICR using RECIST v1.1 or death due to any cause (whichever occurs first). OS was defined as the time from the first dose of repotrectinib to the date of death due to any cause.
Determine the intracranial objective response rate (IC-ORR) of repotrectinib and central nervous system progression-free survival (CNS-PFS) in subjects presenting with measurable brain metastases at baseline, using Response Assessment in Neuro-Oncology Brain Metastases modified RECIST v1.1 assessment.	IC-ORR and CNS-PFS	Intracranial ORR was defined as the percent of subjects with PR/CR based on the assessment of intracranial target lesions, non-target lesions, and new lesions in subjects with measurable CNS metastasis at baseline. CNS-PFS was defined as the time from the first dose of repotrectinib to first evidence of radiographic CNS disease progression or death due to any cause (whichever occurs first) + 1 day.
Exploratory (All Descriptive)		
Explore association between ORR by subgroups including demographic and baseline risk factors in each expansion cohort.		ORR was defined as above.

Table 10. Success criteria for Expansion cohorts 1-6

Cohort	Prespecified limit of ORR defining success
EXP-1 ROS1 TKI-Naïve ROS1+ NSCLC	ORR (lower 95% CI)> 66% Considered superior to crizotinib.
EXP-2 1 Prior ROS1 TKI AND 1 Platinum-based Chemotherapy ROS1+ NSCLC	ORR (lower 95% CI)> 23% Considered superior to currently approved chemotherapy in the second line setting for NSCLC in this subject expansion cohort including the combination of docetaxel + ramucirumab
EXP-3 2 Prior ROS1 TKI and NO Chemotherapy or Immunotherapy ROS1+ NSCLC	ORR (lower 95% CI)> 10% Considered efficacious
EXP-4 1 Prior ROS1 TKI and NO Chemotherapy or Immunotherapy ROS1+ NSCLC	ORR (lower 95% CI)> 35% Considered superior to first line chemotherapy in NSCLC
EXP-5 TRK TKI-Naïve NTRK+ Solid Tumours	ORR (lower 95% CI)> 35% Considered efficacious
EXP-6 TRK TKI-Pretreated NTRK+ Advanced Solid Tumours	ORR (lower 95% CI)> 10% Considered efficacious

Sample size

Table 11. Sample size justification for Expansion cohorts 1-6

Cohort	Sample size justification
EXP-1 ROS1 TKI-Naïve ROS1+ NSCLC N=110	For the ROS1 TKI-naïve expansion cohort, if the ORR is 66% or less, then it is assumed that repotrectinib is not adequately effective. If 44 out of 55 subjects have a confirmed objective response (ORR = 80%; 95% CI: 67.0 – 89.6) where the lower limit of the 95% CI is > 66%, repotrectinib is considered to be superior to the currently approved therapy in this subject expansion cohort, crizotinib (Xalkori® USPI, 2019). After enrolment of 55 subjects for the primary analysis, an additional 55 subjects are to be enrolled for a total of 110 subjects in EXP-1. If 88 out of 110 subjects have a confirmed objective response, the ORR (95% CI) will be 80% (71.3, 87.0) which will rule out an ORR ≤ 66% with at least 90% statistical power at the one-sided alpha level of 0.025 if the true ORR is 80%.
EXP-2 1 Prior ROS1 TKI AND 1 Platinum-based Chemotherapy ROS1+ NSCLC N=120	For this cohort, if the ORR is 23% or less, then it is assumed that repotrectinib is not effective. If 21 subjects out of 60 subjects have a confirmed objective response (ORR = 35 %; 95% CI: 23.1 – 48.4) where the lower limit of the 95% CI is > 23%, repotrectinib is considered to be superior to the currently approved chemotherapy in the second line setting for NSCLC in this subject expansion cohort including the combination of docetaxel + ramucirumab (Cyramza® USPI, 2020) which has an ORR of 23% (95% CI: 20 – 26). After enrolment of 60 subjects in the EXP-2 cohort as for the primary analysis, an additional 60 subjects are to be enrolled for a total of 120 subjects in EXP-2.

Cohort	Sample size justification
EXP-3 2 Prior ROS1 TKI and NO Chemotherapy or Immunotherapy ROS1+ NSCLC N=80	For this cohort, if the ORR is 10% or less, then it is assumed that repotrectinib is not effective. If 10 subjects out of 40 subjects have a confirmed objective response (ORR = 25.0%; 95% CI: 12.7 – 41.2) where the lower limit of 95% CI >10%, repotrectinib will be considered efficacious in this cohort. After enrolment of 40 subjects in the EXP-3 cohort for the primary analysis, an additional 40 subjects are to be enrolled for a total of 80 subjects in EXP-3.
EXP-4 1 Prior ROS1 TKI and NO Chemotherapy or Immunotherapy ROS1+ NSCLC N=120	Assuming a target ORR of 50%, with a sample size of 60, the 95% CI will be 36.8% - 63.2% with the lower bound greater than 35%, which shows a superiority to first line chemotherapy in NSCLC. The ORR from platinum-based doublets or in combination with bevacizumab was in the range 25 – 35% (Abraxane® USPI, 2019; Alimta® USPI, 2019; Gemzar® USPI, 2019; Taxotere® USPI, 2019; Avastin USPI, 2009). After enrolment of 60 subjects in the EXP-4 cohort for the primary analysis, an additional 60 subjects are to be enrolled for a total of 120 subjects in EXP-4.
EXP-5 TRK TKI-Naïve NTRK+ Solid Tumours N=110	For the TRK-naïve expansion cohort, if the ORR is 35% or less, then it is not considered as effective. If 27 subjects out of 55 subjects have a confirmed objective response (ORR = 49.1%; 95% CI: 35.4 – 62.9) where the lower limit of the 95% CI is > 35%, repotrectinib is considered to be efficacious in this subject expansion cohort. After enrolment of 55 subjects in the EXP-5 cohort for the primary analysis, an additional 55 subjects are to be enrolled for a total of 110 subjects in EXP-5
EXP-6 TRK TKI-Pretreated NTRK+ Advanced Solid Tumours N=80	For this cohort, if the ORR is 10% or less, then it is assumed that repotrectinib is not effective. If 9 out of 40 subjects have a confirmed objective response (ORR = 22.5%; 95% CI: 10.8 – 38.5) where the lower limit of 95% CI >10%, repotrectinib will be considered efficacious in this cohort. After enrolment of 40 subjects in the EXP-6 cohort for the primary analysis, an additional 40 subjects are to be enrolled for a total of 80 subjects in EXP-6.

Randomisation and blinding (masking)

N/A

Statistical methods

The study population to be used for efficacy assessment was the Full Analysis Set (FAS) consisting of all subjects who received at least 1 full or partial dose of repotrectinib. This was the same as the safety analysis set. Subjects were classified according to the assigned treatment (dose cohort for Phase 1 and study cohort for Phase 2). All analyses were to be performed by cohort, except when it was deemed necessary to pool them together.

For Phase 2, the FAS was to be used for the summary of subject dispositions, demographics, baseline characteristics, and utilized for the safety and primary efficacy analysis.

The primary endpoint was ORR by BICR, to be reported as the proportion of responders along with the corresponding 2-sided 95% Clopper-Pearson exact CI

Time to event endpoints (DOR, PFS, CNS-PFS and OS) were estimated using the Kaplan-Meier method and was to be displayed graphically where appropriate. The median event time (if appropriate) and 2-sided 95% CI for the median were provided. Landmark survival probabilities at 6 (DOR only), 12 and 18 months were to be tabulated with number and percent. Intercurrent events for DoR were to be handled as described in the table below.

Table 12. Intercurrent event strategies for time to event endpoints

Situation	Date of Event of Censoring	Outcome
No documented radiologic progression	Date of last tumour assessment with documented non-progression	Censored
Death or radiologic progression after two or more consecutive missed scheduled visits for tumour assessment	Date of last tumour assessment with documented non-progression	Censored
Documented radiologic progression before or after start of new anticancer therapy or tumour-related surgery	First date of tumour assessment with documented progression regardless of the timing of the new anticancer therapy or tumour-related surgery	Event
Death without documented radiologic progression within two tumour assessments window after last evaluable tumour assessment	Date of death	Event
No evaluable baseline or post-baseline tumour assessment with no documented death **(Applicable for PFS only)**	Date of first dose of study treatment	Censored

The IC-ORR and its 95% CI was to be estimated following same methods as ORR. Time to Response (TTR) was to be presented using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Clinical Benefit Rate (CBR) and its 95% CI were to be estimated using Clopper-Pearson exact confidence interval.

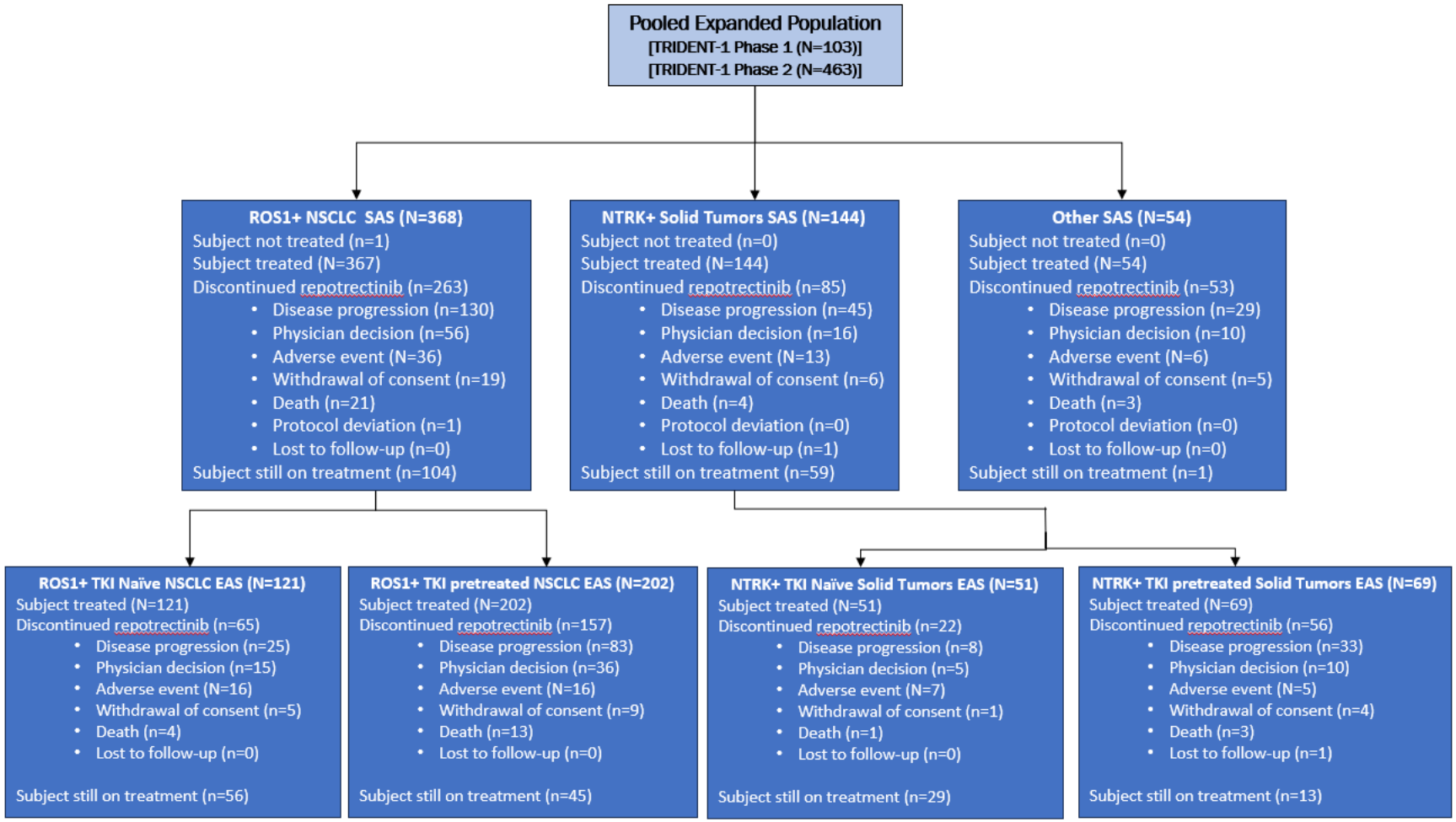
No multiplicity adjustment was planned, and the six cohorts were treated as six independent single arm trials. No interim analysis was planned. Only the primary endpoint was seen as inferential.

Results

Participant flow

Of the 200 screening failures, the majority occurred in USA or China and were mostly due to absence of ROS1 or NTRK fusion or presence of non-measurable disease by BICR assessment. By the time of the 15 Oct 2023 DCO, 566 (565dosed) subjects were enrolled across all treatment cohorts of the Phase 1 and Phase 2 study. Of these, 368 ROS1+ NSCLC subjects and 144 NTRK+ subjects were enrolled. 104 (28,2%) and 59 (40,9%) of the participants were still on treatment in the ROS1+ NSCLC and NTRK+ solid tumour population, respectively.

Figure 9. Subject Disposition (pooled expanded dataset, DCO 15 Oct 2023)



Clarification: The numbers in this figure correspond to the overall disposition of patients, but in the following sections, certain cohorts and pools were selected for the efficacy datasets based on sufficient follow-up to assess response.

Recruitment

TRIDENT-1 was initiated 07 March 2017 (phase 1, first patient first visit (FPFV)). Initiation of phase 2 occurred on 28 June 2019 (FPFV). Enrolment into Phase 1 is completed and EXP-1-4 of Phase 2 is stopped. Last patient first visit (LPFV) is anticipated in December 2026 for the NTRK cohorts of TRIDENT-1, and last patient last visit (LPLV) is anticipated in February 2028. A majority of participants in Phase 1 and Phase 2 are recruited form study sites in the USA, China and South Korea.

Conduct of the study

The phase 2 of the study is conducted at 152 study sites in 19 countries: Austria, Belgium, Canada, China, Germany, Denmark, Spain, France, UK, Hong Kong, Hungary, Italy, Japan, South Korea, The Netherlands, Poland, Singapore, Taiwan and US.

Nearly all the patients from phase 1 were recruited in the USA and Singapore.

Protocol amendments

The original global protocol TPX-0005-01 document (dated 29 September 2016) was amended 12 times in total. Protocol versions 1-6 were written prior to study initiation 20 Aug 2019, whereas later amendments, versions 7-13, were made while the study was ongoing.

Table 13. Global Protocol Versions of Trident-1 Study

Protocol Version	Date	Subject Enrollment[a] Phase 1 = P1 Phase 2 = P2	Category	Main Change	Rationale
Original Version 1	29-Sep-2016	0		N/A	
Version 2.0. Amendment 1	3-Nov-2016	0	Change in inclusion criteria	Modified Inclusion Criterion for EXP-1: *ROS1*-positive NSCLC and EXP-4: ALK+ NSCLC, EXP-9: ALK+ non-NSCLC, *ROS1*-positive non-NSCLC, or *NTRK*-positive solid tumours cohorts would not start to enroll until a RP2D was determined AND clinical activity of repotrectinib was established in treatment-refractory patients.	Initiate Phase 2 enrollment after determination of RP2D and establishment of study drug clinical activity
Version 3.0. Amendment 2	5-Jun-2018	P1: 70	Sample size recalculations and updating of SAP	Updated the SAP and Sample Size Justification section with current findings, and the recalculated estimated ORR and 95% CI for the targeted subject enrolment numbers.	Update SAP due to recent data
Version 4.0. Amendment 3	2-Nov-2018	P1: 73	Change/ adjusting of endpoints	Clarified that the Phase 2 primary objective to determine the confirmed ORR was the confirmed ORR as assessed by BICR	Clarity cORR assessed by BICR
				Changed the Phase 2 secondary objective assessment to determine IC-ORR and CNS-PFS from RECIST v1.1 to Response Assessment in Neuro-Oncology-Brain	Update endpoint assessment for alignment with standard practice
				Updated the study design of the Phase 2 study to modify cohorts (total of 6 instead of 8)	Update study design to reflect the population of participants
Version 5.0. Amendment 4	20-May-2019	P1: 87	• Change/ adjusting of endpoints	Changed the Phase 2 secondary objective assessment to determine IC-ORR and CNS-PFS from RANO-BM to modified RECIST	Update endpoint assessment for alignment with standard practice Include a secondary objective to ensure PK analysis

Protocol Version	Date	Subject Enrollment[a] Phase 1 = P1 Phase 2 = P2	Category	Main Change	Rationale
				Added new secondary objective for Phase 2 to confirm PK of repotrectinib at the RP2D	Include a secondary objective to ensure PK analysis
			• Change in inclusion criteria	Clarified that Phase 2 of the study would start after determination of the RP2D as the MTD might not be reached	Clarity the initiation of Phase 2 after determination of RP2D
				Defined that RP2D dose was 160 mg QD for the first 14 days and may be increased to 160 mg BID	Establish RP2D
				Added dose modification guidelines for dose reduction and dose escalation in Phase-2	Include dose modification guidance for safety
			• Sample recalculations	Modified the total number of subjects required across all six cohorts in Phase 2 to approximately 320 subjects, which included 5 additional subjects in EXP-1 (ROS1 TKI-Naïve *ROS1*-positive NSCLC) and 5 additional subjects in EXP-5 (TRK TKI-Naïve *NTRK*-positive Solid Tumours)	Update the required number of subjects to reflect sample size
				Clarified that the FAS set would be utilized for the summary of subject dispositions, demographics, baseline characteristics, and the safety and primary efficacy analysis in Phase 2	Clarity FAS set
Version 6.0. Amendment 5	7-Jun-2019	P1: 88	Change in inclusion criteria	Amended eligibility criteria to exclude the pediatric patient population (patients age 12 to 17) per regulatory request	Update per Regulatory request
Version 7.0. Amendment 6	13-Nov-2019	P1: 95 P2: 5	Sample recalculations	Due to limited clinical activity reported in previously treated ALK+ NSCLC subjects, further investigation of repotrectinib in this subject population in Phase 2 was no longer planned; thus, all references to the ALK+ subject population were	Remove ALK+ eligibility due to limited clinical activity in this population

Protocol Version	Date	Subject Enrollment[a] Phase 1 = P1 Phase 2 = P2	Category	Main Change	Rationale
				removed throughout the protocol for Phase 2; Modified the sample size for Phase 2 EXP-4 to N = 30.	
Version 8.0. Amendment 7	2-Jan-2020	P1: 95 P2: 10	Change in inclusion criteria	Modified Inclusion Criterion with removing option to utilize the Memorial Sloan Kettering Center IMPACT™ test for documentation of a *ROS1* or *NTRKI-3* gene fusion.	Clarify testing for ROS1 or NTRK1-3 gene fusion
				Modified Inclusion Criterion with adding EXP-4 to expansion cohorts requiring a washout time related to prior TKI treatment.	Clarify washout time for EXP-4
Version 9.0. Amendment 8	23-Mar-2020	P1: 97 P2: 32	1) Change in inclusion criteria	Modified Phase 2 Inclusion Criterion #2 requirements for prospective testing, allowing NGS or qPCR tests to be utilized for enrolment	Amend prospective testing requirements
			2) Updating/ specifying study procedures	Specified for the Phase 2 study that if an NGS or qPCR was used for local testing, the fusion status would be retrospectively confirmed using adequate tumour tissue by a central diagnostic laboratory test selected by the Sponsor and that prospective confirmation of a ROS1+ or NTRK+ gene fusion by a central diagnostic laboratory test selected by the Sponsor was required before enrolment if a FISH test was used for local testing	Clarify confirmation of gene rearrangement by central lab in the presence of local testing results
Version 10.0. Amendment 9	20-Oct-2020	P1: 99 P2: 81	• Change in inclusion criteria	Modified the Phase 2 Inclusion Criterion #7 for EXP-3 to remove requirement that all subjects in EXP-3 must have been previously treated with one line of platinum-based chemo/immuno-therapy due to limited activity of repotrectinib in 4th line setting (2 prior TKIs + 1 line chemotherapy)	Modify inclusion criterion based on the observed limited activity of repotrectinib in the 4th line setting
			• Sample recalculations	Modified the number of subjects for Phase 2 EXP-2 to N = 60 and EXP-4 to N = 60.	Adjust sample size

Protocol Version	Date	Subject Enrollment[a] Phase 1 = P1 Phase 2 = P2	Category	Main Change	Rationale
Version 11.0. Amendment 10	23-Jun-2021	P1: 101 P2: 165	Sample recalculation	Modified the number of subjects for enrolment in Phase 2 from approximately 320 to 365 by increasing enrolment in EXP-1 to N = 110, an additional 55 subjects, to allow continued enrolment in rest of world (China, Japan, EU, etc) along with the US sites in anticipation of future regulatory submission and to evaluate safety and efficacy in the regional patient populations	Increase diversity in enrollment to allow for regional safety evaluations in anticipation of future regulatory submissions
Version 12.0. Amendment 11	14-Jan-2022	P1: 101 P2: 267	Sample recalculations and updating of SAP	Increased the number of subjects enrolled in Phase 2 to approximately 620	Increase sample size
				Increased the planned enrolment in cohorts EXP-2 through EXP-6 as follows to allow continued enrolment in rest of world (China, Japan, EU, etc) along with the US sites in anticipation of future regulatory submission and to evaluate safety and efficacy in the regional patient populations: EXP-2 from n = 60 to n = 120; EXP-3 from n = 40 to n = 80; EXP-4 from n = 60 to n = 120; EXP-5 from n = 55 to n = 110; and EXP-6 from n = 40 to n = 80	Increase diversity in enrollment of cohorts to allow for regional safety and efficacy evaluations in anticipation of future regulatory submissions
				Clarified the statistical analysis language for EXP-4 that, assuming a target ORR of 50% with a sample size of 60, the lower bound of the 95% CI would be greater than 35%, which would show superiority to first line chemotherapy in NSCLC.	Clarity statistical analysis for EXP-4
Version 15.0, Amendment 14	16-Aug-2023	P1: 101 P2: 457	a. Updating / specifyin	Updated contraception language to align with BMS requirements	Align with Sponsor's contraceptive standards

Protocol Version	Date	Subject Enrollment[a] Phase 1 = P1 Phase 2 = P2	Category	Main Change	Rationale
			g study procedures		
			b. Sample recalculation	Increased sample size to 630 patients with additional enrollments in the EXP-5 and EXP-6 cohorts, while capping NSCLC enrollment	Update per Health Authority post marketing requirement

a Cumulative subject enrollment at the time of global protocol amendment released (amendment date)

Protocol amendments prior to study initiation (version 2-6) dealt with inclusion and exclusion criteria, added exploratory endpoints, clarified tests, time schedules and updated sample size justification.

In protocol version 5 (Amendment 4, May 2019) adolescents ≥ 12 years were added as an eligible age group. No data has been provided from TRIDENT-1 in this age group.

Protocol deviations:

Overall, for 63 (15.1%) of the totally 416 enrolled subjects at least one important protocol deviation was reported. The most commonly reported important deviation types (≥ 1% of all enrolled subjects) included informed consent (29 [7.0%] subjects), safety assessments (17 [4.1%] subjects), overdose or misuse (6 [1.4%] subjects) and prohibited co-medication (7 [1.7%] subjects). The majority of deviations (> 80%) related to informed consent and were due to delay in reconsenting on updated versions or using a wrong version of the ICF.

Table 14. Important protocol deviations (full analysis set, DCO 19 Dec 2022)

Deviation or Violation	*ROS1*-positive NSCLC Subjects (N=312)	*NTRK*-positive Solid Tumor Subjects (N=104)	Total (N=416)
Subjects with Important Deviations, n (%)	52 (16.7)	11 (10.6)	63 (15.1)
Important Deviation Type, n (%)			
Informed consent	25 (8.0)	4 (3.8)	29 (7.0)
Assessment - safety	13 (4.2)	4 (3.8)	17 (4.1)
Prohibited co-medication	5 (1.6)	2 (1.9)	7 (1.7)
Overdose/misuse	6 (1.9)	0	6 (1.4)
Lab/endpoint data	3 (1.0)	0	3 (0.7)
Assessment - efficacy	2 (0.6)	0	2 (0.5)
Inclusion	2 (0.6)	0	2 (0.5)
Other	1 (0.3)	1 (1.0)	2 (0.5)
Exclusion	1 (0.3)	0	1 (0.2)
Informed Consent and Process	1 (0.3)	0	1 (0.2)
Overdose / misuse - Drug accountability	1 (0.3)	0	1 (0.2)
Study Drug	0	1 (1.0)	1 (0.2)
Violation of ICH, GCP, CFR, ISO 14155:2011.	1 (0.3)	0	1 (0.2)
Visit Window	1 (0.3)	0	1 (0.2)

Notes:
"*ROS1*-positive NSCLC Subjects" includes 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 meet criteria for any cohort in protocol version 10.
"*NTRK*-positive Solid Tumor Subjects" includes expansion cohorts EXP-5 and EXP-6.
Percentages are based on the number of subjects in the Full Analysis Set.

Amendments to the Statistical Analysis Plan

There are four statistical analysis plans with amendments, all written after study initiation, and three after first DCO. The CSR is based on SAP phase 2 v1, but the analyses are not fully aligned introducing an efficacy evaluable set not mentioned in the SAP or any of the protocols.

- Integrated SAP for ROS1 cohorts where data from Phase 1 and 2 were to be combined.
    - 08.03.2021 Integrated SAP v1
    - 25.03.2022 Integrated SAP v2
    - 12.12.2022 Integrated SAP v3
- SAP for phase 2.
    - 25.03.2022 SAP phase 2 v1
    - 09.12.2022 SAP phase 2 v2
- SAP for phase 1.
    - 05.08.2022 SAP phase 1
- Integrated SAP for the NTRK population including patients from phase 1 and 2 of TRIDENT as well as patients from CARE.
    - 24.02.2023 Integrated SAP NTRK

Baseline data

Baseline data as well as outcome data are presented per cohort. Demographics and baseline characteristics presented for the ROS1+ NSCLC are based on the latest DCO of 15 Oct 2023. Subject demographic baseline data for the *pooled expanded* efficacy analysis sets are presented in the tables below. For the NTRK positive solid tumour population the baseline data are based on the DCO of 19 December 2022.

Overall, baseline demographic characteristics were balanced across cohorts and overall consistent with the distribution in the total population. Furthermore, the baseline data remained consistent between data cutoffs as well as between phase 2 and pooled data sets (ROS1+ NSCLC population).

Table 15. Subject demographics and disease characteristics by cohort- pooled expanded, ROS1+ NSCLC efficacy analysis set

		TKI-Pretreated				
	TKI-Naive EXP-1 (N=121)	EXP-2 (N=53)	EXP-3 (N=42)	EXP-4 (N=107)	Pooled pre-treated (N=202)	Total (N=323)
Phase, n (%)						
Phase 1	8 (6.6)	3 (5.7)	1 (2.4)	3 (2.8)	7 (3.5)	15 (4.6)
Phase 1a, 1b, and 1c	8 (6.6)	3 (5.7)	1 (2.4)	3 (2.8)	7 (3.5)	15 (4.6)
Midazolam Substudy	0	0	0	0	0	0
Phase 2	113 (93.4)	50 (94.3)	41 (97.6)	104 (97.2)	195 (96.5)	308 (95.4)
Age (years) [1]						
n	121	53	42	107	202	323
Mean	55.8	52.1	51.5	56.7	54.4	54.9
Standard Deviation	12.18	11.90	10.73	12.50	12.18	12.18
Median	57.0	55.0	50.5	57.0	55.0	56.0
Min, Max	28,93	27,72	29,74	33,81	27,81	27,93
Age Group, n (%)						
≥ 12 to < 18	0	0	0	0	0	0
≥ 18 to < 65	93 (76.9)	47 (88.7)	37 (88.1)	76 (71.0)	160 (79.2)	253 (78.3)
≥ 65 to < 75	22 (18.2)	6 (11.3)	5 (11.9)	22 (20.6)	33 (16.3)	55 (17.0)
≥ 75	6 (5.0)	0	0	9 (8.4)	9 (4.5)	15 (4.6)
Missing	0	0	0	0	0	0
Sex, n (%)						
Male	53 (43.8)	19 (35.8)	21 (50.0)	28 (26.2)	68 (33.7)	121 (37.5)
Female	68 (56.2)	34 (64.2)	21 (50.0)	79 (73.8)	134 (66.3)	202 (62.5)
Race, n (%)						
American Indian or Alaskan Native	2 (1.7)	0	0	0	0	2 (0.6)
Asian	73 (60.3)	29 (54.7)	22 (52.4)	45 (42.1)	96 (47.5)	169 (52.3)
Black or African American	3 (2.5)	1 (1.9)	0	4 (3.7)	5 (2.5)	8 (2.5)
Native Hawaiian or Other Pacific Islander	1 (0.8)	0	0	2 (1.9)	2 (1.0)	3 (0.9)
White	36 (29.8)	23 (43.4)	15 (35.7)	52 (48.6)	90 (44.6)	126 (39.0)
Other	0	0	0	0	0	0
Not Reported	5 (4.1)	0	4 (9.5)	3 (2.8)	7 (3.5)	12 (3.7)
Unknown	1 (0.8)	0	1 (2.4)	1 (0.9)	2 (1.0)	3 (0.9)
Ethnicity, n (%)						
Hispanic or Latino	6 (5.0)	0	0	3 (2.8)	3 (1.5)	9 (2.8)
Not Hispanic or Latino	114 (94.2)	53 (100.0)	40 (95.2)	101 (94.4)	194 (96.0)	308 (95.4)
Missing	1 (0.8)	0	2 (4.8)	3 (2.8)	5 (2.5)	6 (1.9)
Region[2], n (%)						

	TKI-Naive	TKI-Pretreated				
	EXP-1 (N=121)	EXP-2 (N=53)	EXP-3 (N=42)	EXP-4 (N=107)	Pooled pre-treated (N=202)	Total (N=323)
US	18 (14.9)	14 (26.4)	8 (19.0)	26 (24.3)	48 (23.8)	66 (20.4)
Asia	63 (52.1)	26 (49.1)	17 (40.5)	37 (34.6)	80 (39.6)	143 (44.3)
Other	40 (33.1)	13 (24.5)	17 (40.5)	44 (41.1)	74 (36.6)	114 (35.3)
Baseline ECOG Performance Status[3], n (%)						
0 - Fully Active	46 (38.0)	19 (35.8)	14 (33.3)	36 (33.6)	69 (34.2)	115 (35.6)
1 - Restricted in Physically Strenuous Activity	75 (62.0)	33 (62.3)	28 (66.7)	71 (66.4)	132 (65.3)	207 (64.1)
Missing	0	1 (1.9)	0	0	1 (0.5)	1 (0.3)
Height (cm)						
n	121	50	42	107	199	320
Mean	165.498	165.592	166.659	165.330	165.676	165.609
Standard Deviation	9.5967	9.6011	9.2730	9.2124	9.2911	9.3932
Median	164.000	163.550	167.350	165.000	165.000	164.750
Min, Max	149.6,192.0	151.2,189.0	149.6,187.9	149.0,187.0	149.0,189.0	149.0,192.0
Baseline Weight (kg)						
n	121	53	42	107	202	323
Mean	67.83	69.61	72.58	69.64	70.24	69.34
Standard Deviation	15.347	15.152	24.157	16.208	17.844	16.968
Median	64.00	69.40	69.25	68.30	69.00	66.70
Min, Max	40.5,123.2	42.7,113.0	41.0,140.2	39.5,119.3	39.5,140.2	39.5,140.2
Baseline Body Mass Index (BMI) (kg/m2)						
n	121	50	42	107	199	320
Mean	24.653	25.474	25.808	25.364	25.485	25.171
Standard Deviation	4.5209	4.9813	7.0744	5.0625	5.5004	5.1605
Median	23.915	24.200	23.882	24.185	23.999	23.938
Min, Max	17.3,45.1	17.7,44.1	18.1,46.0	17.0,40.9	17.0,46.0	17.0,46.0
Smoking Status, n (%)						
Current Smoker	4 (3.3)	0	0	1 (0.9)	1 (0.5)	5 (1.5)
Former Smoker	33 (27.3)	17 (32.1)	18 (42.9)	30 (28.0)	65 (32.2)	98 (30.3)
Never Smoked	76 (62.8)	33 (62.3)	23 (54.8)	73 (68.2)	129 (63.9)	205 (63.5)
Not Collected	8 (6.6)	3 (5.7)	1 (2.4)	3 (2.8)	7 (3.5)	15 (4.6)
Tumour Type, n (%)						
NSCLC	121 (100.0)	53 (100.0)	42 (100.0)	107 (100.0)	202 (100.0)	323 (100.0)
Histological Classification, n (%)						
CARCINOMA	1 (0.8)	0	0	0	0	1 (0.3)

	TKI-Naive	TKI-Pretreated				
	EXP-1 (N=121)	EXP-2 (N=53)	EXP-3 (N=42)	EXP-4 (N=107)	Pooled pre-treated (N=202)	Total (N=323)
PAPILLARY LUNG CARCINOMA	0	0	1 (2.4)	0	1 (0.5)	1 (0.3)
ADENOCARCINOMA	117 (96.7)	49 (92.5)	41 (97.6)	103 (96.3)	193 (95.5)	310 (96.0)
ADENOSQUAMOUS CARCINOMA	1 (0.8)	2 (3.8)	0	1 (0.9)	3 (1.5)	4 (1.2)
SQUAMOUS	2 (1.7)	1 (1.9)	0	1 (0.9)	2 (1.0)	4 (1.2)
MUCOEPIDERMAL CARCINOMA	0	0	0	1 (0.9)	1 (0.5)	1 (0.3)
NON-SQUAMOUS	0	1 (1.9)	0	0	1 (0.5)	1 (0.3)
UNKNOWN	0	0	0	1 (0.9)	1 (0.5)	1 (0.3)
Brain Metastasis per BICR[4], n (%)						
Yes	30 (24.8)	22 (41.5)	16 (38.1)	43 (40.2)	81 (40.1)	111 (34.4)
No	91 (75.2)	31 (58.5)	26 (61.9)	64 (59.8)	121 (59.9)	212 (65.6)
Brain Metastasis per Investigator[4], n (%)						
Yes	35 (28.9)	25 (47.2)	16 (38.1)	51 (47.7)	92 (45.5)	127 (39.3)
No	86 (71.1)	28 (52.8)	26 (61.9)	56 (52.3)	110 (54.5)	196 (60.7)
Time since Diagnosis (years)[5]						
n	121	53	42	107	202	323
Mean	1.08	2.70	3.36	1.95	2.44	1.93
Standard Deviation	2.319	1.993	4.598	2.132	2.839	2.733
Median	0.11	2.42	2.06	1.31	1.77	1.13
Min, Max	0.0,14.8	0.0,8.4	0.8,26.5	0.0,15.8	0.0,26.5	0.0,26.5
Stage at Diagnosis, n (%)						
I	8 (6.6)	1 (1.9)	1 (2.4)	2 (1.9)	4 (2.0)	12 (3.7)
II	5 (4.1)	2 (3.8)	1 (2.4)	3 (2.8)	6 (3.0)	11 (3.4)
III	12 (9.9)	6 (11.3)	3 (7.1)	5 (4.7)	14 (6.9)	26 (8.0)
IIIA	1 (0.8)	0	0	0	0	1 (0.3)
IIIB	12 (9.9)	3 (5.7)	0	7 (6.5)	10 (5.0)	22 (6.8)
IV	81 (66.9)	41 (77.4)	37 (88.1)	90 (84.1)	168 (83.2)	249 (77.1)
Missing	2 (1.7)	0	0	0	0	2 (0.6)
Unknown	0	0	0	0	0	0
Stage at Study Entry[6], n (%)						
III	4 (3.3)	0	3 (7.1)	0	3 (1.5)	7 (2.2)
IIIB	6 (5.0)	2 (3.8)	1 (2.4)	2 (1.9)	5 (2.5)	11 (3.4)

	TKI-Naive	TKI-Pretreated				
	EXP-1 (N=121)	EXP-2 (N=53)	EXP-3 (N=42)	EXP-4 (N=107)	Pooled pre-treated (N=202)	Total (N=323)
IV	111 (91.7)	51 (96.2)	38 (90.5)	105 (98.1)	194 (96.0)	305 (94.4)
Missing	0	0	0	0	0	0
Resistance Mutation[7]						
Solvent Front	0	9 (17.0)	15 (35.7)	11 (10.3)	35 (17.3)	35 (10.8)
Gatekeeper	0	0	0	2 (1.9)	2 (1.0)	2 (0.6)
Activating	0	0	0	0	0	0
Other	0	2 (3.8)	4 (9.5)	2 (1.9)	8 (4.0)	8 (2.5)
Mutation Negative	104 (86.0)	36 (67.9)	23 (54.8)	81 (75.7)	140 (69.3)	244 (75.5)
Mutation Status Unknown [8]	17 (14.0)	6 (11.3)	2 (4.8)	11 (10.3)	19 (9.4)	36 (11.1)

Note: Data cutoff date of 15-Oct-2023

TKI-Naive ROS1-positive NSCLC includes 8 Phase 1 TKI-Naive subjects who are eligible for pooling per SAP and all Phase 2 subjects enrolled in EXP-1.

TKI-Pretreated ROS1-positive NSCLC includes 7 Phase 1 subjects (3 in EXP-2, 1 in EXP-3, 3 in EXP-4) who are eligible for pooling per SAP and all Phase 2 subjects enrolled in EXP-2, EXP-3 and EXP-4.

Percentages are based on the number of subjects in the Expanded Efficacy Analysis Set (Pooled, ROS1-positive NSCLC).

[1] Age in years is calculated based on the number of years between the informed consent date and the birth date.

[2] Countries grouped to 'Other' include: Australia, Canada, Spain, France, United Kingdom, Italy, Poland.

[3] ECOG Performance Status (0 = Fully Active to 5 = Dead) is assessed for subjects ≥18 years.

[4] Brain metastasis present if target or non-target lesion selected in the brain at baseline.

[5] Time since diagnosis in years is calculated based on the number of years from diagnosis to inform consent date.

[6] III/IIIB = Locally Advanced, IV = Metastatic

[7] Subjects can be counted in more than one category.

[8] Mutation Status Unknown includes no sample, QC failure, invalid sample/assay type (i.e., tested before the initial TKI)

Table 16. Subject demographics and baseline disease characteristics by cohort in NTRK+ solid tumour subjects (pooled expanded efficacy analysis set)

	TKI-naïve Subjects (EXP-5) (N=51)	TKI-pretreated Subjects (EXP-6) (N=69)	Total (N=120)
Phase, n (%)			
Phase 1	5 (9.8)	4 (5.8)	9 (7.5)
Phase 1a, 1b, and 1c	5 (9.8)	4 (5.8)	9 (7.5)
Midazolam Substudy	0	0	0
Phase 2	46 (90.2)	65 (94.2)	111 (92.5)
Age (years) [1]			
n	51	69	120
Mean (SD)	59.5 (13.94)	54.2 (16.27)	56.4 (15.49)
Median	61.0	56.0	59.0
Min, Max	25, 84	18, 81	18, 84
Age Group, n (%)			
≥ 12 to < 18	0	0	0
≥ 18 to < 65	30 (58.8)	44 (63.8)	74 (61.7)
≥ 65 to < 75	15 (29.4)	20 (29.0)	35 (29.2)
≥ 75	6 (11.8)	5 (7.2)	11 (9.2)
Missing	0	0	0
Sex, n (%)			
Male	24 (47.1)	36 (52.2)	60 (50.0)
Female	27 (52.9)	33 (47.8)	60 (50.0)
Race, n (%)			
American Indian or Alaskan Native	0	0	0
Asian	26 (51.0)	21 (30.4)	47 (39.2)
Black or African American	2 (3.9)	2 (2.9)	4 (3.3)
Native Hawaiian or Other Pacific Islander	0	0	0
White	13 (25.5)	40 (58.0)	53 (44.2)
Other	1 (2.0)	0	1 (0.8)
Not Reported	9 (17.6)	6 (8.7)	15 (12.5)
Unknown	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	2 (3.9)	1 (1.4)	3 (2.5)
Not Hispanic or Latino	46 (90.2)	64 (92.8)	110 (91.7)
Missing	3 (5.9)	4 (5.8)	7 (5.8)
Region[2], n (%)			
US	8 (15.7)	24 (34.8)	32 (26.7)
Asia	23 (45.1)	15 (21.7)	38 (31.7)
Other	20 (39.2)	30 (43.5)	50 (41.7)
Baseline ECOG Performance Status[3], n (%)			
0 - Fully Active	23 (45.1)	27 (39.1)	50 (41.7)
1 - Restricted in Physically Strenuous Activity	28 (54.9)	42 (60.9)	70 (58.3)
Missing	0	0	0
Height (cm)			
n	51	69	120
Mean (SD)	166.667 (9.2992)	169.055 (9.2086)	168.040 (9.2842)
Median	168.000	168.000	168.000
Min, Max	144.00, 187.00	148.00, 188.50	144.00, 188.50
Baseline Weight (kg)			
n	51	69	120

	TKI-naïve Subjects (EXP-5) (N=51)	TKI-pretreated Subjects (EXP-6) (N=69)	Total (N=120)
Mean (SD)	65.78 (11.864)	75.50 (18.431)	71.37 (16.630)
Median	64.70	72.90	70.00
Min, Max	44.8, 93.5	42.0, 116.3	42.0, 116.3
Baseline Body Mass Index (BMI) (kg/m2)			
n	51	69	120
Mean (SD)	23.651 (3.6772)	26.181 (4.9788)	25.106 (4.6286)
Median	23.175	26.304	24.630
Min, Max	17.92, 31.60	16.41, 38.22	16.41, 38.22
Smoking Status, n (%)			
Current Smoker	4 (7.8)	2 (2.9)	6 (5.0)
Former Smoker	18 (35.3)	23 (33.3)	41 (34.2)
Never Smoked	24 (47.1)	40 (58.0)	64 (53.3)
Not Collected	5 (9.8)	4 (5.8)	9 (7.5)
Tumour Type, n (%)			
NSCLC	27 (52.9)	17 (24.6)	44 (36.7)
Salivary Gland Cancer	5 (9.8)	12 (17.4)	17 (14.2)
Sarcoma, Soft Tissue	3 (5.9)	10 (14.5)	13 (10.8)
Thyroid Cancer	6 (11.8)	7 (10.1)	13 (10.8)
Colorectal Cancer	2 (3.9)	4 (5.8)	6 (5.0)
Glioblastoma	1 (2.0)	3 (4.3)	4 (3.3)
Breast Cancer	2 (3.9)	1 (1.4)	3 (2.5)
Cholangiocarcinoma	1 (2.0)	2 (2.9)	3 (2.5)
Neuroendocrine Tumour	0 (0.0)	3 (4.3)	3 (2.5)
Pancreatic Cancer	0 (0.0)	3 (4.3)	3 (2.5)
Peripheral Nerve Sheath Tumour	1 (2.0)	2 (2.9)	3 (2.5)
Cervical Cancer	0 (0.0)	1 (1.4)	1 (0.8)
Esophageal Cancer	1 (2.0)	0 (0.0)	1 (0.8)
GIST	0 (0.0)	1 (1.4)	1 (0.8)
Gallbladder Cancer	0 (0.0)	1 (1.4)	1 (0.8)
Head and Neck Cancer	1 (2.0)	0 (0.0)	1 (0.8)
Mucoepidermoid Carcinoma	0 (0.0)	1 (1.4)	1 (0.8)
Prostate Cancer	1 (2.0)	0 (0.0)	1 (0.8)
Unknown Primary Cancer	0 (0.0)	1 (1.4)	1 (0.8)
Histological Classification, n (%)			
ADENOCARCINOMA	31 (60.8)	32 (46.4)	63 (52.5)
PAPILLARY THYROID CARCINOMA	6 (11.8)	3 (4.3)	9 (7.5)
SECRETORY CARCINOMA	2 (3.9)	4 (5.8)	6 (5.0)
SARCOMA	1 (2.0)	4 (5.8)	5 (4.2)
SPINDLE CELL SARCOMA	0 (0.0)	5 (7.2)	5 (4.2)
GLIOBLASTOMA	1 (2.0)	3 (4.3)	4 (3.3)
NEUROENDOCRINE	1 (2.0)	3 (4.3)	4 (3.3)
SQUAMOUS	3 (5.9)	1 (1.4)	4 (3.3)
MALIGNANT PERIPHERAL NERVE SHEATH NEOPLASM	1 (2.0)	2 (2.9)	3 (2.5)
CARCINOMA	0 (0.0)	2 (2.9)	2 (1.7)
FIBROSARCOMA	1 (2.0)	1 (1.4)	2 (1.7)
ACINIC CELL CARCINOMA	0 (0.0)	1 (1.4)	1 (0.8)
ANGIOSARCOMA	1 (2.0)	0 (0.0)	1 (0.8)

	TKI-naïve Subjects (EXP-5) (N=51)	TKI-pretreated Subjects (EXP-6) (N=69)	Total (N=120)
ATYPICAL CARCINOID	0 (0.0)	1 (1.4)	1 (0.8)
CHOLANGIOSARCOMA	0 (0.0)	1 (1.4)	1 (0.8)
ENDOMETRIAL STROMAL SARCOMA	1 (2.0)	0 (0.0)	1 (0.8)
EPITHELOID	0 (0.0)	1 (1.4)	1 (0.8)
FOLLICULAR CARCINOMA	0 (0.0)	1 (1.4)	1 (0.8)
HISTIOCYTIC SARCOMA	0 (0.0)	1 (1.4)	1 (0.8)
INSULAR CARCINOMA	0 (0.0)	1 (1.4)	1 (0.8)
LARGE CELL CARCINOMA	0 (0.0)	1 (1.4)	1 (0.8)
PROSTATE MESENCYMAL TUMOUR	1 (2.0)	0 (0.0)	1 (0.8)
SCHWANNOMA	0 (0.0)	1 (1.4)	1 (0.8)
UNKNOWN	1 (2.0)	0 (0.0)	1 (0.8)
Brain Metastasis per BICR[4], n (%)			
Yes	10 (19.6)	16 (23.2)	26 (21.7)
No	41 (80.4)	53 (76.8)	94 (78.3)
Brain Metastasis per Investigator[4], n (%)			
Yes	10 (19.6)	16 (23.2)	26 (21.7)
No	41 (80.4)	53 (76.8)	94 (78.3)
Time since Diagnosis (years)[5]			
n	51	69	120
Mean (SD)	4.60 (7.953)	5.18 (6.455)	4.93 (7.104)
Median	1.13	3.28	2.67
Min, Max	0.0, 42.5	0.4, 40.0	0.0, 42.5
Stage at Diagnosis, n (%)			
I	4 (7.8)	4 (5.8)	8 (6.7)
II	5 (9.8)	9 (13.0)	14 (11.7)
III	7 (13.7)	14 (20.3)	21 (17.5)
IIIB	2 (3.9)	4 (5.8)	6 (5.0)
IV	31 (60.8)	33 (47.8)	64 (53.3)
Missing	2 (3.9)	5 (7.2)	7 (5.8)
Stage at Study Entry[6], n (%)			
III	1 (2.0)	4 (5.8)	5 (4.2)
IIIB	1 (2.0)	1 (1.4)	2 (1.7)
IV	49 (96.1)	63 (91.3)	112 (93.3)
Missing	0 (0.0)	1 (1.4)	1 (0.8)
Resistance Mutation[7]			
Solvent Front	0 (0.0)	30 (43.5)	30 (25.0)
Gatekeeper	0 (0.0)	4 (5.8)	4 (3.3)
Activating	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	3 (4.3)	3 (2.5)
Mutation Negative	41 (80.4)	33 (47.8)	74 (61.7)
Mutation Status Unknown [8]	10 (19.6)	2 (2.9)	12 (10.0)
NTRK Gene Type			
NTRK1	25 (49.0)	22 (31.9)	47 (39.2)
NTRK2	2 (3.9)	4 (5.8)	6 (5.0)
NTRK3	24 (47.1)	43 (62.3)	67 (55.8)

	TKI-naïve Subjects (EXP-5) (N=51)	TKI-pretreated Subjects (EXP-6) (N=69)	Total (N=120)

Note: Data cutoff date of 15-Oct-2023
Percentages are based on the number of subjects in the Efficacy Analysis Set (NTRK+ Solid Tumour Subjects).
[1] Age in years is calculated based on the number of years between the informed consent date and the birth date.
[2] Countries grouped to 'Other' include: Australia, Canada, Spain, France, United Kingdom, Italy, Poland.
[3] ECOG Performance Status (0 = Fully Active to 5 = Dead) is assessed for subjects ≥18 years.
[4] Brain metastasis present if target or non-target lesion selected in the brain at baseline.
[5] Time since diagnosis in years is calculated based on the number of years from diagnosis to inform consent date.
[6] III/IIIB = Locally Advanced, IV = Metastatic
[7] Subjects can be counted in more than one category.
[8] Mutation Status Unknown includes no sample, QC failure, invalid sample/assay type (i.e. tested before the initial TKI).
Cross Reference: ADSL.

Resistance mutations

Resistance mutations (y/n) was not a prespecified subgroup, however, a post-hoc defined subgroup analysis. More details regarding patients with and without resistance mutations both in ROS1+ NSCLC and NTRK+ patients (EXP-2, EXP-3, EXP-4 and EXP-6) are provided in section *Subgroup analyses*.

Concomitant use of corticosteroids:

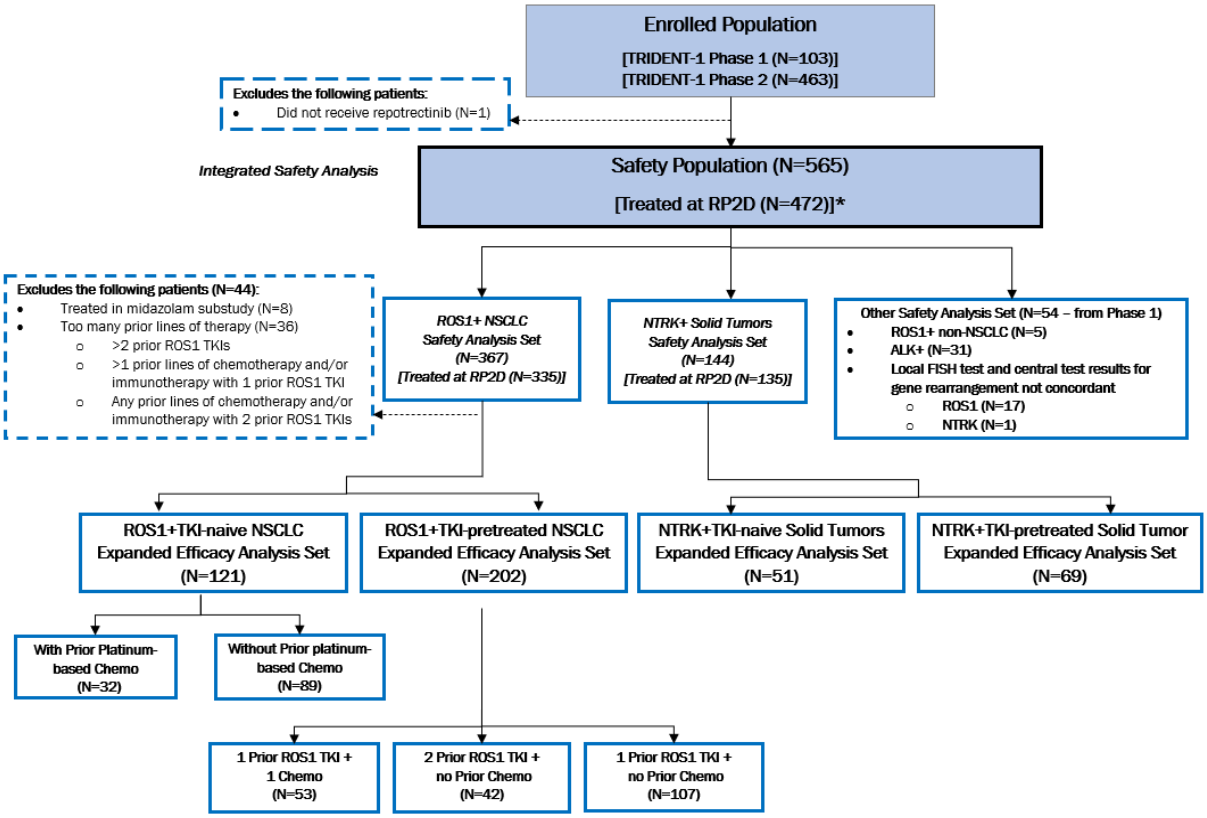
Concomitant glucocorticosteroids were allowed in TRIDENT-1. In the four NSCLC ROS1+ cohorts, 28,2% (44 of 156) participants in total used concomitant glucocorticosteroids. 7 subjects (4,5%) had doses exceeding dexamethasone 12 mg/day or equivalent. The main indication for lower dose steroids (dexamethasone ≤ 12 mg /day or equivalent) were respiratory reasons, prophylaxis or musculoskeletal. The main reasons for using higher dose (dexamethasone > 12 mg/day or equivalent) were CNS worsening (1.3%) or respiratory (1,3%).

Numbers analysed

The primary analyses occurred at the DCO date of 20 June 2022 for the ROS1+ NSCLC population and at the DCO of 19 Dec 2022 for the NTRK+ population, respectively (with ≥ 6 months of follow-up after first post-baseline assessment). The pooled (Phase 1 and Phase 2) expanded safety and efficacy

analysis sets of ROS1+ NSCLC and NTRK+ solid tumour corresponds to the most recent DCO of 15 Oct 2023 (with ≥ 6 months of follow-up after first post-baseline scan).

Figure 10. TRIDENT-1 Pooled expanded safety and efficacy analysis sets (DCO 15 Oct 2023)



Note:
* 2 subjects in "Other" group were treated at RP2D.

The safety analysis set consists of all subjects who are enrolled and have received at least one dose of repotrectinib. This analysis set is referred to as Full analysis set (FAS) by the applicant due to the same definition.

To evaluate CNS metastasis response, a subset of the FAS analysis set is used to include only those subjects with measurable brain metastasis at baseline by BICR for tumour assessment per modified RECIST criteria.

Pooled efficacy and safety analysis sets:

Integrated efficacy and safety analyses were based on pooling of the Phase 2 Full Analysis Set in the ROS1 positive NSCLC and NTRK positive solid tumour cohorts, respectively, and eligible patients from Phase 1 who met similar Phase 2 eligibility criteria. Dose level (i.e. RP2D reception) was not an eligibility criterion for pooling. The integrated analysis was performed for each cohort.

The pooling of data from Phase 1 and Phase 2 was prespecified in an integrated SAP for the ROS1 positive NSCLC population. The integrated analyses of Phase 1 and Phase 2 data from the two NRTK+

cohorts (EXP-5 and EXP-6) was not pre-specified before the DCO of Dec 2022 as the integrated SAP for NTRK+ population was published later (24 February 2023).

The pooling criteria for Phase 1 subjects into the expanded pooled populations are the same as the pooling criteria for primary efficacy.

Table 17. Summary of pooling for efficacy in the updated analysis based on expanded population by phase- Safety analysis set

	***ROS1*+ NSCLC Subjects (N=367)**	***NTRK*+ Solid Tumour Subjects (N=144)**	**Other Treated Subjects (N=54)**	**Total (N=565)**
Phase 1 Including Midazolam DDI Substudy, n	40	9	54	103
Subjects in the Efficacy Analysis set, n	15	9	0	24
Subjects not in the Efficacy Analysis set, n	25	0	54	79
Not pooled by reasons [1] [2], n(%)				
Part of the Midazolam Substudy	8 (20.0%)	0	2 (3.7%)	10 (9.7%)
ALK Subject	0	0	31 (57.4%)	31 (30.1%)
ROS1+ or NTRK+ by FISH, but not Concordant with NGS Testing	0	0	18 (33.3%)	18 (17.5%)
ROS1+, but not NSCLC	0	0	5 (9.3%)	5 (4.9%)
Prior Lines of Treatment Not Met per ROS1+ Efficacy Analysis Set Definition	23 (57.5%)	0	6 (11.1%)	29 (28.2%)
With 1 prior TKI and >1 prior of chemo and or I/O therapies	3 (7.5%)	0	4 (7.4%)	7 (6.8%)
With 2 prior TKIs and any prior chemo and or I/O therapies	7 (17.5%)	0	1 (1.9%)	8 (7.8%)
With >2 prior TKIs	13 (32.5%)	0	1 (1.9%)	14 (13.6%)
Phase 2, n	327	135	0	462
Subjects in the Expanded Efficacy Analysis set, n	308	111	0	419
Subjects not in the Expanded Efficacy Analysis set, n	19	24	0	43
Not pooled by reasons [3], n(%)				
Receiving too many lines of prior treatment (enrolled in EXP-Other)	19 (5.8%)	0	0	19 (4.1%)
Starting treatment <8 months prior to data cutoff date [4]	0 [5]	24 (17.8%)	0	24 (5.2%)

Note: 15-Oct-2023 data cutoff

[1] A subject could be counted in multiple categories.

[2] Percentages are based on total subjects in Phase 1 including Midazolam DDI Substudy only.

[3] Percentages are based on total subjects in Phase 2 only.

[4] Subjects who first dosed after 15 February 2023 will not be included in the expanded efficacy analysis set as the requirement of 8 months follow up prior to the most recent DCO of 15 October 2023 is not met.

[5] As enrollment for ROS1+ NSCLC has been completed, the last enrolled subject from ROS1+ NSCLC EXP-1 (TKI-naive) cohort is included in the updated efficacy analysis although this subject was treated on 29-Mar-2023 (ie, less than <8 months prior to data cutoff).

Outcomes and estimation

The primary analysis in the ROS1+ NSCLC population occurred at the DCO of 20 June 2022 and at the DCO of 19 Dec 2022 for the NTRK+ population. The applicant performed updated efficacy analyses for all the 6 cohorts using the most recent data cutoff of 15-Oct-2023. These analyses were based on the primary populations (with longer follow-up) and expanded populations including subjects who received any dose of repotrectinib and had at least 6 months of follow-up for response as of 15 Oct 2023. Results are presented by cohort with ROS1+NSCLC and NTRK+ population in separate tables.

Efficacy in ROS1-positive advanced NSCLC populations

As the enrolment for ROS1-positive NSCLC has been completed, and the last enrolled ROS1-positive NSCLC subject in EXP-1 had first dose of repotrectinib on 29-Mar-2023, all Phase 2 ROS1-positive NSCLC subjects are included in the ROS1 expanded pooled population. Expanded pooled analysis efficacy set consists of **15** phase 1 participants and all subjects in expanded phase 2.

Table 18. Overall summary of efficacy data TRIDENT-1 ROS 1+ NSCLC subjects- Expanded pooled analysis set

	TKI-naïve Subjects	TKI-pretreated Subjects			
	EXP-1 (N = 121)	EXP-2 (N = 53)	EXP-3 (N = 42)	EXP-4 (N = 107)	Pooled Pre-treated (N = 202)
Confirmed ORR (CR + PR)[a]					
n (%)	93 (76.9)	20 (37.7)	13 (31.0)	52 (48.6)	85 (42.1)
95% CI	68.3, 84.0	24.8, 52.1	17.6, 47.1	38.8, 58.5	35.2, 49.2
Best Overall Response, n (%)					
CR	15 (12.4)	2 (3.8)	1 (2.4)	8 (7.5)	11 (5.4)
PR	78 (64.5)	18 (34.0)	12 (28.6)	44 (41.1)	74 (36.6)
SD	19 (15.7)	18 (34.0)	10 (23.8)	33 (30.8)	61 (30.2)
PD	4 (3.3)	11 (20.8)	15 (35.7)	17 (15.9)	43 (21.3)
NE	1 (0.8)	3 (5.7)	0 (0.0)	2 (1.9)	5 (2.5)
Missing	4 (3.3)	1 (1.9)	4 (9.5)	3 (2.8)	8 (4.0)
Median Time to First Response, months (range)	1.84 (1.5, 7.4)	1.86 (1.0, 3.7)	1.87 (1.7, 5.6)	1.84 (1.6, 22.1)	1.84 (1.0, 22.1)
Duration of Response (DoR), months[b]					
Events, n(%)	36 (38.7)	13 (65.0)	10 (76.9)	27 (51.9)	50 (58.8)
Censored, n(%)	57 (61.3)	7 (35.0)	3 (23.1)	25 (48.1)	35 (41.2)
Q1 (95%CI)	12.06 (7.98, 20.27)	4.50 (3.71, 8.67)	3.71 (3.65, 7.20)	5.55 (4.53, 7.69)	5.49 (4.40, 7.20)
Median (95%CI)	33.61 (25.46, NE)	9.30 (5.55, 12.91)	7.20 (3.71, NE)	14.75 (7.56, NE)	9.66 (7.46, 17.54)
Q3 (95%CI)	NE (33.74, NE)	12.91 (9.30, NE)	33.91 (7.20, NE)	31.44 (17.81, NE)	31.44 (17.81, NE)
Min, Max	1.4+, 49.7+	1.8+, 38.5+	3.5, 33.9	1.8+, 31.4	1.8+, 38.5+
Reason for Censoring[c]**, n (%)**					
No documented progression or death	56 (46.3)	6 (11.3)	3 (7.1)	24 (22.4)	33 (16.3)
Two or more consecutive missed scheduled visits before PD or death	1 (0.8)	1 (1.9)	0 (0.0)	1 (0.9)	2 (1.0)
DoR Landmark Analyses					
≥ 6 months					
At Risk (%)	75 (80.6)	12 (60.0)	6 (46.2)	33 (63.5)	51 (60.0)
Survival Percentage by KM (95% CI)[b]	88.8 (82.2, 95.3)	63.2 (41.5, 84.8)	53.8 (26.7, 80.9)	71.7 (59.1, 84.3)	66.9 (56.7, 77.1)
≥ 12 months					
At Risk (%)	56 (60.2)	6 (30.0)	3 (23.1)	20 (38.5)	29 (34.1)
Survival Percentage	76.3 (67.2, 85.4)	45.6 (22.4, 68.8)	26.9 (1.5, 52.4)	52.2 (37.4, 67.0)	46.6 (35.2, 58.0)

Note: Data cutoff = 15-Oct-2023.

a 95% CIs are calculated using the Clopper-Pearson Exact method.

b 95% CIs are based on Kaplan-Meier methodology using the Greenwood variance estimate.

c The denominator is the total sample size for each cohort.

Sources: refer to Appendix 1a, Table 14.2.2.4.1.eu (Overall Response), Table 14.2.2.6.1.eu (OS), Table 14.2.2.5.1.eu (PFS), Table 14.2.2.4.1.2.eu (Sensitivity analysis I for DoR), and Table 14.2.2.4.1.4.eu (Sensitivity analysis II for DoR).

Intracranial efficacy, IC-ORR and IC-DOR, is shown based on the expanded Phase 2 (not pooled) data set (DCO 15 Oct 2023, with a minimum of 6 months follow-up post first evaluation):

Table 19. Intracranial response for ROS1+ NSCLC per BICR, expanded Phase 2

	TKI-Naive	TKI-Pretreated			
	EXP-1 (N=14)	EXP-2 (N=10)	EXP-3 (N=6)	EXP-4 (N=23)	Pooled Pretreated (N=39)
IC-Best Overall Response, n (%)					
CR	3 (21.4)	0 (0.0)	0 (0.0)	2 (8.7)	2 (5.1)
PR	9 (64.3)	5 (50.0)	0 (0.0)	8 (34.8)	13 (33.3)
SD	1 (7.1)	3 (30.0)	2 (33.3)	9 (39.1)	14 (35.9)
PD	0 (0.0)	1 (10.0)	2 (33.3)	3 (13.0)	6 (15.4)
NE	0 (0.0)	1 (10.0)	1 (16.7)	0 (0.0)	2 (5.1)
Missing	1 (7.1)	0 (0.0)	1 (16.7)	1 (4.3)	2 (5.1)
IC-ORR (CR + PR), n (%)[a]					
n (%)	12 (85.7)	5 (50.0)	0 (0.0)	10 (43.5)	15 (38.5)
95% CI	57.2, 98.2	18.7, 81.3	0.0, 45.9	23.2, 65.5	23.4, 55.4
Time to First Response (months)					
n	12	5	0	10	15
Mean	1.79	3.90	NA	2.72	3.11
Standard Deviation	0.157	3.986	NA	1.308	2.443
Median	1.79	1.84	NA	1.89	1.87
Min, Max	1.6, 2.2	1.4, 10.9	NA	1.7, 5.5	1.4, 10.9
IC-Duration of Response (months)[b]					
Events, n(%)	4 (33.3)	1 (20.0)	0 (NA)	3 (30.0)	4 (26.7)
Censored, n(%)	8 (66.7)	4 (80.0)	0 (NA)	7 (70.0)	11 (73.3)
Q1 (95%CI)	22.54 (9.23, NE)	3.71 (3.71, NE)		18.43 (2.69, NE)	11.07 (2.96, NE)
Median (95%CI)	27.83 (22.54, NE)	NE (3.71, NE)		NE (18.43, NE)	NE (18.43, NE)
Q3 (95%CI)	NE (27.83, NE)	NE (3.71, NE)		NE (18.43, NE)	NE (18.43, NE)
Min, Max	1.9+, 35.1+	1.8+, 11.5+	NA	2.7, 26.0+	1.8+, 26.0+
Landmark Analysis of Duration of Response					
≥6 months					
At Risk (%)	10 (83.3)	1 (20.0)	0 (NA)	8 (80.0)	9 (60.0)
Survival Percentage by KM (95% CI)[b]	100.0 (100.0, 100.0)	50.0 (0.0, 100.0)		80.0 (55.2, 100.0)	75.0 (50.5, 99.5)
≥9 months					
At Risk (%)	9 (75.0)	1 (20.0)	0 (NA)	8 (80.0)	9 (60.0)
Survival Percentage by KM (95% CI)[b]	100.0 (100.0, 100.0)	50.0 (0.0, 100.0)		80.0 (55.2, 100.0)	75.0 (50.5, 99.5)

	TKI-Naive	TKI-Pretreated			
	EXP-1 (N=14)	**EXP-2 (N=10)**	**EXP-3 (N=6)**	**EXP-4 (N=23)**	**Pooled Pretreated (N=39)**
≥12 months					
At Risk (%)	7 (58.3)	0 (0.0)	0 (NA)	6 (60.0)	6 (40.0)
Survival Percentage by KM (95% CI)[b]	77.8 (50.6, 100.0)	NE, (NE, NE)		80.0 (55.2, 100.0)	75.0 (50.5, 99.5)
≥18 months					
At Risk (%)	6 (50.0)	0 (0.0)	0 (NA)	3 (30.0)	3 (20.0)
Survival Percentage by KM (95% CI)[b]	77.8 (50.6, 100.0)	NE, (NE, NE)		80.0 (55.2, 100.0)	75.0 (50.5, 99.5)
≥24 months					
At Risk (%)	4 (33.3)	0 (0.0)	0 (NA)	1 (10.0)	1 (6.7)
Survival Percentage by KM (95% CI)[b]	62.2 (27.4, 97.1)	NE, (NE, NE)		53.3 (7.6, 99.1)	50.0 (6.8, 93.2)
CBR (CR + PR + SD), n (%)[a]					
n (%)	13 (92.9)	8 (80.0)	2 (33.3)	19 (82.6)	29 (74.4)
95% CI	66.1, 99.8	44.4, 97.5	4.3, 77.7	61.2, 95.0	57.9, 87.0
Reason for Censoring, n (%)					
No documented progression or death	8 (57.1)	4 (40.0)	0 (0.0)	7 (30.4)	11 (28.2)

Note: Data cutoff date of 15-Oct-2023

[a] 95% CIs are calculated using the Clopper-Pearson Exact method.

[b] 95% CIs are based on Kaplan-Meier methodology using the Greenwood variance estimate.

Patient Reported Outcomes (PROs) ROS1+ NSCLC

Patient-reported outcomes were evaluated as secondary objectives as of the data cutoff date (20 June 2022). All subjects with ROS1+ NSCLC had started treatment at least 8 months before the data cutoff date (to allow for 6 months of follow-up for tumour assessment after first post-baseline scan in the primary efficacy analyses). They were assessed using self-administered validated questionnaires: the EORTC-QLQ-C30 and QLQ-LC13. The PRO assessments were performed at Screening, before the first dose of repotrectinib on Cycle 1 Day 1, predose on Day 1 of each subsequent treatment cycle, and at the EOT visit. After Cycle 12, clinical visits were reduced per protocol at the discretion of the Investigator.

Overall, the mean change from baseline in EORTC-QLQ-C30 GHS/QOL score in ROS1 TKI pretreated and TKI-naïve subjects remained stable over time at each cycle. Most subjects in the ROS1+ TKI-pretreated group reported stable responses in many of the symptoms on the EORTC-QLQ-LC13 scale, with more improvement seen in the ROS1+ TKI-naïve group. Dyspnoea was however worsened in ~40% of patients compared to baseline across Cycle 6 and 12 in the TKI-pretreated patients.

Efficacy results in NTRK-positive advanced solid tumour populations

Since the enrolment for subjects with NTRK-positive solid tumours is still ongoing, Phase 2 subjects with NTRK-positive solid tumours who were treated prior to 15-Feb-2023 (therefore had at least 6 months of follow-up after the first post-baseline tumour assessment) are included in the NTRK-positive expanded Phase 2 population. NTRK+ expanded pooled population consists of a total of **9** Phase 1 subjects and NTRK+ expanded Phase 2. Overall summary of efficacy data (expanded pooled) in EXP-5 and EXP-6 is shown below.

Table 20. Overall summary of efficacy data TRIDENT-1 NTRK+ solid tumours, expanded pooled dataset

	TKI-naïve Subjects EXP-5 (N = 51)	TKI-pretreated Subjects EXP-6 (N = 69)
Confirmed ORR (CR + PR)[a]		
n (%)	30 (58.8)	33 (47.8)
95% CI	44.2, 72.4	35.6, 60.2
Best Overall Response, n (%)		
CR	8 (15.7)	2 (2.9)
PR	22 (43.1)	31 (44.9)
SD	13 (25.5)	16 (23.2)
PD	5 (9.8)	13 (18.8)
NE	0 (0.0)	3 (4.3)
Missing	3 (5.9)	4 (5.8)
Median Time to First Response, months (range)	1.82 (1.6, 7.3)	1.87 (1.7, 3.7)
Duration of Response, months (DoR)[b]		
Events, n(%)	4 (13.3)	23 (69.7)
Censored, n(%)	26 (86.7)	10 (30.3)
Q1 (95%CI)	NE (12.91, NE)	5.55 (5.45, 9.23)
Median (95%CI)	NE (NE, NE)	9.76 (7.36, 12.98)
Q3 (95%CI)	NE (NE, NE)	17.54 (11.07, NE)
Min, Max	1.7+, 43.9+	1.8, 26.5+
Reason for Censoring[c]**, n (%)**		
No documented progression or death	26 (51.0)	10 (14.5)
DoR Landmark Analyses		
≥ 6 months		
At Risk (%)	26 (86.7)	23 (69.7)
Survival Percentage by KM (95% CI)[b]	93.1 (83.9, 100.0)	72.7 (57.5, 87.9)
≥ 12 months		
At Risk (%)	20 (66.7)	11 (33.3)
Survival Percentage by KM (95% CI)[b]	89.4 (78.0, 100.0)	41.6 (23.8, 59.3)
Sensitivity Analysis I for DoR, months[b]		
Events, n(%)	7 (23.3)	24 (72.7)
Censored, n(%)	23 (76.7)	9 (27.3)
Q1 (95%CI)	31.34 (5.55, NE)	5.55 (5.45, 9.10)
Median (95%CI)	NE (31.34, NE)	9.56 (7.36, 12.91)
Q3 (95%CI)	NE (31.34, NE)	17.54 (11.07, NE)
Reason for Censoring[c]**, n (%)**		
No documented progression or death	23 (45.1)	9 (13.0)
DoR Landmark Analyses		
≥ 6 months		
At Risk (%)	26 (86.7)	23 (69.7)
Survival Percentage by KM (95% CI)[b]	86.7 (74.5, 98.8)	72.7 (57.5, 87.9)
≥ 12 months		
At Risk (%)	20 (66.7)	11 (33.3)
Survival Percentage by KM (95% CI)[b]	83.2 (69.8, 96.6)	39.4 (22.1, 56.7)

Note: Data cutoff = 15-Oct-2023.

a 95% CIs are calculated using the Clopper-Pearson Exact method.

b 95% CIs are based on Kaplan-Meier methodology using the Greenwood variance estimate.

c The denominator is the total sample size for each cohort.

Sources: refer to Appendix 1a, Table 14.2.2.4.2.eu (Overall Response), Table 14.2.2.6.3.eu (OS), Table 14.2.2.5.3.eu (PFS), Table 14.2.2.4.2.2.eu (Sensitivity analysis I for DoR), and Table 14.2.2.4.2.4.eu (Sensitivity analysis II for DoR).

Intracranial efficacy, IC-ORR and IC-DOR, is shown based on the expanded Phase 2 (not pooled) data set in the table below (DCO 15 Oct 2023, minimum 6 months follow-up post first evaluation):

Table 21. Intracranial response for NTRK+ solid tumour subjects per BICR- expanded Phase 2

	EXP-5 (N=3)	EXP-6 (N=6)
Best Overall Response, n (%)		
CR	2 (66.7)	0 (0.0)
PR	0 (0.0)	4 (66.7)
SD	1 (33.3)	0 (0.0)
PD	0 (0.0)	1 (16.7)
NE	0 (0.0)	0 (0.0)
Missing	0 (0.0)	1 (16.7)
ORR (CR + PR), n (%)[a]		
n (%)	2 (66.7)	4 (66.7)
95% CI	9.4, 99.2	22.3, 95.7
Time to First Response (months)		
n	2	4
Mean	2.83	2.25
Standard Deviation	1.347	0.936
Median	2.83	1.86
Min, Max	1.9, 3.8	1.6, 3.6
Duration of Response (months) [b]		
Events, n(%)	0 (0.0)	4 (100.0)
Censored, n(%)	2 (100.0)	0 (0.0)
Q1 (95%CI)	NE (NE, NE)	5.59 (5.45, 7.39)
Median (95%CI)	NE (NE, NE)	6.55 (5.45, NE)
Q3 (95%CI)	NE (NE, NE)	9.02 (5.72, NE)
Min, Max	17.5+, 24.0+	5.5, 10.6
Landmark Analysis of Duration of Response		
≥6 months		
At Risk (%)	2 (100.0)	2 (50.0)
Survival Percentage by KM (95% CI) [b]	100.0 (100.0, 100.0)	50.0 (1.0, 99.0)
≥9 months		
At Risk (%)	2 (100.0)	1 (25.0)
Survival Percentage by KM (95% CI) [b]	100.0 (100.0, 100.0)	25.0 (0.0, 67.4)
≥12 months		
At Risk (%)	2 (100.0)	0 (0.0)
Survival Percentage by KM (95% CI) [b]	100.0 (100.0, 100.0)	NE, (NE, NE)
≥18 months		
At Risk (%)	1 (50.0)	0 (0.0)
Survival Percentage by KM (95% CI) [b]	100.0 (100.0, 100.0)	NE, (NE, NE)
≥24 months		
At Risk (%)	1 (50.0)	0 (0.0)
Survival Percentage by KM (95% CI) [b]	100.0 (100.0, 100.0)	NE, (NE, NE)
CBR (CR + PR + SD), n (%)[a]		
n (%)	3 (100.0)	4 (66.7)
95% CI	29.2, 100.0	22.3, 95.7
Reason for Censoring, n (%)		

	EXP-5 (N=3)	EXP-6 (N=6)
No documented progression or death	2 (66.7)	0 (0.0)

Note: Data cutoff date of 15-Oct-2023
[a] 95% CIs are calculated using the Clopper-Pearson Exact method.
[b] 95% CIs are based on Kaplan-Meier methodology using the Greenwood variance estimate.

Patient Reported Outcomes (PROs) NTRK1-3

The PRO assessments were performed at Screening, before the first dose of repotrectinib on Cycle 1 Day 1, predose on Day 1 of each subsequent treatment cycle, and at the EOT visit. After Cycle 12, clinical visits were reduced per protocol at the discretion of the Investigator. The PRO data reported in the NTRK solid tumour population is collected through the DCO of 19 Dec 2022, with at least 6 months of follow-up for tumour assessment after the first post-baseline scan in the primary efficacy analyses. The FAS population used for the PRO analyses included NTRK positive solid tumour subjects dosed as of 19 April 2022, including 35 TKI-naïve subjects and 45 TKI pretreated subjects. Completion rates for the QLQ-C30 were high (≥ 89%) for all subjects at baseline, Cycle 6 and Cycle 12

Overall, the mean change form baseline in EORTC-QLQ-C30 GHS/QoL score remained stable over time at each cycle in both TKI-naïve and -pretreated. The majority of subjects had stable symptom scores, however, a large proportion experienced worsened fatigue (50%), dyspnoea (44%) and constipation (53.8%) initially (at Cycle 6) in the TKI-naïve population (EXP-5). Overall, in the TKI-pretreated population (EXP-6) symptom scores showed lower trend of worsening, especially for fatigue (17-21%) and dyspnoea (17-14%).

Ancillary analyses

Subgroup analyses

Subgroup analyses of primary endpoint ORR were performed by BICR and Investigator assessment for prespecified demographic and baseline risk factors. However, the study was not powered to detect statistical differences in the subgroups due to small sample sizes. The presented subgroup analyses are collected through the final DCO of 15 Oct2023 and based on the pooled expanded efficacy data set per population.

Efficacy analyses per tumour type in NTRK solid tumour population (EXP-5 and EXP-6), IC-ORR according to CNS intervention and efficacy per resistance mutations were post-hoc analyses.

Table 22 Subgroups analyses for ORR for ROS1+ NSCLC subjects per BICR (pooled expanded efficacy analysis set)

	TKI-naïve Subjects	TKI-pretreated Subjects			
	EXP-1 (N = 121)	EXP-2 (N = 53)	EXP-3 (N = 42)	EXP-4 (N = 107)	Pooled Pre-treated (N = 202)
Subgroup	N n (%) 95% CI	N n (%) 95% CI	N n (%) 95% CI	N n (%) 95% CI	N n (%) 95% CI
Age					

	TKI-naïve Subjects	TKI-pretreated Subjects			
	EXP-1 (N = 121)	EXP-2 (N = 53)	EXP-3 (N = 42)	EXP-4 (N = 107)	Pooled Pre-treated (N = 202)
Subgroup	**N n (%) 95% CI**	**N n (%) 95% CI**	**N n (%) 95% CI**	**N n (%) 95% CI**	**N n (%) 95% CI**
≥ 18 to < 65	93 72 (77.4) 67.6, 85.4	47 18 (38.3) 24.5, 53.6	37 11 (29.7) 15.9, 47.0	76 40 (52.6) 40.8, 64.2	160 69 (43.1) 35.3, 51.2
≥ 65 to < 75	22 16 (72.7) 49.8, 89.3	6 2 (33.3) 4.3, 77.7	5 2 (40.0) 5.3, 85.3	22 8 (36.4) 17.2, 59.3	33 12 (36.4) 20.4, 54.9
≥ 75	6 5 (83.3) 35.9, 99.6	0 0 (NA) NA	0 0 (NA) NA	9 4 (44.4) 13.7, 78.8	9 4 (44.4) 13.7, 78.8
Sex (%)					
Female	68 55 (80.9) 69.5, 89.4	34 12 (35.3) 19.7, 53.5	21 3 (14.3) 3.0, 36.3	79 38 (48.1) 36.7, 59.6	134 53 (39.6) 31.2, 48.4
Male	53 38 (71.7) 57.7, 83.2	19 8 (42.1) 20.3, 66.5	21 10 (47.6) 25.7, 70.2	28 14 (50.0) 30.6, 69.4	68 32 (47.1) 34.8, 59.6
Race					
American Indian or Alaskan Native	2 1 (50.0) 1.3, 98.7	0 0 (NA) NA	0 0 (NA) NA	0 0 (NA) NA	0 0 (NA) NA
Asian	73 58 (79.5) 68.4, 88.0	29 14 (48.3) 29.4, 67.5	22 9 (40.9) 20.7, 63.6	45 20 (44.4) 29.6, 60.0	96 43 (44.8) 34.6, 55.3
Black or African American	3 1 (33.3) 0.8, 90.6	1 0 (0.0) 0.0, 97.5	0 0 (NA) NA	4 2 (50.0) 6.8, 93.2	5 2 (40.0) 5.3, 85.3
Native Hawaiian or Other Pacific Islander	1 1 (100.0) 2.5, 100.0	0 0 (NA) NA	0 0 (NA) NA	2 2 (100.0) 15.8, 100.0	2 2 (100.0) 15.8, 100.0

	TKI-naïve Subjects	TKI-pretreated Subjects			
	EXP-1 (N = 121)	EXP-2 (N = 53)	EXP-3 (N = 42)	EXP-4 (N = 107)	Pooled Pre-treated (N = 202)
Subgroup	**N n (%) 95% CI**	**N n (%) 95% CI**	**N n (%) 95% CI**	**N n (%) 95% CI**	**N n (%) 95% CI**
White	36 27 (75.0) 57.8, 87.9	23 6 (26.1) 10.2, 48.4	15 4 (26.7) 7.8, 55.1	52 26 (50.0) 35.8, 64.2	90 36 (40.0) 29.8, 50.9
Not Reported	5 4 (80.0) 28.4, 99.5	0 0 (NA) NA	4 0 (0.0) 0.0, 60.2	3 2 (66.7) 9.4, 99.2	7 2 (28.6) 3.7, 71.0
Unknown	1 1 (100.0) 2.5, 100.0	0 0 (NA) NA	1 0 (0.0) 0.0, 97.5	1 0 (0.0) 0.0, 97.5	2 0 (0.0) 0.0, 84.2
Region					
US	18 11 (61.1) 35.7, 82.7	14 4 (28.6) 8.4, 58.1	8 2 (25.0) 3.2, 65.1	26 12 (46.2) 26.6, 66.6	48 18 (37.5) 24.0, 52.6
Europe	30 23 (76.7) 57.7, 90.1	8 2 (25.0) 3.2, 65.1	14 2 (14.3) 1.8, 42.8	38 22 (57.9) 40.8, 73.7	60 26 (43.3) 30.6, 56.8
Asia	63 54 (85.7) 74.6, 93.3	26 12 (46.2) 26.6, 66.6	17 9 (52.9) 27.8, 77.7	37 15 (40.5) 24.8, 57.9	80 36 (45.0) 33.8, 56.5
Other	10 5 (50.0) 18.7, 81.3	5 2 (40.0) 5.3, 85.3	3 0 (0.0) 0.0, 70.8	6 3 (50.0) 11.8, 88.2	14 5 (35.7) 12.8, 64.9
ECOG					
0 – Fully active	46 37 (80.4) 66.1, 90.6	19 8 (42.1) 20.3, 66.5	14 4 (28.6) 8.4, 58.1	36 19 (52.8) 35.5, 69.6	69 31 (44.9) 32.9, 57.4
1 – Restricted in physically strenuous Activity	75 56 (74.7) 63.3, 84.0	33 12 (36.4) 20.4, 54.9	28 9 (32.1) 15.9, 52.4	71 33 (46.5) 34.5, 58.7	132 54 (40.9) 32.4, 49.8
Prior ROS1 TKI					
Crizotinib	- - -	41 16 (39.0) 24.2, 55.5	39 12 (30.8) 17.0, 47.6	82 40 (48.8) 37.6, 60.1	162 68 (42.0) 34.3, 50.0

	TKI-naïve Subjects	TKI-pretreated Subjects			
	EXP-1 (N = 121)	EXP-2 (N = 53)	EXP-3 (N = 42)	EXP-4 (N = 107)	Pooled Pre-treated (N = 202)
Subgroup	**N n (%) 95% CI**	**N n (%) 95% CI**	**N n (%) 95% CI**	**N n (%) 95% CI**	**N n (%) 95% CI**
Entrectinib	- - -	9 2 (22.2) 2.8, 60.0	11 6 (54.5) 23.4, 83.3	22 10 (45.5) 24.4, 67.8	42 18 (42.9) 27.7, 59.0
Brain Metastasis at Baseline					
Yes	30 24 (80.0) 61.4, 92.3	22 8 (36.4) 17.2, 59.3	16 4 (25.0) 7.3, 52.4	43 22 (51.2) 35.5, 66.7	81 34 (42.0) 31.1, 53.5
No	91 69 (75.8) 65.7, 84.2	31 12 (38.7) 21.8, 57.8	26 9 (34.6) 17.2, 55.7	64 30 (46.9) 34.3, 59.8	121 51 (42.1) 33.2, 51.5
Resistance Mutation					
Solvent front	- - -	9 4 (44.4) 13.7, 78.8	15 6 (40.0) 16.3, 67.7	11 8 (72.7) 39.0, 94.0	35 18 (51.4) 34.0, 68.6
Gatekeeper	- - -	0 0 (NA) NA	0 0 (NA) NA	2 2 (100.0) 15.8, 100.0	2 2 (100.0) 15.8, 100.0
Other	- - -	2 0 (0.0) 0.0, 84.2	4 1 (25.0) 0.6, 80.6	2 2 (100.0) 15.8, 100.0	8 3 (37.5) 8.5, 75.5
Mutation Negative	- - -	36 12 (33.3) 18.6, 51.0	23 6 (26.1) 10.2, 48.4	81 35 (43.2) 32.2, 54.7	140 53 (37.9) 29.8, 46.4
Mutation Status Unknown	- - -	6 4 (66.7) 22.3, 95.7	2 1 (50.0) 1.3, 98.7	11 5 (45.5) 16.7, 76.6	19 10 (52.6) 28.9, 75.6

Note: Data cutoff = 15-Oct-2023.

95% CIs are calculated using the Clopper-Pearson Exact method

Table 23. Summary of key subgroup analyses of efficacy in NTRK+ solid tumours, EXP-5 and EXP-6 (Efficacy analysis set)

	TKI-Naïve *NTRK*-positive solid tumours (EXP-5)		TKI-Pretreated *NTRK*-positive solid tumours (EXP-6)	
Subgroup	**N**	**ORR (CR + PR) n (%) [95% CI]**	**N**	**ORR (CR + PR) n (%) [95% CI]**
Region				
US	8	3 (37.5) [8.5, 75.5]	24	10 (41.7) [22.1, 63.4]
Europe	17	9 (52.9) [27.8, 77.0]	27	14 (51.9) [31.9, 71.3]
Asia	23	15 (65.2) [42.7, 83.6]	15	8 (53.3.) [26.6, 78.7]
Other	3	3 (100.0) [29.2, 100.0]	3	1 (33.3) [0.8, 90.6]
Race				
Asian	26	17 (65.4) [44.3, 82.8]	21	11 (52.4) [29.8, 74.3]
Black or African American	2	0 (0.0) [0, 84.2]	2	2 (100.0) [15.8, 100.0]
White	13	8 (61.5) [31.6, 86.1]	40	15 (37.5) [22.7, 54.2]
Other	1	1 (100.0) [2.5, 100.0]	0	0 (NA) [NA]
Not Reported	9	4 (44.4) [13.7, 78.8]	6	5 (83.3) [35.9, 99.6]
Sex				
Female	27	17 (63.0) [42.4, 80.6]	33	14 (42.4) [25.5, 60.8]
Male	24	13 (54.2) [32.8, 74.4]	36	19 (52.8) [35.5, 69.6]
Age				
≥ 18 to < 65	30	19 (63.3) [43.9, 80.1]	44	26 (59.1) [43.2, 73.7]
≥ 65 to < 75	15	9 (60.0) [32.3, 83.7]	20	6 (30.0) [11.9, 54.3]
≥ 75	6	2 (33.3) [4.3, 77.7]	5	1 (20.0) [0.5, 71.6]
ECOG Performance Status				
0	23	15 (65.2) [42.7, 83.6]	27	15 (55.6) [35.3, 74.5]
1	28	15 (53.6) [33.9, 72.5]	42	18 (42.9) [27.7, 59.0]
Prior TRK TKI				
Larotrectinib	-	-	36	14 (38.9) [23.1, 56.5]
Entrectinib	-	-	32	18 (56.3) [37.7, 73.6]
Brain Metastasis at Baseline				
Yes	10	5 (50.0) [18.7, 81.3]	16	7 (43.8) [19.8, 70.1]
No	41	25 (61.0) [44.5, 75.8]	53	26 (49.1) [35.1, 63.2]

Notes: Data cutoff date of 15-Oct-2023.
[a] Defined as having a target and/or non-target lesion in the brain selected at baseline for RECIST v1.1

Table 24 Overall Response for *NTRK*-positive Solid Tumor Subjects per BICR by Resistance Mutation Type - Expanded NTRK Pooled TKI-Pretreated Population

	EXP-6
ORR (CR + PR), n (%)	
Solvent Front Mutation	
N	30
n (%)	16 (53.3)
95% CI	34.3, 71.7
Gatekeeper	
N	4
n (%)	1 (25.0)
95% CI	0.6, 80.6
Other	
N	3
n (%)	0 (0.0)
95% CI	0.0, 70.8
Mutation Negative	
N	33
n (%)	16 (48.5)
95% CI	30.8, 66.5
Mutation Status Unknown	
N	2
n (%)	0 (0.0)
95% CI	0.0, 84.2

Note: data cutoff date of 15-Oct-2023

95% CIs are calculated using the Clopper-Pearson Exact method.

Table 25. Subgroup analyses by tumour type (ORR by BICR) in the TKI-naive (EXP-5) and TKI-pretreated (EXP-6) subjects with NTRK+ solid tumours (pooled expanded efficacy analysis set)

	TKI-Naïve *NTRK*-positive solid tumours		**TKI-Pretreated *NTRK*-positive solid tumours**	
Subgroup	**N**	**ORR (CR + PR)**	**N**	**ORR (CR + PR)**
Tumour type				
NSCLC	27	17 (63.0) [42.4, 80.6]	17	9 (52.9) [27.8, 77.0]
Salivary Gland Cancer	5	4 (80.0) [28.4, 99.5]	12	9 (75.0) [42.8, 94.5]
Sarcoma, Soft Tissue	3	1 (33.3) [0.8, 90.6]	10	1 (10.0) [0.3, 44.5]
Thyroid Cancer	6	6 (100.0) [54.1, 100.0]	7	2 (28.6) [3.7, 71.0]
Glioblastoma	1	0 (0.0) [0.0, 97.5]	3	1 (33.3) [0.8, 90.6]
Breast Cancer	2	0 (0.0) [0.0, 84.2]	1	1 (100.0) [2.5, 100.0]
Cholangiocarcinoma	1	0 (0.0) [0.0, 97.5]	2	1 (50.0) [1.3, 98.7]
Colorectal Cancer	2	1 (50.0) [1.3, 98.7]	4	2 (50.0) [6.8, 93.2]
Peripheral Nerve Sheath Tumour	1	1 (100.0) [2.5, 100.0]	2	2 (100.0) [15.8, 100.0]
Neuroendocrine Tumour	0	0 (NA) [NA]	3	3 (100.0) [29.9, 100.0]
Pancreatic Cancer	0	0 (NA) [NA]	3	0 (0.0) [0.0, 70.8]

	TKI-Naïve *NTRK*-positive solid tumours		TKI-Pretreated *NTRK*-positive solid tumours	
Subgroup	**N**	**ORR (CR + PR)**	**N**	**ORR (CR + PR)**
Other	3	0 (0.0) [0.0, 70.8]	5	2 (40.0) [5.3, 85.3]

Notes: Data cutoff date of 15-Oct-2023.

Efficacy according to CNS intervention (post-hoc):

Among the 62 subjects who had measurable CNS metastases at baseline in the expanded data set (all cohorts, data cutoff 15-Oct-2023): 31 subjects had prior CNS intervention (brachytherapy: 4, brain operation: 1, electron radiation therapy: 8, Gamma radiation therapy: 4, radiotherapy: 14), including 15 subjects whose CNS procedure was completed (i.e., end date) within 60 days prior to first dose study treatment.

8 subjects underwent their CNS procedure within 30 days prior to the first dose repotrectinib (1 in EXP-1, 1 in EXP-2, 1 in EXP-3, 4 in EXP-4, 1 in EXP-6).

7 subjects had their CNS procedure between 30-60 days prior to first dose of repotrectinib (2 in EXP-1, 1 in EXP-2, 3 in EXP-4, and 1 in EXP-6).

A post-hoc subgroup analysis to assess the impact of prior CNS intervention was conducted based on the DCO of 15 Oct 2023. The groups were patients receiving CNS intervention within 60 days of starting treatment (yes or no) analysed by cohort.

Results for the ROS1 positive NSCLC population (all four cohorts) and NTRK positive solid tumour population (two cohorts), respectively, are presented in separate tables below.

Table 26 Post-hoc subgroup analysis of IC-ORR according to timing of CNS intervention before study treatment in TKI-naive and TKI-pretreated cohorts in ROS1+ NSCLC (expanded phase 2 analysis set)

	TKI-Naive		TKI-Pretreated							
	EXP-1		EXP-2		EXP-3		EXP-4		Pooled Pre-treated	
	≤ 60 days	> 60 days	≤ 60 days	> 60 days	≤ 60 days	> 60 days	≤ 60 days	> 60 days	≤ 60 days	> 60 days
	N=4	N=10	N=2	N=8	N=1	N=5	N=7	N=16	N=10	N=29
• **IC-ORR (CR + PR)**[a]	•	•	•	•	•	•	•	•	•	•
•n (%)	• 4 (100.0)	• 8 (80.0)	• 1 (50.0)	• 4 (50.0)	• 0 (0.0)	• 0 (0.0)	• 2 (28.6)	• 8 (50.0)	• 3 (30.0)	• 12 (41.4)

	TKI-Naive		TKI-Pretreated							
	EXP-1		EXP-2		EXP-3		EXP-4		Pooled Pre-treated	
	≤ 60 days	> 60 days	≤ 60 days	> 60 days	≤ 60 days	> 60 days	≤ 60 days	> 60 days	≤ 60 days	> 60 days
	N=4	N=10	N=2	N=8	N=1	N=5	N=7	N=16	N=10	N=29
• 95% CI	• 39.8, 100.0	• 44.4, 97.5	• 1.3, 98.7	• 15.7, 84.3	• 0.0, • 97.5	• 0.0, 52.2	• 3.7, 71.0	• 24.7, 75.3	• 6.7, 65.2	• 23.5, • 61.1
• **Best Overall Response, n (%)**	•	•	•	•	•	•	•	•	•	•
• CR	• 0 (0.0)	• 3 (30.0)	• 0 (0.0)	• 0 (0.0)	• 0 (0.0)	• 0 (0.0)	• 0 (0.0)	• 2 (12.5)	• 0 (0.0)	• 2 (6.9)
• PR	• 4 (100.0)	• 5 (50.0)	• 1 (50.0)	• 4 (50.0)	• 0 (0.0)	• 0 (0.0)	• 2 (28.6)	• 6 (37.5)	• 3 (30.0)	• 10 (34.5)
• SD	• 0 (0.0)	• 1 (10.0)	• 1 (50.0)	• 2 (25.0)	• 0 (0.0)	• 2 (40.0)	• 4 (57.1)	• 5 (31.3)	• 5 (50.0)	• 9 (31.0)
• PD	• 0 (0.0)	• 0 (0.0)	• 0 (0.0)	• 1 (12.5)	• 0 (0.0)	• 2 (40.0)	• 0 (0.0)	• 3 (18.8)	• 0 (0.0)	• 6 (20.7)
• NE	• 0 (0.0)	• 0 (0.0)	• 0 (0.0)	• 1 (12.5)	• 0 (0.0)	• 1 (20.0)	• 0 (0.0)	• 0 (0.0)	• 0 (0.0)	• 2 (6.9)
• Missing	• 0 (0.0)	• 1 (10.0)	• 0 (0.0)	• 0 (0.0)	• 1 (100.0)	• 0 (0.0)	• 1 (14.3)	• 0 (0.0)	• 2 (20.0)	• 0 (0.0)

[a] 95% CIs are calculated using the Clopper-Pearson Exact method.

Of the responders in the ROS1 positive NSCLC cohorts all were PRs in the subgroup group without CNS intervention within 60 days (≤ 60 days) of starting treatment.

Table 27 Post-hoc subgroup analysis of IC-ORR according to timing of CNS intervention before study treatment in TKI-naive and TKI-pretreated cohorts in the NTRK+ solid tumour population (expanded phase 2 analysis set)

	TKI-Naive EXP-5		TKI-Pretreated EXP-6	
	≤ 60 days	**> 60 days**	**≤ 60 days**	**> 60 days**
	N=0	**N=3**	**N=2**	**N=4**
• **Confirmed ORR (CR + PR)**[b]	•	•	•	•
• n (%)	• -	• 2 (66.7)	• 1 (50.0)	• 3 (75.0)
• 95% CI	• -	• 9.4, 99.2	• 1.3, 98.7	• 19.4, 99.4
• **Best Overall Response, n (%)**	•	•	•	•
• CR	• -	• 2 (66.7)	• 0 (0.0)	• 0 (0.0)
• PR	• -	• 0 (0.0)	• 1 (50.0)	• 3 (75.0)
• SD	• -	• 1 (33.3)	• 0 (0.0)	• 0 (0.0)
• PD	• -	• 0 (0.0)	• 0 (0.0)	• 1 (25.0)
• NE	• -	• 0 (0.0)	• 0 (0.0)	• 0 (0.0)
• Missing	• -	• 0 (0.0)	• 1 (50.0)	• 0 (0.0)

[a] 95% CIs are calculated using the Clopper-Pearson Exact method.

Two patients in EXP-6 received CNS intervention within 60 days of starting treatment. One responded with PR.

Efficacy in patients with resistance mutations (post-hoc):

ROS1-positive NSCLC TKI-Pretreated Subjects (EXP-2, EXP-3, EXP-4) with resistance mutations at baseline

Of a total of 202 previously treated ROS1+ NSCLC patients (EXP-2, EXP-3 and EXP-4) in the expanded pooled population (cut-off 15 October 2023), 185 patients were tested for resistance mutations. Solvent front mutation was found in 35 patients across the three cohorts, Gatekeeper mutation was registered for only 2 patients (EXP-4), and "Other" mutations were found in 8 patients. Since the number of patients with resistance mutations is low in the studied population, no certain estimation of ORR can be performed per cohort and mutation type. However, since overall 22 of the 45 patients with resistance mutations (49%) achieved either CR or PR, which is in line with the ORR in the overall pretreated population, it seems that repotrectinib has the potential for overcoming resistance mutations in patients with ROS1+ NSCLC.

TKI-Pretreated NTRK-Positive Solid Tumours (EXP-6) with resistance mutations at baseline

Of the 77 patients who were tested for mutations in EXP-6, 30 patients had Solvent front mutation at baseline, 4 patients had Gatekeeper mutation and 3 patients had "Other" mutations. Approximately half of the patients with Solvent front mutations obtained a complete or partial response (16/30) while one other patient responded among the patients with Gatekeeper mutation (1/4).

As for the ROS1+ NSCLC population, no certain estimation of ORR can be performed per mutation type. However, among the total number of patients with resistance mutations 17/37 (46%) obtained a response, and thus it can be concluded that repotrectinib has the potential for overcoming resistance mutations also in the NTRK+ population.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28 Summary of Efficacy for TRIDENT-1 Phase 2 Study

Title: A Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumour Activity of TPX-0005 in Patients with Advanced Solid Tumours Harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1)	
Study identifier	CA1271024
Design	Phase 1/2, open-label, multi-center, multiple-dose, dose escalation, safety, PK, pharmacodynamics, and anticancer efficacy exploration study of repotrectinib as a single agent in subjects with *ALK*-positive, *ROS1*-positive, *NTRK1*-positive, *NTRK2*-positive, or *NTRK3*-positive advanced solid malignancies
	The total enrollment of Phase 2 was originally planned to be approximately 310 subjects to evaluate efficacy in 6 expansion cohorts, defined according to prior treatment and ROS1 or NTRK rearrangement. Phase 2 enrollment was expanded to a total of approximately 620 subjects across expansion cohorts to allow continued enrollment in rest of world (China, Japan, EU, etc.) along with US sites in anticipation of future regulatory submissions and to evaluate safety and efficacy in regional populations.

Treatments groups	Repotrectinib 160 mg QD for the first 14 days, followed by possible increase to 160 mg BID.	
ENDPOINTS AND ANALYSES		
Objectives	**Endpoints**	**Endpoint Description**
Primary		
To determine the confirmed ORR as assessed by BICR of repotrectinib in each subject population expansion cohort of solid tumours that harbor a ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement.	ORR by BICR per RECIST v1.1 in each expansion cohort	ORR was defined as the proportion of subjects with a confirmed CR or PR. A confirmed response is a response that persists on a repeat-imaging performed at least 4 weeks after initial documentation of response. Subjects with a confirmed objective response (CR or PR) were referred to as responders. Non-responders included subjects without a confirmed objective response, stable disease, or PD.
Secondary		
To determine the duration of response (DoR), TTR, and clinical benefit rate (CBR) of repotrectinib, as assessed by BICR, in each subject population expansion cohort of advanced solid tumours that harbor a ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement.	DoR, TTR, and CBR by BICR	DoR was defined from the first date of objective response (either CR or PR) to first documentation of radiographic disease progression, as assessed by RECIST v1.1. TTR was defined as the time from the first dose of repotrectinib to the first documentation of objective response (either CR or PR), as assessed by RECIST v1.1. CBR was defined as the proportion of subjects with CR, PR, or SD. Stable disease refers to a condition where the tumour is neither increasing nor decreasing in extent or severity for at least 6 weeks after the first dose of repotrectinib, as assessed by RECIST v1.1.
To estimate the progression-free survival (PFS) and overall survival (OS) of subjects treated with repotrectinib with advanced solid tumours that harbor a ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement.	PFS and OS	PFS was defined as the time from the first dose of repotrectinib to first documentation of radiographic disease progression by BICR using RECIST v1.1 or death due to any cause (whichever occurs first). OS was defined as the time from the first dose of repotrectinib to the date of death due to any cause.
To determine the intracranial objective response rate (IC-ORR) of repotrectinib and central nervous system progression-free survival (CNS-PFS) in subjects presenting with measurable brain	IC-ORR and CNS-PFS	Intracranial ORR was defined as the percent of subjects with PR/CR based on the assessment of intracranial target lesions, non-target lesions, and new lesions in subjects with measurable CNS metastasis at baseline. CNS-PFS was defined as the time from the first dose of repotrectinib to first evidence of radiographic CNS disease progression or death due to any cause (whichever occurs first) + 1 day.

metastases at baseline, using Response Assessment in Neuro-Oncology Brain Metastases modified RECIST v1.1 assessment.		
Exploratory (All Descriptive)		
To explore association between ORR by subgroups including demographic and baseline risk factors in each expansion cohort.		ORR was defined as above.
Database Lock	15-Oct-2023	
Analysis Population	N = 463	
RESULTS AND ANALYSES		
Overall Response and Associated Efficacy Endpoints by BICR - - *Integrated Efficacy Analysis Set*		

Efficacy Endpoint	***ROS1*+ NSCLC TKI-naïve EXP-1 (N = 71)**	***ROS1*+ NSCLC TKI-pretreated 1 Prior TKI + 1 Chemo EXP-2 (N=26)**	***ROS1*+ NSCLC TKI-pretreated 2 Prior TKI + No Chemo EXP-3 (N=18)**	***ROS1*+ NSCLC TKI-pretreated 1 Prior TKI + No Chemo EXP-4 (N=56)**	***NTRK*+ NSCLC TKI-naïve EXP-5 (N = 40)**	***NTRK*+ NSCLC TKI-pretreated EXP-6 (N = 48)**
BOR, n (%)						
CR	9 (12.7)	1 (3.8)	1 (5.6)	4 (7.1)	6 (15.0)	1 (2.1)
PR	47 (66.2)	10 (38.5)	4 (22.2)	19 (33.9)	17 (42.5)	23 (47.9)
Stable disease	11 (15.5)	8 (30.8)	3 (16.7)	21 (37.5)	9 (22.5)	12 (25.0)
PD	2 (2.8)	5 (19.2)	7 (38.9)	9 (16.1)	5 (12.5)	8 (16.7)
NE	0 (0.0)	2 (7.7)	0 (0.0)	2 (3.6)	0 (0.0)	2 (4.2)
Missing	2 (2.8)	0 (0.0)	3 (16.7)	1 (1.8)	3 (7.5)	2 (4.2)
ORR (CR + PR)[a], n (%)	56 (78.9)	11 (42.3)	5 (27.8)	23 (41.1)	23 (57.5)	24 (50.0)
(95% CI)	67.6, 87.7	23.4, 63.1	9.7, 53.5	28.1, 55.0	40.9, 73.0	35.2, 64.8
CBR (CR + PR + SD), n (%)	67 (94.4)	19 (73.1)	8 (44.4)	44 (78.6)	32 (80.0)	36 (75.0)
(95% CI)	86.2, 98.4	52.2, 88.4	21.5, 69.2	65.6, 88.4	64.4, 90.9	60.4, 86.4
Time to first response (months)						
n	56	11	5	23	23	24
Mean	2.48	1.98	2.60	3.77	2.36	2.31
Standard Deviation	1.304	0.713	1.658	5.790	1.316	0.783
Median	1.84	1.84	1.87	1.84	1.81	1.87
Min, Max	1.5, 5.6	1.0, 3.7	1.7, 5.6	1.6, 22.1	1.6, 7.3	1.7, 3.7
DoR[b] (months)						
Events, n(%)	21 (37.5)	8 (72.7)	5 (100.0)	13 (56.5)	4 (17.4)	19 (79.2)
Censored, n (%)	35 (62.5)	3 (27.3)	0 (0.0)	10 (43.5)	19 (82.6)	5 (20.8)
Q1 (95% CI)	19.78 (10.18, 28.68)	4.40 (3.65, 7.39)	3.71 (3.52, 11.04)	7.46 (5.16, 14.75)	NE (7.43, NE)	5.54 (2.04, 9.56)
Median (95% CI)	34.10 (27.40, NE)	7.39 (4.40, NE)	7.36 (3.52, NE)	17.81 (7.56, NE)	NE (NE, NE)	9.86 (7.36, 12.98)

Q3 (95% CI)	NE (34.10, NE)	NE (7.39, NE)	11.04 (3.71, NE)	31.44 (17.81, NE)	NE (NE, NE)	17.54 (11.07, NE)
Min, Max	1.4+, 49.7+	3.6, 38.5+	3.5, 33.9	2.2+, 31.4	3.7+, 43.9+	1.8, 26.5+
Landmark Analysis of DoR[b]						
Survival Probabilities by KM (95% CI)						
≥ 6 months	90.8 (83.1, 98.5)	54.5 (25.1, 84.0)	60.0 (17.1, 100.0)	77.0 (59.3, 94.7)	90.9 (78.9, 100.0)	70.8 (52.6, 89.0)
≥ 9 months	88.9 (80.6, 97.3)	36.4 (7.9, 64.8)	40.0 (0.0, 82.9)	62.6 (42.0, 83.2)	86.4 (72.0, 100.0)	62.5 (43.1, 81.9)
≥ 12 months	83.1 (73.1, 93.2)	27.3 (1.0, 53.6)	20.0 (0.0, 55.1)	57.8 (36.7, 78.8)	86.4 (72.0, 100.0)	41.7 (21.9, 61.4)
≥ 18 months	77.0 (65.6, 88.5)	27.3 (1.0, 53.6)	20.0 (0.0, 55.1)	46.7 (24.7, 68.6)	81.8 (65.7, 97.9)	21.9 (3.5, 40.3)
≥ 24 months	70.1 (57.2, 82.9)	27.3 (1.0, 53.6)	20.0 (0.0, 55.1)	40.0 (17.6, 62.4)	81.8 (65.7, 97.9)	10.9 (0.0, 28.7)
Intracranial PFS[b] **(months)**						
n	9	4	2	13	2	4
Q1 (95% CI)	24.71 (12.88, NE)	1.31 (1.02, NE)	0.76 (0.76, NE)	3.45 (1.81, 8.44)	NE (NE, NE)	5.34 (1.61, 9.23)
Median (95% CI)	29.63 (24.71, NE)	NE (1.02, NE)	1.79 (0.76, NE)	8.44 (3.45, NE)	NE (NE, NE)	9.15 (1.61, NE)
Q3 (95% CI)	NE (29.63, NE)	NE (1.61, NE)	2.83 (0.76, NE)	NE (5.82, NE)	NE (NE, NE)	10.84 (9.07, NE)
Min, Max	0.0+, 36.7+	1.0, 13.2+	0.8, 2.8	0.0+, 27.8+	19.4+, 27.8+	1.6, 12.5
Landmark Analysis of Intracranial PFS[b]						
Survival Probabilities by KM (95% CI)						
n	9	4	2	13	2	4
≥ 6 months	100.0 (100.0, 100.0)	50.0 (1.0, 99.0)	NE, (NE, NE)	50.5 (19.5, 81.5)	100.0 (100.0, 100.0)	75.0 (32.6, 100.0)
≥ 9 months	100.0 (100.0, 100.0)	50.0 (1.0, 99.0)	NE, (NE, NE)	40.4 (9.9, 70.9)	100.0 (100.0, 100.0)	75.0 (32.6, 100.0)
≥ 12 months	100.0 (100.0, 100.0)	50.0 (1.0, 99.0)	NE, (NE, NE)	40.4 (9.9, 70.9)	100.0 (100.0, 100.0)	25.0 (0.0, 67.4)
≥ 18 months	85.7 (59.8, 100.0)	NE, (NE, NE)	NE, (NE, NE)	40.4 (9.9, 70.9)	100.0 (100.0, 100.0)	NE, (NE, NE)
≥ 24 months	85.7 (59.8, 100.0)	NE (NE, NE)	NE (NE, NE)	26.9 (0.0, 56.5)	100.0 (100.0, 100.0)	NE, (NE, NE)
OS (months)[b]						
Q1 (95% CI)	24.71 (19.45, NE)	9.79 (6.31, 22.80)	2.37 (0.76, 6.37)	9.79 (6.18, 15.84)	11.30 (2.53, 27.43)	7.36 (3.88, 10.91)
Median (95% CI)	44.42 (37.32, NE)	25.92 (10.48, NE)	6.37 (3.45, 34.17)	25.13 (14.55, NE)	55.59 (22.21, NE)	16.79 (9.56, 22.28)

Q3 (95% CI)	74.64 (44.42, NE)	NE (25.92, NE)	34.17 (6.37, NE)	55.66 (31.38, NE)	55.59 (NE, NE)	32.46 (19.32, NE)
Min, Max	1.0+, 74.6	1.2, 43.9+	0.7, 35.5	0.9+, 55.7	0.9, 55.6	0.8, 43.9+
Landmark Analysis of OS[b]						
Survival Probabilities by KM (95% CI)						
≥ 12 months	91.0 (84.2, 97.9)	66.4 (47.3, 85.5)	39.4 (15.3, 63.5)	69.2 (56.2, 82.2)	75.0 (61.6, 88.4)	59.1 (44.5, 73.7)
≥ 18 months	86.4 (78.1, 94.7)	57.2 (36.9, 77.5)	39.4 (15.3, 63.5)	56.2 (42.1, 70.3)	72.5 (58.7, 86.3)	46.5 (31.4, 61.7)
≥ 24 months	75.4 (64.9, 85.9)	52.0 (31.1, 72.8)	39.4 (15.3, 63.5)	51.9 (37.6, 66.1)	63.6 (48.1, 79.0)	33.8 (18.4, 49.2)

Data cutoff date:15-Oct-2023

Notes: TKI-Naïve Subjects include expansion cohort EXP-1; TKI-Pretreated Subjects include expansion cohort EXP-2, EXP-3, and EXP-4; TKI-Naïve Subjects include expansion cohort EXP-5; and TKI-Pretreated Subjects include expansion cohort EXP-6.
Percentages are based on the number of subjects in the Efficacy Analysis Set.
Confirmed objective tumour response and duration of response censoring are defined in the statistical analysis plan.
a 95% CIs are calculated using the Clopper-Pearson Exact method.
b 95% CIs are based on Kaplan-Meier methodology using the Greenwood variance estimate.

2.6.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	0	0	0
Non Controlled Trials	105/463	35/463	1/463

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Repotrectinib is an oral, next-generation, ATP-competitive small-molecule inhibitor of the tyrosine kinases ROS1 (encoded by the gene ROS1), TRK (encoded by genes NTRK1, NTRK2 and NTRK3), and ALK (encoded by the gene ALK).

ROS1 gene rearrangements are observed in approximately 1% to 2% of patients with NSCLC, as well as in cholangiocarcinoma, glioblastoma, ovarian, gastric, and colorectal cancers. NTRK fusions are identified across multiple paediatric and adult cancer histologies with a frequency varying from < 1% up to 25%. Thus, testing is required to identify the patients eligible for treatment with repotrectinib.

For study TRIDENT-1, a prototype CDx was developed, validated, and used as a Clinical Trial Assay (CTA) in Almac's CLIA/CAP accredited laboratory. This test is a qualitative in vitro diagnostic assay that uses targeted next-generation sequencing to detect fusions in ALK, ROS1, and NTRK1-3 genes. The assay profiles RNA isolated from FFPE solid tumour tissue. The analytically validated test was granted IDE approval in May 2019 (G190086) and IRB approval in May 2019. European Conformity (CE) marking was obtained in May 2019. Originally, Almac's test was developed to be used as a CDx for Augtyro. However, it was determined that this assay is no longer the best testing option for patients in the EU, and the sponsor has now contracted with Foundation Medicine, Inc. for the

validation of a CDx assay (F1CDx) for the identification of patients that are candidates for treatment with repotrectinib.

Originally, prospective central confirmation testing with the Almac test was performed for all patients in TRIDENT-1 locally tested with either FISH, qPCR or an NGS. However, the protocol was later amended, and prospective confirmatory central testing was no longer required if the test was performed locally by qPCR or NGS. Later, also retrospective central testing was omitted for patients tested locally with qPCR and NGS. Approximately half of all patients included in TRIDENT-1 did not have a confirmation by central testing with the CTA after the change in testing strategy. Most of the local testing was performed with an NGS method. However, for ROS1+ NSCLC a large proportion of patients were also included in the Phase 2 part of the study based on local qPCR test (22%). Among the NTRK fusion positive subjects, only 4 were locally tested with a qPCR, none of which were confirmed by CTA. All Phase 2 patients of TRIDENT-1 locally tested for ROS1 or NTRK1/2/3 fusions by FISH were prospectively confirmed by central CTA. The 6 patients in the pooled analysis included from Phase 1 who were locally tested with FISH, were retrospectively confirmed as ROS1+. The applicant has provided information on the agreement between the results of local NGS testing and prospective central testing with the CTA which shows acceptable agreement between the tests (PPA 92.9%). Based on information from all 26 patients with local qPCR test and central CTA test, a relatively low agreement between the tests (PPA 69.2%) was shown, thus, 30% of the qPCR tested patients without central confirmation were potentially ROS1 negative but received treatment with repotrectinib.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

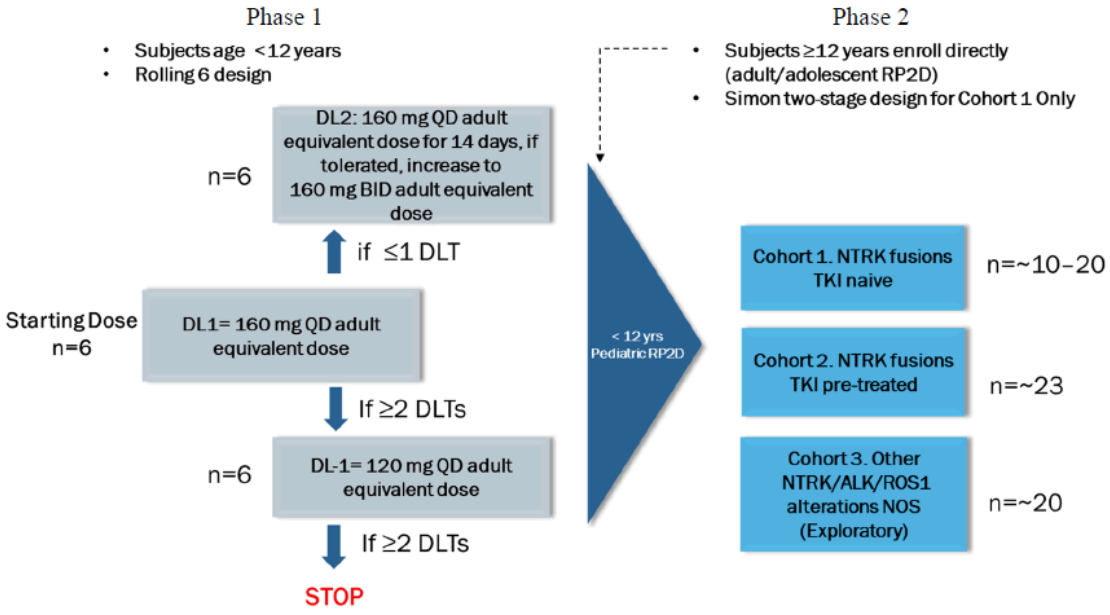
2.6.5.6. Supportive study(ies)

Study TPX-0005-07 (CARE)

CARE is an ongoing, Phase 1/2, open-label, single-arm, multicentre, multicohort study to evaluate the safety, tolerability, PK, and efficacy of repotrectinib in paediatric, adolescents, and young adult (up to 25 years of age) patients with advanced or metastatic solid tumours with ALK, ROS1, or NTRK alterations.

The study includes a Phase 1 dose escalation, MTD/RP2D determining part which has completed enrolment, and a Phase 2 part which is ongoing.

Figure 11. CARE phase 1/2 study schema



Study population:

Phase 1: Paediatric subjects < 12 years of age were enrolled into 2 dose levels, using a rolling 6 design, to determine the paediatric RP2D for subjects ≥ 12 years old in phase 2. Please see further information regarding phase 1 CARE study in section 3.2 *Dose response study(ies).*

Phase 2: Subjects 0-25 years of age were eligible. Subjects age < 12 years were enrolled in Phase 2 only after determination of the paediatric RP2D in Phase 1. However, subjects 12 years of age and above could be enrolled directly in the Phase 2 part of the study while Phase 1 was underway. Eligible participants were included in one of 3 cohorts based on their disease characteristics and prior treatments:

- Cohort 1: NTRK-positive solid tumours and TRK TKI-naïve
- Cohort 2: NTRK-positive solid tumours and TRK TKI-pretreated
- Cohort 3 (Exploratory):

- Subjects with NTRK gene fusion positive advanced solid tumours with measurable disease that are pretreated with > 2 lines of prior TKI therapy

- Subjects with NTRK gene fusion positive advanced solid tumours that are pretreated with < 2 lines of prior TKI therapy and without centrally confirmed measurable disease by BICR

- Subjects with advanced solid tumours with ALK or ROS1 gene fusions or other ALK/ROS1/NTRK aberrations (including amplifications and point mutations).

The presence of NTRK1-3 gene fusions in tumour specimens was prospectively determined in local laboratories using NGS, PCR or FISH tests. If local FISH testing was the basis for enrolment, retrospective confirmation by a central laboratory using an analytically validated NGS test was required.

Trial intervention:

RP2D was established through phase 1. All subjects will receive repotrectinib 160 mg QD AED for 14 days, then 160 mg BID AED, if tolerated, i.e., no grade ≥ 3 TRAE; unmanageable grade ≥ 2 dizziness, ataxia, or paraesthesia; or grade ≥ 3 clinically significant laboratory abnormalities.

Treatment with repotrectinib may continue until either disease progression, subject refusal, or unacceptable toxicity occurs, whichever occurs first. Subjects with documented progressive disease who are tolerating treatment and, in the opinion of the Investigator, are deriving clinical benefit from continuing study treatment, may continue treatment with sponsor approval.

Table 29. CARE phase 1/2 objectives and endpoints

Objective	Endpoint	Analysis	Included in this report?
Phase 1 Primary			
Evaluate the safety and tolerability at different dose levels of repotrectinib in pediatric and young adult subjects with advanced or metastatic malignancies harboring *ALK, ROS1,* or *NTRK*1-3 alterations to estimate the MTD or MAD, and select the pediatric RP2D/schedule.	MTD/MAD and pediatric RP2D	MTD is the highest dose where less than 33% of subjects experience first cycle DLT. RP2D will be based on totality of clinical data at a dose at or below the MTD.	Y
Phase 1 Secondary			
Characterize the PK of repotrectinib in pediatric and young adult subjects with advanced malignancies with *ALK, ROS1,* or *NTRK*1-3 alterations	PK parameters	Blood will be collected to determine repotrectinib plasma PK parameters following single and multiple doses.	Y
Determine the preliminary antitumor activity of repotrectinib in pediatric subjects with advanced malignancies with *ALK, ROS1,* or *NTRK*1-3 alterations.	ORR by BICR, CBR, TTR, DOR, IC-ORR	ORR is the proportion of subjects with BOR of CR or PR. ORR analysis will include BOR and DOR. DOR is time from first date of CR or PR to first documentation of disease progression, or death due to any cause, whichever occurs first CBR: proportion of subjects with CR, PR, or SD TTR: time from the first dose of repotrectinib to first documented response by RECIST v1.1 or RANO	DOR and ORR only
Phase 2 Primary			
Determine the antitumor activity of repotrectinib in pediatric and young adult subjects with advanced or metastatic malignancies harboring *ALK, ROS1,* or *NTRK*1-3 alterations.	ORR by BICR using RECIST v1.1 (or RANO for subjects with primary CNS)	ORR analysis will include BOR and DOR	Y
Phase 2 Secondary			
Determine the antitumor activity in terms of DOR, OS and PFS following treatment with repotrectinib	DOR, TTR, CBR, PFS, OS	DOR, TTR CBR: see above PFS: time from the first dose of repotrectinib to first documentation of disease progression or death due to any cause, whichever occurs first OS: time from the first dose of repotrectinib to the date of death	DOR only
Determine the intracranial antitumor activity of repotrectinib	Intracranial tumor response, CNS-PFS (also referred to as IC-PFS)	Same method as above, in subjects with primary CNS tumors	N
Evaluate the safety and tolerability of repotrectinib at the pediatric RP2D	AEs	Type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory abnormalities will be tabulated	Y
Characterize the PK of repotrectinib at the pediatric RP2D	PK parameters	See above	N

The planned analyses for CARE were similar to TRIDENT-1 and detailed in a joint NTRK SAP (Integrated statistical analysis plan – NTRK V. 1.0 dated 24 February 2023). The CARE data was to be regarded as supportive to TRIDENT-1 for the paediatric indication.

Recruitment:

The CARE study was initiated by FPFV on 30 April 2020 in phase 1 and FPFV 20 March 2020 in phase 2. The phase enrolment is completed by 10 subjects, while the phase 2 part is still recruiting study participants. Enrolment of 30 patients with NTRK-positive tumours to the CARE study is expected to be completed in March 2029 (LPFV), with LPLV in November 2029.

Table 30. CARE study enrolment status as of 09 May 2024

Cohort	Molecular Alteration	Actual Enrolled/ Planned
1	NTRK fusions TKI-naïve	2/10-20
2	NTRK fusions TKI-pretreated	9/23
3	Other NTRK/ALK/ROS1 alterations NOS	22/20 (6 NTRK)
Total		33/63

Conduct of the study:

The CARE study is conducted at 40 sites across 10 participating countries in Europe, North-America, Asia and Australia. Ten additional sites are selected and pending activation in Europe. Feasibility is ongoing to add more sites and potentially expand into other countries, such as Latin America.

Table 31. Key changes to CARE protocol

Protocol Version	Date	Category	Key Change and Rationale
Original Version 1	12-Jul-2019	N/A	N/A
Global Version 2 Amendment 2	17-Jul-2020	Inclusion Criteria Sample Size	Updated age range inclusion and weight-based dosing due to availability of oral suspension. Phase 1 age range updated to 0-25 from the original 4-25 years of age. Incorporated data monitoring committee for Phase 1 and Phase 2 of the study Modified Sample size determination and efficacy decision rules: If 15 or more responses out of 20 are observed, repotrectinib will be considered efficacious
Global Version 3 Amendment 3	25-Jan-2022	Study Sites Objectives & Endpoints Inclusion Criteria	Number of study sites increased globally to 50 to account for EU expansion Acceptability/Palatability assessments and exploratory objectives and endpoints were added in response to PDCO feedback for the PIP Updated contraception requirement to 5 weeks following last dose for female subjects to standardize with repotrectinib program requirements
Global Version 4 Amendment 4	21-Apr-2022	Addition of RP2D	RP2D was determined by the safety review committee and language updated in protocol

Protocol Version	Date	Category	Key Change and Rationale
Global Version 5 Amendment 5	08-Mar-2023	Study Endpoints Inclusion Criteria Dose Regimen Tumour Response Assessment	Added PK parameters to Phase 2 secondary endpoints Updated to clarify cohort-specific inclusion criteria for Cohorts 1,2 and 3 Clarifications made to inclusion criteria (prior therapy, steroid dosing prior to enrolment) Specified that dosing is AED (Adult Equivalent Dose) since subjects 12 to ≤ 25 years of age would need an adjustment to dose that is considered equivalent to the adult dose. Provision for palliative radiation added and electrocardiogram analysis was added to safety analysis section Added language about performing bone scans at baseline if bone metastases are suspected.
Global Version 6 Amendment 6	25-Jul-2023	Study Population	Updated study population for exploratory Cohort 3. ALK+ and NTRK+ subjects are no longer the focus of the exploratory analysis in alignment with the clinical development plan for repotrectinib and will no longer be enrolled in Cohort 3.
Global Version 7 Amendment 7	12-Dec-2023	Assessments	Updated to include clinical assessments to evaluate potential signals of ocular toxicity given the concerns in the drug class and growth plate monitoring per health authority request.
Global Version 8 Amendment 8	28-Mar-2024	Inclusion Criteria Dose Modifications for AEs Statistics	Updated the inclusion criteria to increase overall enrolment and reduce enrolment barriers: Removed requirement of prospective confirmation of measurable disease at baseline by blinded independent central review (BICR) for Cohorts 1 and 2; Updated absolute neutrophil count (ANC) screening range based on clinical landscape, repotrectinib safety profile and Investigator feedback; Updated that if a fresh tumour biopsy is not clinically feasible, the Sponsor's Medical Monitor may be contacted to assess eligibility to decrease patient and site burden. Updated dose interruption and modification language for adverse events (AEs) (skeletal fracture and weight increase) to allow treatment continuation based on Investigator assessment of benefit. Updated primary endpoint analysis to indicate it will be limited to subjects with measurable disease at baseline confirmed by BICR; subjects without measurable

Protocol Version	Date	Category	Key Change and Rationale
			disease at baseline will be replaced until enrollment targets are met. Updated to clarify study will have 1 Statistical Analysis Plan (SAP)will that includes details on secondary and sensitivity analyses.

The proportion of subjects with important protocol deviations (24%) is reasonable and mostly entailed safety assessment deviations (e.g., SAE not reported within 24 hours).

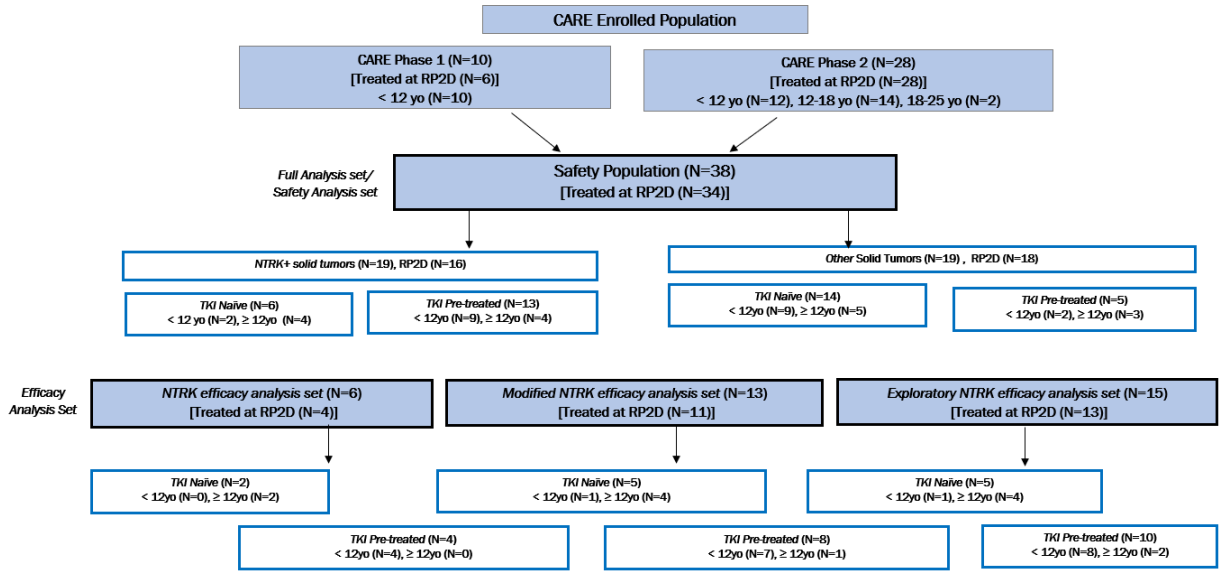
Numbers analysed:

Data submitted in the interim study report is collected through the DCO date of 19 Dec 2022. Updated safety and efficacy analysis sets are based on the DCO of 15 Oct 2023 and is demonstrated in the flow chart below.

Table 32. Definition of CARE analysis sets

CARE Analysis Set	Definition
Full Analysis Set (FAS)	The FAS includes all subjects who are enrolled and have received at least one dose of study treatment.
RP2D Analysis Set	The RP2D set consists of all subjects assigned to Dose Level 2 of Phase 1 of the study and all subjects from Phase 2.
Safety Analysis Set	The Safety Analysis Set includes all subjects who are enrolled and have received any dose of repotrectinib in either the Phase 1 or Phase 2 portion of the CARE study.
NTRK Efficacy Analysis Set	The NTRK Efficacy Evaluable Analysis Set includes all enrolled NTRK subjects who received study treatment, had a baseline tumour assessment with documentation of measurable disease per central reviewer, and started treatment at least 8 months prior to the data cutoff date (had at least one post-baseline assessment and first dose date prior to 19-Apr-2022).
Modified NTRK Efficacy Analysis Set	The Modified NTRK Efficacy Evaluable Set includes all enrolled NTRK subjects who received study treatment, had a baseline tumour assessment with documentation of measurable disease per central reviewer, and had at least one post-baseline assessment and first dose date prior to 19-Oct-2022.
Exploratory NTRK Efficacy Analysis Set	The Exploratory NTRK Efficacy Evaluable Set includes all enrolled NTRK subjects who received study treatment, had a baseline tumour assessment with documentation of measurable disease per central reviewer, and had at least one post-baseline assessment and first dose date prior to 15-Aug-2023.

Figure 12. CARE study flow chart



Notes: Data cutoff date of 15-Oct-2023
RP2D set consists of all subjects assigned to Dose Level 2 of Phase 1 of the study and all subjects from Phase 2.

Pooling criteria for safety analysis set and NTRK efficacy analysis set are summarised in the table below:

Table 33. Pooling criteria safety and NTRK efficacy analysis sets (CARE)

Analysis	Pooling Criteria
Safety Analysis	NTRK - All NTRK subjects regardless of phase Other - All ROS1 and ALK subjects regardless of phase
NTRK Efficacy Analysis	Only NTRK subjects, in both Phases, are considered for efficacy and grouped as TKI pre-treated or TKI-naive.

Baseline data:

Table 34. CARE Subject Demographics- Full Analysis Set (DCO 15 Oct 2023)

	NTRK (N = 19)	Other (N = 19)	Overall Total (N = 38)
Age (years) [a]			
Mean	9.3	9.2	9.2
Standard Deviation	6.33	6.24	6.20
Median	7.0	10.0	10.0
Min, Max	1, 24	0, 21	0, 24
Age Group, n (%)			
Newborn: 0 to 28 days	0	0	0
Infant and Toddler: > 28 days to < 2 years	2 (10.5)	3 (15.8)	5 (13.2)
Child: 2 years to < 12 years	9 (47.4)	8 (42.1)	17 (44.7)

	NTRK (N = 19)	Other (N = 19)	Overall Total (N = 38)
Adolescent: 12 to < 18 years	7 (36.8)	7 (36.8)	14 (36.8)
Adult: 18 to 25 years	1 (5.3)	1 (5.3)	2 (5.3)
Sex, n (%)			
Female	10 (52.6)	8 (42.1)	18 (47.4)
Male	9 (47.4)	11 (57.9)	20 (52.6)
Race, n (%)			
Asian	3 (15.8)	5 (26.3)	8 (21.1)
Black or African American	1 (5.3)	2 (10.5)	3 (7.9)
White	15 (78.9)	9 (47.4)	24 (63.2)
Multiple	0	1 (5.3)	1 (2.6)
Missing	0	2 (10.5)	2 (5.3)
Ethnicity, n (%)			
Hispanic or Latino	6 (31.6)	1 (5.3)	7 (18.4)
Not Hispanic or Latino	13 (68.4)	17 (89.5)	30 (78.9)
Missing	0	1 (5.3)	1 (2.6)
Karnofsky Performance Status, n (%)			
100	1 (5.3)	0	1 (2.6)
90	0	0	0
80	1 (5.3)	0	1 (2.6)
70	0	1 (5.3)	1 (2.6)
Lansky Performance Status, n (%)			
100	5 (26.3)	7 (36.8)	12 (31.6)
90	5 (26.3)	5 (26.3)	10 (26.3)
80	5 (26.3)	3 (15.8)	8 (21.1)
70	2 (10.5)	2 (10.5)	4 (10.5)
60	0	1 (5.3)	1 (2.6)
Height (cm)			
Mean	133.42	133.08	133.25
Standard Deviation	34.080	41.126	37.254
Median	135.00	149.70	142.15
Min, Max	78.0, 188.2	65.1, 197.0	65.1, 197.0
Baseline Weight (kg)			
Mean	39.59	38.49	39.04
Standard Deviation	23.595	24.007	23.484
Median	40.10	38.40	38.80
Min, Max	11.1, 86.7	5.9, 76.7	5.9, 86.7
Baseline Body Mass Index (BMI) (kg/m^2)			
Mean	20.13	18.95	19.54
Standard Deviation	5.036	3.795	4.439
Median	19.40	18.10	18.60
Min, Max	13.4, 34.2	13.4, 25.6	13.4, 34.2

Note: NTRK summary pools subjects with an NTRK1-NTRK3 genetic alteration. Other summary pools subjects with an ALK or ROS1 genetic alteration. A baseline value is the last non-missing assessment prior to initial administration of study treatment. Percentages are based on the number of subjects in the Full Analysis Set.
For Karnofsky Performance Status Scale, the numeric scores refer to the following: 100 = Normal; 90 = Minor signs; 80 = Normal with effort; 70 = Cares for self; 60 = Occasional assistance; 50 = Considerable assistance; 40 = Disabled; 30 = Severely disabled; 20 = Very sick; 10 = Moribund.
For Lansky Performance Score, the numeric scores refer to the following: 100 = Fully active, normal; 90 = Minor restrictions in strenuous physical activity; 80 = Active, but tired more quickly; 70 = Greater restriction of plan and less time spent in play activity; 60 = Up and around, but active play minimal; keeps busy by being involved in quieter activities; 50 = Lying around much of the day, but gets dressed; no active playing, participates in all quiet play and activities; 40 = Mainly in bed; participates in quiet activities; 30 = Bed bound; needing assistance even for quiet play; 20 = Sleeping often; play entirely limited to very passive activities; 10 = Doesn't play; doesn't get out of bed.
[a]Age in years is calculated based on the number of years between the informed consent date and the birth date.

Table 35. Baseline disease history- Full Analysis Set (DCO 23 Oct 2023)

	NTRK (N = 19)	Other (N = 19)	Overall Total (N = 38)
Type of Cancer, n (%)			
CNS Tumour	9 (47.4)	7 (36.8)	16 (42.1)
Sarcoma, Soft Tissue	8 (42.1)	5 (26.3)	13 (34.2)
Kidney Cancer	1 (5.3)	1 (5.3)	2 (5.3)
Neuroblastoma	0	2 (10.5)	2 (5.3)
ALCL	0	1 (5.3)	1 (2.6)
Head and Neck Cancer	1 (5.3)	0	1 (2.6)
NSCLC	0	1 (5.3)	1 (2.6)
Neuroendocrine Tumour	0	1 (5.3)	1 (2.6)
Thyroid Cancer	0	1 (5.3)	1 (2.6)
Histological Classification, n (%)			
Glioblastoma	2 (10.5)	3 (15.8)	5 (13.2)
Inflammatory Myofibroblastic Tumour	0	5 (26.3)	5 (13.2)
Infantile Sarcoma	4 (21.1)	0	4 (10.5)
Glioneuronal Tumour	2 (10.5)	1 (5.3)	3 (7.9)
Infant-Type Hemispheric Glioma	2 (10.5)	1 (5.3)	3 (7.9)
Low Grade Glioma	0	2 (10.5)	2 (5.3)
Spindle Cell Sarcoma	2 (10.5)	0	2 (5.3)
Adenocarcinoma	0	1 (5.3)	1 (2.6)
Alk+ Alcl	0	1 (5.3)	1 (2.6)
Anaplastic Ependymoma	1 (5.3)	0	1 (2.6)
Anaplastic Pleomorphic	1 (5.3)	0	1 (2.6)
Xanthoastrocytoma			
Congenital Mesoblastic Nephroma	1 (5.3)	0	1 (2.6)
Desmoplastic Infantile Ganglioglioma	1 (5.3)	0	1 (2.6)
Ewing Sarcoma	1 (5.3)	0	1 (2.6)
Ganglioneuroblastoma	0	1 (5.3)	1 (2.6)
Medullary Thyroid Carcinoma	0	1 (5.3)	1 (2.6)
Mesenchymal Tumour	1 (5.3)	0	1 (2.6)
Nephroblastoma	0	1 (5.3)	1 (2.6)
Neuroblastoma	0	1 (5.3)	1 (2.6)
Neuroendocrine Carcinoma	0	1 (5.3)	1 (2.6)
Retroperitoneal Tumour	1 (5.3)	0	1 (2.6)
Brain Metastasis, n (%)			
Yes	2 (10.5)	5 (26.3)	7 (18.4)
No	17 (89.5)	14 (73.7)	31 (81.6)
Molecular Alteration Type			
NTRK	19 (100)	0	19 (50.0)
ALK	0	10 (52.6)	10 (26.3)
ROS1	0	9 (47.4)	9 (23.7)

Note: NTRK summary pools subjects with an NTRK1-NTRK3 genetic alteration. Other summary pools subjects with an ALK or ROS1 genetic alteration. Percentages are based on the number of subjects in the Full Analysis Set. Central nervous system (CNS) tumour comprises of the following histological types: glioblastoma (N = 5), Infant-Type Hemispheric Glioma (N = 3), Glioneuronal Tumour (N = 3), Low-grade Glioma (N = 2), Anaplastic ependymoma (N = 1), Anaplastic pleomorphic xanthoastrocytoma (N = 1) and Desmoplastic infantile ganglioglioma (N = 1). Soft tissue sarcoma comprises of the following histological types: Inflammatory myofibroblastic tumour (N = 5), Infantile Sarcoma (N = 4), Spindle Cell Sarcoma (N = 2), Ewing Sarcoma (N = 1) and Retroperitoneal Tumour (N = 1). Kidney cancer comprises of the following histological types: Congenital mesoblastic nephroma (N = 1) and Nephroblastoma (N = 1). Neuroblastoma comprises of the following subtypes: Ganglioneuroblastoma (N = 1), Neuroblastoma (N = 1).

Prior treatment history shown in the Table below is collected through the DCO date of 19 Dec 2022:

Table 36. Prior treatment history- full analysis set

	NTRK (N=16)	Other (N=10)	Overall Total (N=26)
Number of Prior Lines Systemic Therapy, n (%)			
Median (Min, Max)	2.0 (0, 10)	1.0 (0, 9)	1.5 (0, 10)
0	1 (6.3)	3 (30.0)	4 (15.4)
1	5 (31.3)	4 (40.0)	9 (34.6)
2	6 (37.5)	1 (10.0)	7 (26.9)
≥3	4 (25.0)	2 (20.0)	6 (23.1)
Number of Prior Lines TKI Therapy, n (%)			
Median (Min, Max)	1.0 (0, 2)	0.0 (0, 2)	0.0 (0, 2)
0	6 (37.5)	8 (80.0)	14 (53.8)
1	8 (50.0)	1 (10.0)	9 (34.6)
2	2 (12.5)	1 (10.0)	3 (11.5)
≥3	0	0	0
Subjects with:			
Prior Surgery, n (%)	14 (87.5)	7 (70.0)	21 (80.8)
Prior Radiotherapy, n (%)	8 (50.0)	2 (20.0)	10 (38.5)

Note: NTRK summary pools subjects with an NTRK1-NTRK3 genetic alteration. Other summary pools subjects with an ALK or ROS1 genetic alteration.

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

Dose and formulation:

Table 37. Dose level received at enrolment and formulation type by each analysis set (CARE)

	FAS and Safety Analysis Set (n=38) (RP2D Set = 34)		**NTRK Efficacy Analysis Set (n =6) (RP2D Set = 4)**		**Exploratory Efficacy Analysis Set (n =15) (RP2D Set = 13)**		**Modified NTRK Efficacy Analysis Set (n =13) (RP2D Set = 11)**	
	TKI-Naïve (n = 20)	**TKI-Pretreated (n = 18)**	**TKI-Naïve (n = 2)**	**TKI-Pretreated (n = 4)**	**TKI-Naïve (n = 5)**	**TKI-Pretreated (n = 10)**	**TKI-Naïve (n = 5)**	**TKI-Pretreated (n = 8)**
Age < 12 years	RP2D (n=5) • Suspension (n=5) Phase 1/DL2 (n=4) • Suspension (n=3) • Capsule (n=1) Phase 1/DL1 (n=2) • Capsule (n=1) • Suspension (n=1)	RP2D (n=7) • Capsule (n=2) • Suspension (n=5) Phase 1/DL2 (n=2) • Capsule (n=1) • Suspension (n=1) Phase 1/DL1 (n=2) • Suspension (n=2)	N/A	Phase 1/DL2 (n=2) • Suspension (n=1) • Capsule (n=1) Phase 1/DL1 (n=2) • Suspension (n=2)	RP2D (n=1) • Suspension (n=1)	RP2D (n=4) • Suspension (n=4) Phase 1/DL2 (n=2) •Suspension (n=1) •Capsule (n=1) Phase 1/DL1 (n=2) • Suspension (n=2)	RP2D (n=1) • Suspension (n=1)	RP2D (n=3) • Suspension (n=3) Phase 1/DL2 (n=2) • Suspension (n=1) • Capsule (n =1) Phase 1/DL1 (n=2) • Suspension (n=2)
Age > 12 years	RP2D (n=9) • Capsule (n=9)	RP2D (n=7) • Capsule (n=7)	RP2D (n=2) • Capsule (n=2)	N/A	RP2D (n=4) • Capsule (n=4)	RP2D (n=2) • Capsule (n=2)	RP2D (n=4) • Capsule (n=4)	RP2D (n=1) • Capsule (n=1)

Note: **RP2D Set** consists of all subjects assigned to Dose Level 2 of Phase 1 of the study and all subjects from Phase 2.
DL = dose level.

Outcomes and estimation:

As of the 19-Dec-2022 DCO, 13 NTRK+ subjects received study treatment and had measurable disease. 6 NTRK+ subjects (4 from Phase 1, 2 from Phase 2) with centrally confirmed measurable disease with at least 6 months of follow-up from their first post-baseline scan (i.e. NTRK Efficacy Evaluable Set) were included in the primary efficacy analysis.

Updated estimates of ORR and DoR in addition to IC-ORR as of the 15-Oct-2023 data cutoff are presented in the tables below (NTRK Efficacy Evaluable Set and Modified Efficacy Evaluable Set, respectively). As of Oct 2023, all patients in the Modified NTRK efficacy set had at least 6 months follow up for DOR.

Table 38. Overall efficacy for NTRK subjects by BIRC, CARE (NTRK Efficacy Evaluable Set)

	TKI-Naïve (N=2)	**TKI-Pretreated (N=4)**
Best Overall Response, n (%)		
CR	1 (50.0)	0
PR	0	1 (25.0)
SD	0	0
PD	1 (50.0)	3 (75.0)
NE	0	0
ORR (CR + PR), n (%)	1 (50.0)	1 (25.0)
(95% CI)	1.3, 98.7	0.6, 80.6
Duration of Response (months)		
Events, n (%)	0	1 (100.0)
Censored, n (%)	1 (100.0)	0
Min, Max	7.6+, 7.6+	9.2, 9.2

Notes: 15-Oct-23 data cutoff
Percentages are based on the number of subjects in the *NTRK* Efficacy Evaluable Set.
95% CIs for ORR are based on Clopper-Pearson Exact method.
'+' indicates a censored value.

Complete response per BICR-RECIST was observed in a 13-year-old female subject with soft tissue sarcoma (TKI-naïve) with a DOR of 7.6+ months. Partial response per BICR-RANO was observed in a 7-year-old female subject with high-grade glioma (TKI pretreated) with a DOR of 9.2 months.

Table 39. Overall Response and Associated Efficacy Endpoints for NTRK Subjects by BICR - Modified NTRK Efficacy Evaluable Set (CARE)

	TKI-Naïve (N=5)	**TKI-Pretreated (N=8)**
Best Overall Response, n (%)		
CR	1 (20.0)	0
PR	2 (40.0)	2 (25.0)
SD	0	3 (37.5)
PD	2 (40.0)	3 (37.5)
NE	0	0
ORR (CR + PR), n (%)	3 (60.0)	2 (25.0)

(95% CI)	14.7, 94.7	3.2, 65.1
Duration of Response (months)		
Events, n	0	1 (50.0)
Censored, n (%)	3 (100.0)	1 (50.0)
Min, Max	7.6+, 14.8+	9.2, 9.3+

Notes: 15-Oct-23 data cutoff
Percentages are based on the number of subjects in the Modified *NTRK* Efficacy Evaluable Set
Modified *NTRK* Efficacy Evaluable Set includes all enrolled *NTRK* subjects who received study treatment, had a baseline tumour assessment with documentation of measurable disease per central reviewer, and at least one post baseline assessment.
95% CIs for ORR are based on Clopper-Pearson Exact method.
'+' indicates a censored value

Table 40. IC-ORR for NTRK subjects by BICR in CARE (efficacy evaluable set)

	TKI-Naive (N=3)	**TKI-Pretreated (N=3)**
Subjects with Measurable Brain Lesions by BICR	3	3
Best Overall Response, n (%)		
CR	1 (33.3)	0
PR	1 (33.3)	1 (33.3)
SD	0	1 (33.3)
PD	1 (33.3)	1 (33.3)
NE	0	0
IC-ORR (CR + PR), n (%)	2 (66.7)	1 (33.3)
(95% CI)	9.4, 99.2	0.8, 90.6
Intracranial Duration of Response (months)		
Events, n (%)	0	1 (100.0)
Censored, n (%)	2 (100.0)	0
Min, Max	11.1+, 14.8+	9.2, 9.2

Note: Data cutoff date of 15-Oct-2023
Note: IC-ORR Evaluable Set includes all enrolled NTRK subjects who received study treatment and had a baseline CNS tumour assessment with documentation of measurable disease per central reviewer. Percentages for Best Overall Response and Overall Response Rate are based on the number of subjects in the IC-ORR Evaluable Set. Percentages for Duration of Response are based on the number of Responders.
Note: 95% CIs for IC-ORR are based on Clopper-Pearson Exact method.
Note: Not Done are assigned to Not Evaluable (NE).
"+" indicates a censored value.

2.6.6. Discussion on clinical efficacy

The applicant is seeking two separate therapeutic indications for repotrectinib: one in the NTRK fusion-positive solid tumour and one in ROS1 positive NSCLC.

To support both indications, the applicant has presented data from one pivotal single arm phase 1-2 trial (TRIDENT-1). This evaluation is based on the updated and pooled efficacy datasets; one for ROS1 positive NSCLC (n=323), divided into four separate cohorts and one for NTRK positive solid tumour (n= 120), divided into two cohorts. The CSR is based on Phase 2.

The study is conducted worldwide and started recruitment on 07 March 2017 (phase 1, FPFV). Initiation of phase 2 occurred on 28 June 2019 (FPFV). Enrolment into Phase 1 and EXP-1-4 of Phase 2 is completed. LPLV for the NTRK+ population (EXP-5 and EXP-6) is anticipated in February 2028.

The CARE study, a single arm phase 1-2 study, is submitted to support the proposed tumour agnostic NTRK-indication in adolescents ≥ 12 years, with interim data from paediatric participants, adolescents and young adults ≤ 25 years (n=38 [6 efficacy evaluable]). The study is conducted worldwide. An expansion to include European study sites and two years delay of study completion was agreed by PDCO/EMA in August 2023. The first subject was enrolled 30 Apr 2020 and the study is still ongoing (phase 2). CARE is expected to be completed with (LPFV) in March 2029, and LPLV in Nov 2029.

Data from adults (TRIDENT-1) and paediatric patients (CARE) are presented separately. EMA scientific advice (SA) concerning TRIDENT-1 was given in 2020. SAT design was agreed for the NTRK indication based on the rarity of tumours that harbour NTRK fusions and the rarity of NTRK fusions in more common tumours. However, for ROS1 positive NSCLC it was highlighted that a randomised trial would have been preferred from a scientific point of view and deemed feasible. In addition, the prespecified ORR threshold for success in some of the cohorts were debated.

Design and conduct of the clinical studies

In **TRIDENT-1**, adult subjects with solid malignancies harbouring ROS1, ALK, or NTRK rearrangements were included. The objectives in phase 1 were to determine the MTD, RP2D, safety and tolerability, PK and preliminary assessment of efficacy of repotrectinib. Phase 2 further evaluated the efficacy and safety profile of repotrectinib at the RP2D (160 mg QD).

Subjects were enrolled into six expansion cohorts (EXP) according to tumour type, ROS1 or NTRK rearrangement, and prior treatment. After 14 days, the repotrectinib dose could be increased to 160 mg BID based on subject safety and tolerability. Treatment continued until documented radiographic progression as assessed by BICR, unacceptable toxicity or consent withdrawal.

EXP-1 to EXP-4 included participants with ROS1 positive advanced NSCLC. Patients in EXP-1 were naïve to prior TKI-treatments, whereas patients in EXP-2 to EXP-4 had been treated with one or two prior TKIs (plus or minus chemotherapy). EXP-5 and -6 included participants with NTRK positive advanced solid tumours; the TKI-naïve in EXP-5 and TKI-pretreated in EXP-6 (plus or minus prior chemotherapy or immunotherapy).

For enrolment into TRIDENT-1, patients had to have documented ROS1 or NTRK1-3 gene fusion determined by tissue-based local testing using FISH, NGS or qPCR, or repotrectinib clinical trial assay (CTA). For patients locally tested with NGS or qPCR, central testing with the CTA was performed to retrospectively confirm the ROS1 or NTRK1-3 gene fusion status while local testing with FISH had to be prospectively confirmed with the CTA at a central diagnostic laboratory. The protocol was amended in 2022, and subjects locally tested with an NGS or qPCR were no longer retrospectively tested by the central CTA after enrolment into the trial. Approximately half of all patients included in TRIDENT-1 did not have a confirmation by central CTA . Analyses of agreement between local and central testing has been provided which show good agreement for local NGS and central CTA, while for local qPCR and central CTA the agreement is rather poor (69%). Consequently, a limited number of patients without target mutation have been treated with repotrectinib in the TRIDENT-1 study.

Moderate inducers of CYP3A, such as dexamethasone or other glucocorticoids, may be used at the discretion of the Investigator. In general, this is acceptable in a cancer population, especially among those with known brain metastasis, although glucocorticoids may induce activity in tumour.

Participants with brain metastasis were eligible if measurable by RECIST v.1.1 and confirmed by BICR. A minimum of 14 days must have elapsed from completion of whole brain radiation therapy or a minimum of 7 days from completion of stereotactic radiosurgery before start of study treatment. Subjects requiring steroids at a stable or decreasing dose (≤12 mg/day dexamethasone or equivalent) for at least 14 days were eligible. Intracranial (IC)-ORR was a secondary endpoint and since this short

time interval between radiotherapy and treatment with repotrectinib was allowed, there is a risk that radiotherapy has affected the efficacy results.

The primary endpoint was ORR by BICR using RECIST v1.1. Among secondary endpoints were DoR, PFS, OS, intracranial (IC)-ORR, time to response (TTR) and patients reported outcomes (PROs). The use of ORR, measuring responses in tumour, as a primary endpoint is in principle acceptable in a single arm trial (SAT). The clinical relevance of ORR in all types of NTRK fusions positive solid tumours is not established. In the NSCLC-setting of targeted therapy ORR may be an appropriate surrogate endpoint for PFS. The correlation to OS, is however, uncertain. DoR is essential as a secondary endpoint to support the clinical relevance of the primary endpoint, ORR, in a SAT setting. In order to ascertain clinical benefit from the outcomes of a SAT, the results in terms of ORR and DoR must be "outstanding" in relation to what can be achieved with existing therapeutic options (refer to EMA Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation application EMA/CHMP/458061/2024). As presence of brain metastases at baseline or development of brain metastases during the course of the disease is high among ROS1 NSCLC and NTRK solid tumour patients (30-50%), intracranial efficacy is essential, regardless of treatment line. Knowing that brain metastases influence the overall survival more than other metastases, inclusion of patients with brain metastases at baseline and selecting IC-ORR as a secondary endpoint is endorsed.

Time to event endpoints such as OS and PFS cannot be contextualised in uncontrolled trials and the drug effect cannot be isolated. No efficacy claims can be based on PFS and OS data from the pivotal study provided. PRO endpoints in a SAT are prone to bias and therefore interpretation is difficult rendering these endpoints less useful in a MAA setting.

The study was amended 12 times over a period of 6 years, which is extensive. The last 7 protocol amendments occurred after study initiation (from Nov 2019 to Nov 2022). Currently, none of the protocol amendments are considered to influence the B/R assessment of repotrectinib. The total enrolment of Phase 2 was originally planned to be approximately 310 subjects to evaluate efficacy in six expansion cohorts. Planned Phase 2 enrolment was increased to a total of approximately 620 subjects across expansion cohorts to allow continued enrolment in rest of world (China, Japan, EU, etc.) along with US sites in anticipation of future regulatory submissions and to evaluate safety and efficacy in regional populations. The expansion was decided before the first DCO, and thus acceptable.

After study initiation, patients ≥ 12 years were added to the inclusion criteria. However, no data on adolescents are currently available from TRIDENT-1.

Like the extensive number of protocol amendments there is an extensive number of SAPs, in total 7, written in the period 8 March 2021 to 24 Feb 2023, all after study initiation and three after first DCO. There are three integrated SAPs combining results from phase 1 and 2, two SAPs for phase 2, one SAP for phase 1 and an integrated SAP for NTRK including analyses from the CARE study. The submitted CSR with DCO 20 June 2022 is based on version 1 of the phase 2 SAP.

The dataset used for the primary efficacy analysis of ROS1+ NSCLC population is collected through the DCO date of 20 June 2022 (The primary analysis of NTRK positive solid tumour population was conducted at a later DCO (19 December 2022) An integrated efficacy analysis set was also submitted per indication, consisting of pooled data from Phase 2 and subjects who met the same eligibility criteria in Phase 1. Dose level (i.e. RP2D reception) was not an eligibility criterion for pooling. Even if patients from the pool were started with a lower dose, most of them were escalated to the 160 mg/day RP2D (91% dosed at RP2D). Moreover, the response rates in Phase 1 and 2 are overall consistent. Considering similar precedents in the histology-agnostic NTRK-dependent field, it is overall agreed that the proposed pools for efficacy assessment of repotrectinib in the provided dossier are acceptable. The updated dataset (pooled expanded) with DCO of 15 Oct 2023 and is used as basis for the evaluation.

In **CARE**, paediatric and young adult subjects (≤ 25 years) with advanced or metastatic solid tumours, primary CNS tumours, or ALCL with ALK, ROS1, or NTRK alterations were included. Phase 1 was the dose escalation part to determine RP2D and phase 2 aimed to characterise the antitumour activity of repotrectinib, characterize the PK of repotrectinib, and evaluate safety and tolerability. Subjects < 12 years were enrolled in phase 1, subjects 12 to 25 years directly into Phase 2. All subjects received repotrectinib in 28 days cycles. RP2D for subjects aged 12 to < 25 years (> 50 kg) was defined identical to the adult RP2D, 160 mg QD for 14 days followed by 160 mg BID if tolerated.

In Phase 2, subjects were enrolled in one of 3 cohorts based on disease characteristics and prior treatments. Cohort 1 and 2 include NTRK positive solid tumours only. Cohort 3 is exploratory and includes subjects with advanced solid tumours with ALK, ROS1 and NTRK alterations.

The dataset provided to support the proposed inclusion of adolescents in the tumour agnostic NTRK positive indication, is collected from DCO of 15 Oct 2023, across Phase 1 and 2. A minimum of 6 months of follow-up after the first response assessment was required in the NTRK efficacy evaluable data set.

Efficacy data and additional analyses

ROS1 positive NSCLC

An updated pooled (Phase 1 + Phase 2) expanded dataset with additional 10 months of follow-up has been submitted. At the latest DCO of 15 Oct 2023, totally 323 participants were included in the pooled efficacy set. A minimum follow-up of 6 months post-baseline scan is deemed sufficient to capture most responses in the NSCLC population.

The patients included in the study are considered fitter than the population seen in clinical practice as all patients with ECOG status ≥ 2 were excluded. A majority of participants were female, never-smokers and Asian which is in line with the epidemiology for this oncogenic driver mutated NSCLC consisting of mostly adenocarcinomas. Approximately 30% had brain metastases by BICR at baseline (full analysis set), which is considered a clinically relevant proportion as incidence of brain metastases is higher in patients who harbour oncogenic driver mutations such as ROS1. An increased risk of development of brain metastases through the treatment lines is reflected in the cohorts' compositions. The baseline data remained consistent between data cutoffs as well as between Phase 2 and pooled data sets.

Concomitant glucocorticoids were allowed in TRIDENT-1 (regardless of brain metastases). The proportion of patients using lower dose (≤ 12 mg/day dexamethasone or equivalent) of glucocorticoids (23,7%) is as expected in a population with advanced lung cancer. The proportion of patients using higher doses (> 12 mg/day dexamethasone or equivalent) was relatively low (4.5%) and is not assumed to influence the benefit/risk balance.

In the TKI-naïve (EXP-1, n=113), updated data from the expanded Phase 2 population (DCO of 15 Oct 2023) confirms a consistency of efficacy over time: ORR 76.1% (95%CI:67.2, 83.6) and median DOR 33.61 (25.46, NE). The pooled expanded analysis adds 8 participants from Phase 1 (n=121) and are in line with the updated Phase 2 data.

In the primary analysis, ORR in the TKI-pretreated population (EXP-4) was, as expected, lower than in the TKI-naïve population: 37.7% (95%CI: 24.8, 52.1) with 3 CRs (5.7%). The primary endpoint was formally not reached at the prespecified ORR threshold of 35%. The median DoR of 17.81 months (7.6, NE) is deemed clinically relevant to the 20 (out of 53) responders.

With regards to the uncertainty of the clinical relevance of the obtained ORR, the major objection raised during the evaluation procedure was addressed satisfactorily with provision of updated efficacy dataset.

In the Pooled ROS-1 Efficacy Analysis Set (n=56), a minimum DOR follow-up of 22 months is available for all subjects: ORR 41% [95% CI: 28.1, 55.0] and median DOR (14.75 months [7.56, NE]), which implicates that the responses are maintained over time, i.e. at a 10 months later data cutoff. In the expanded Phase 2 population of EXP-4 (N=104), ORR is 49% [95% CI: 39.1, 59.0] and median DOR 14.75 months (7.56, NE). In total, 8 CRs were observed among 51 responders. The pooled analysis (3 additional participants from Phase 1) showed similar estimates for ORR and mDoR. In summary, the updated more mature and expanded dataset confirms a relevant benefit also in patients with TKI-pretreated ROS1-positive NSCLC.

In both populations, the short time to response (TTR; median 1-2 months) is considered clinically relevant for the patients as it may alleviate symptoms after tumour shrinkage and may support the clinician in decision making related to toxicities.

Intracranial responses (IC-ORR):

At the time of the primary analyses only 8 of the 16 patients with BICR assessed brain metastasis at baseline were evaluated for response in EXP-1. The IC-ORR by BICR was 87.5% (95% CI: 47.3, 99.7). In EXP-4, 12 of the 24 subjects with BICR assessed brain metastasis at baseline were evaluated for response in the primary analysis. The IC-ORR by BICR was 41.7% (95% CI: 15.2, 72.3). The IC-ORR is in line with the overall ORR (primary endpoint) in both EXP-1 and EXP-4. In the updated IC-ORR analyses in the NSCLC ROS1 population, sample size has increased to 14 participants in the TKI-naïve group (EXP-1) and to 39 in TKI-pretreated (EXP-2, EXP-3 and EXP-4). With a minimum of 6 months follow-up, updated responses are in line with the primary analyses. Keeping in mind the limited numbers of patients with brain metastasis by BICR, an IC-ORR in line with overall ORR indicates intracranial activity of repotrectinib.

Of note, 24% (15/62) of the participants in the expanded (Phase 2) efficacy population (all cohorts) with brain metastasis by BICR had received CNS intervention ≤ 60 days before initiation of study treatment. Confounding of efficacy results by recent CNS intervention is foreseen, however, the exact degree is uncertain. A post-hoc subgroup analysis of IC-ORR according to time since CNS intervention (≤ or > 60 days) was provided. While small numbers, the results seem to hold for patients who did not receive CNS intervention ≤ 60 days before initiation of study treatment.

The applicant has an ongoing phase 3 superiority study of repotrectinib versus crizotinib in participants with locally advanced or metastatic TKI-naïve ROS1+ NSCLC (TRIDENT-3). The study started recruitment 21 Dec 2023 and is estimated to be completed by 27 Jan 2031. The study is multinational, including several EU sites, and will enrol approximately 230 patients randomized to repotrectinib or crizotinib 1:1, and is part of a clinical development programme for repotrectinib. TRIDENT-3 was not considered as a SOB for this CMA because that trial does not enrol patients with NTRK-positive solid tumours. According to the applicant, the recruitment of patients with brain metastasis could be challenged by other available treatment options in some regions (entrectinib, repotrectinib [US]). Although limitations in design and population is acknowledged, the future IC-ORR data from the phase 3 TRIDENT-3 would obviously serve as a support to TRIDENT-1 while the data are randomized and are, thus, of high clinical interest. The applicant has agreed to provide the final data from TRIDENT-3 as a recommendation (**REC**).

NTRK positive solid tumours

The main data (expanded pooled Phase 1 and Phase 2) supporting the sought tumour agnostic indication of repotrectinib in adult patients with NTRK+ solid tumours, is represented by 120 participants (across EXP-5, n= 51 and EXP-6, n=69) with measurable disease, receiving at least one dose of repotrectinib and at least 6 months of follow-up after first response evaluation.

The patient populations in EXP-5 and EXP-6 are highly heterogeneous in terms of tumour type and incidence of NTRK gene alterations. 18 tumour types are included in the NTRK-cohorts, divided on totally 120 participants. The most represented tumour type (approximately 36%) in EXP-5 and EXP-6 was NSCLC, wherein NTRK fusions are rare. Other tumour types are rare cancers wherein NTRK fusions are common (secretory breast cancer and salivary gland carcinoma). Baseline diseases as salivary gland cancer (14.2%) soft tissue sarcoma (10.8%)) and breast tumours (2.5%)) constituted very small subgroups. The representation of NSCLC in the NTRK efficacy analyses sets (EXP-5 and 6) is relatively high compared to both the prevalence of NTRK mutation (0.23%) in NSCLC in general (Solomon et al., Mod Pathol 2020) and to the representation of patients with NSCLC in the pivotal trials of larotrectinib and entrectinib. Since NSCLC is one of the commonest cancers and depending on the particular expertise of investigators, the rate of recruitment of NTRK+ NSCLC is likely to exceed those of other tumours. Considering that this higher than expected proportion of NTRK+ NSCLC would cause an imbalance in the other cohorts, the sponsor amended the protocol to cap NSCLC enrolment.

In the TKI-naïve cohort (EXP-5) the updated, expanded and pooled (Phase 1 and Phase 2, n=51) dataset based on 10 months later DCO (15 Oct 2023) confirms a stable ORR (30/51, 58.8% [95%CI: 44.2, 72.4]) although median DOR is still not reached. At the primary analyses 8 out of28 responding subjects achieved CR. Objective responses (CR or PR) were seen across 6 different tumour types (NSCLC, salivary gland cancer, thyroid cancer, sarcoma, head and neck cancer and peripheral nerve sheath tumour). The response is promising in a TKI-naïve NTRK positive solid tumour population and considered in range with the observed responses in the conditionally approved products (entrectinib and larotrectinib). However, the heterogeneity in terms of histology in this population, adds uncertainty to the efficacy estimates. The expected DoR in a TKI-naïve NTRK population should be at least as durable as DoR in approved products in the same population (entrectinib and larotrectinib) which are in the range of 20 to 43 months.

The efficacy in the TKI-pretreated (EXP-6, n=69) is confirmed and deemed stable over time by the expanded pooled dataset: ORR 47.8% (95%CI: 35.6, 60.2) and median DOR 9.76 months 87.36, 12.98). with 2 CRs out of 32 responders. Objective responses (CR or PR) were seen in 10 different tumour types (secretory breast cancer, glioblastoma, NSCLC, CRC, neuroendocrine tumour, salivary gland cancer, thyroid cancer, sarcoma, cholangiocarcinoma). The assessment of the clinical relevance of an ORR and DoR in a TKI-pretreated NTRK positive solid tumour population is obscured by the great heterogeneity in terms of histology seen in EXP-6. Overall, a median DoR of 9.76 months is deemed durable in a 2nd or 3rd line setting with advanced solid tumour, often with rare mutations or rare cancers, and limited systemic treatment options left. Median PFS of 7.36 (95%CI: 2.9, 9.7) and median OS at 19.12 months (95%CI:9.6, 25.7) are considered supportive to a durable and clinically relevant tumour response (ORR) in a single arm, uncontrolled setting.

The short median TTR (1-2 months) is considered valuable for the patients as tumour shrinkage may alleviate symptoms and also support the clinician in decision making related to toxicities.

Contextualization of the efficacy results in EXP-6 is challenging as historical data in NTRK+ patients are mainly from the TKI-naïve setting with approved agents (entrectinib, larotrectinib). In addition, the large heterogeneity in terms of histology across trials hampers a fair comparison.

Notably, response per tumour type was not a prespecified subgroup analysis. With an ORR ranging from 0 to 100% according to the type of tumour, it seems like the overall ORR is not reflective of efficacy per tumour type. In the 51 TKI-naïve subjects, objective responses (CR or PR) were seen across 6 different tumour types (NSCLC, salivary gland cancer, thyroid cancer, sarcoma, head and neck cancer and peripheral nerve sheath tumour). In the 69 TKI-pretreated participants, objective responses (CR or PR) were seen in 10 different tumour types (secretory breast cancer, glioblastoma, NSCLC, CRC, neuroendocrine tumour, salivary gland cancer, thyroid cancer, sarcoma,

cholangiocarcinoma and peripheral nerve sheath tumour). Although, additional data on efficacy per tumour type is expected from an ongoing study, TRIDENT-1, a comprehensive assessment of the efficacy data by tumour type is likely not feasible. The uncertainty in the ORR estimate per tumour type and the fact that ORR in the total population may not reflect the expected response in a specific tumour type is reflected in the SmPC section 5.1. The applicant has presented a plan to enrich the data in each tumour type post-authorization in the context of a CMA. This plan is further assessed in the section 3.7.3. *Additional efficacy data needed in the context of a conditional MA*.

Intracranial responses (IC-ORR):

Based on the updated dataset (expanded phase 2) two out of three participants had intracranial (IC) responses in EXP-5 and four out six in EXP-6. The numbers of participants with measurable brain metastases by BICR at response evaluation are too small to draw any conclusion regarding intracranial activity. The IC response data in the NTRK population are to a certain extent supported by the IC-ORRs provided from the ROS1+ NSCLC population, where 53 participants with brain metastasis by BICR at baseline are presented. Currently, no claims can be made in the SmPC section 5.1 based on these limited IC data in NTRK+ solid tumours. In order to address these limitations in the IC response data, the applicant has committed to submit the final data, including IC-responses, from TRIDENT-1 as a **SOB**.

ROS1 positive NSCLC and NTRK positive solid tumours

Sensitivity analysis:

Two sensitivity analyses of DoR, one where patients with documented progression or death after two or more missing assessments were imputed as events, and one where all non-administrative censorings (dropout/lost to follow-up etc.) were imputed as events have been provided. The sensitivity analyses were consistent with the primary analysis.

Resistance mutations:

It is acknowledged and described in the literature that patients on treatment with other ROS1 and TRK kinase inhibitors are prone to developing resistance mutations in the TRK- and ROS1-kinase domain. SFMs has been reported to occur in up to 50% of patients failing therapy with current ROS1 TKIs.

In the expanded pooled population of TRIDENT-1 with ROS1+ NSCLC (EXP-2, EXP-3, EXP-4), there were 45 patients with resistance mutations of a total of 202 patients, of which 185 were tested for mutations. Of the 45 patients with resistance mutation, 22 (49%) responded to treatment with repotrectinib which is in line with the response in the overall population. In the NTRK+ population (EXP-6), there were 77 patients tested for mutations and 37 were found to be positive, of which 46% (17/37) responded to treatment with repotrectinib. Although promising results, for both populations, i.e. ROS1+ and NTRK+, the number of patients studied is limited, and no certain estimation of ORR can be performed per mutation type. For further confirmation of efficacy in the NTRK pretreated population, the applicant has proposed to report efficacy by baseline resistance mutation status as part of the broader NTRK data generation plan for the CMA.

The characterisation of acquired resistance to repotrectinib was described as an exploratory endpoint for TRIDENT-1, however, not further highlighted in the submitted dossier. The applicant has informed that the ongoing TRIDENT-3 study will include investigations of mechanisms of resistance to repotrectinib, and ctDNA will be explored and evaluated for post-treatment changes in mutation status of genes, including ROS1 gene. The results on acquired resistance to repotrectinib is confirmed by the applicant to be provided when final data from TRIDENT-3 are available (**REC**).

Subgroups:

Overall, there were confirmed responses across predefined subgroups for age (18 to <65 years, 65 to <75 years, ≥75 years), sex, race (Caucasian, Asian, Other), region (US, Europe, Asia, Other), performance status (0, 1), baseline brain metastases (yes or no) and prior TKI treatment. The responses seem in line regardless of prior TKI treatment (i.e., entrectinib or larotrectinib), although median durability of response is potentially higher after prior entrectinib. There were some numerical differences in efficacy between subgroups, but no clear patterns identified.

PRO data:

Patients reported outcomes (PROs) were evaluated in terms of QoL and symptom scores (EORTC-QLQ-LC13 scale). Interpretation of PRO data from a single arm, open-label trial is complicated by the high risk of bias. Although the results suggest a stable symptom burden and QoL score over time, no firm conclusion can be drawn regarding PROs. Due to the uncontrolled nature of a single arm trial, no claims can be made regarding PRO data in the SmPC section 5.1.

Biomarker testing:

To avoid the risk of treating patients that are not expected to benefit from repotrectinib treatment patients should be tested by a validated NGS method.

CARE: *paediatric data in NTRK positive solid tumours*

To support the proposed tumour agnostic NTRK-indication in adolescents ≥ 12 years, interim data from the CARE study were submitted. As of 15 Oct 2023 (DCO), a total of 38 patients have been included, 10 in phase 1 and 28 in phase 2. 19 of the enrolled participants had NTRK positive tumours, including 7 adolescents (12 to < 18 years). The (modified) NTRK efficacy evaluable set was limited to 13 subjects who had minimum of 6 months of follow-up for tumour assessment after the first post-baseline scan. 6 months is deemed sufficient to capture the majority of responses.

At the time of the DCO, the study had been ongoing for 4 years. Slow recruitment resulted in a delay in completion of the study to Nov 2029 and expansion to European study sites. Feasibility is ongoing to add more sites and potentially expand into other countries. Enrolment challenge is mainly due to rarity of disease with NTRK fusions observed in paediatric tumours.

The proportion of subjects with important protocol deviations (24%) is reasonable and mostly entailed safety assessment deviations (e.g., SAE not reported within 24 hours).

Seven of the 19 patients with NTRK positive tumour were in the age group relevant for the proposed indication, i.e. adolescents ≥ 12 years. While it is recognized that the applicant submitted data for patients <12 years old, this does not align with the pursued indication in adolescents. TRK inhibitors seem to have comparable efficacy across all age groups. Given the similarity in the biology and histology of NTRK+ tumours between adolescents and children and comparable exposures across different age groups, efficacy and safety data from subjects age <12 yrs from CARE study, along with the adult data from TRIDENT-1 trial, are considered supportive of the proposed adolescent indication (patients aged 12 and above) in NTRK+ tumours.

The majority of the patients had CNS tumour (42%) of various histology or a type of soft tissue sarcoma (34%). Most study participants (>90%) had received one or more lines of prior systemic therapy and 25% ≥ 3 lines. Most of the NTRK patients had had prior surgery (>80%), which is expected in a mixed population of different solid tumours predominantly in CNS and soft tissue sarcoma. 18% had brain metastases at baseline. A critical assessment of baseline characteristics is hampered by the very small sample sizes in the CARE study.

Three out of six (50%) participants had a tumour response at the primary efficacy analysis; 1 CR and 1 PR in TKI-naïve subjects and 1 PR in the TKI-pretreated subjects. All had a DoR lasting > 9 months.

In the modified NTRK efficacy evaluable set, with less than 6 months of follow-up, two additional PR was observed (ORR= 5/13) and 2 responses (PR) were unconfirmed. At the latest DCO, all the responders in the modified efficacy evaluable set (n=13) were confirmed and had a minimum of 6 months of follow-up after first post-baseline scan.

To summarize, the limited number of subjects in the analyses challenges any solid conclusion of efficacy, but, in reflection of results from the NTRK+ adult set, a signal of efficacy in the paediatric population emerges, noting that intracranial responses occurred in both TKI-naïve and TKI-pretreated patients. Furthermore, the uncertainty in activity of repotrectinib across tumour types is remaining. The limitation of the paediatric data is obvious and currently hampers further assessment. The indication in adolescents is primarily supported by extrapolation of efficacy and safety from pivotal adult data through PK exposure matching under the assumption of similarity of disease and response to treatment

Additional efficacy data needed in the context of a conditional MA

Given that the data supporting the NTRK+ solid tumours indication is not considered comprehensive, the applicant provided a justification to support the request for a Conditional Marketing Authorisation (CMA).

The main areas of non-comprehensive data with regard to efficacy are:

- Benefit in subgroups of patients based on histology
- Benefit in patients with intracranial metastases
- Benefit in adolescents
- Magnitude of treatment effect in terms of time to event endpoints (PFS and OS)
- Resistance mutations and benefit of repotrectinib

No confirmatory randomised and controlled study is planned for additional data generation in the NTRK positive solid tumour population. The current dataset will be expanded to a total of approximately 230 adults and paediatric participants with NTRK positive solid tumours across TRIDENT-1 (80 in EXP-5 and 120 in EXP-6) and CARE studies. About 30 paediatric and adolescent patients with NTRK+ solid tumour in total are planned to be recruited in the phase 2 of the CARE study. Data from 19 NTRK positive subjects are presented at this submission (DCO of 15 Oct 2023), including 7 adolescents (12 to < 18 years). The last subject enrolled will be followed for a minimum of 12 months from onset of response. Existing subjects from the MAA will be followed for at least 24 months from onset of response for long-term characterisation of efficacy and safety.

To confirm activity in specific tumour types, a calibrated Bayesian hierarchical model (CBHM) is proposed to evaluate the efficacy of repotrectinib in 4 identified common cancer types that may express NTRK fusions (NSCLC, non-secretory breast cancer, colorectal cancer, sarcomas) by adaptatively borrowing information across cancer types. Given foreseen difficulties in recruiting TKI naive patients the plan is to merge TKI-naive and TKI-pretreated patients in each of the tumour types. Assuming 50-50 mix of TKI-naive to TKI-pretreated gives a merged target ORR rate of 30% based on the ORR thresholds of 50% for TKI-naive and 10% for TKI-pretreated in TRIDENT-1 protocol. Approximately 20 adult subjects, regardless of prior TKI treatment history, are planned for each of the 4 cancer types. Within each tumour type, a minimum of 9 patients will be enrolled at the first stage. If the futility criteria, defined as posterior probability of ORR > 10% being less than 5%, are not met for a certain tumour type, an additional 11 subjects will be enrolled at the second stage. The ORR analysis guided by CBHM model by adaptively borrowing information across tumour types will be performed at planned interim analysis when at least 2 tumour types have completed the enrolment for the first stage and have been followed for a minimum of 12 months for response.

As of DCO 15 Oct 2023 in both TRIDENT-1 and CARE, recruitment was still ongoing and study completion is estimated to February 2028 and November 2029, respectively. A modified PIP was agreed by PDCO in August 2022 issuing delay of study completion of CARE due to slow recruitment. Recruitment is ongoing in phase 2; the study is active in 40 sites across 10 participating countries in Europe, North America and Asia. Further expansion is considered. Enrolment challenges are mainly due to rarity of disease with NTRK fusions in the paediatric population.

The proposed plan for additional data generation is acceptable and the applicant will submit the final data from CARE by Q4 2030 as a specific obligation (SOB). The expanded dataset will provide more information on efficacy and safety of repotrectinib in the NTRK positive solid tumour population of adults, adolescents and children due to longer follow-up and inclusion of more patients.

The currently limited data on efficacy per tumour type will be strengthened regarding number of tumour types and minimum enrolment per tumour type based on additional data from TRIDENT-1 and CARE to allow more precise estimates for ORR and DoR. A minimum of 15 different tumour types is deemed sufficient to confirm efficacy in a wide spectrum of tumours. These requirements are not reflected in the protocol, however an abbreviated post marketing SAP has been provided outlining enrolment requirements for four selected tumour types and a Bayesian model for response evaluation based on TRIDENT-1. The proposed plan is deemed acceptable and the final data from TRIDENT-1 will be submitted by Q1 2029 as a specific obligation (SOB).

Very limited data on CNS responses is provided. This would be a clinically relevant benefit if demonstrated. Although promising, as support is provided by the ROS1+ NSCLC intracranial (IC) response data, it is currently not possible to make a sufficiently robust assessment of these data, and no claims can be made in the SmPC based on the provided data. The applicant has committed to provide the final data from TRIDENT-1 as part of the **SOB**.

Acquired resistance mutations after prior TRK-TKI treatment may result in treatment failure and is part of an unmet medical need in the TKI-pretreated population. The clinical efficacy data indicate similar efficacy in patients with resistance mutations as in the overall population. For further confirmation of efficacy in the NTRK pretreated population, the applicant has proposed to report efficacy by baseline resistance mutation status as part of the broader NTRK data generation plan as a subgroup. These data are agreed to be part of the SOB on reporting of results from TRIDENT-1 and CARE.

2.6.7. Conclusions on the clinical efficacy

ROS1 positive NSCLC

Available efficacy data in terms of ORR and DoR are expected to translate into clinical benefit for the treatment of adults with ROS1 positive NSCLC, both in TKI-naïve and TKI-pretreated patients. In the TKI-naïve population, the response rate seems in line with what has been demonstrated in already approved products for the same indication although no direct comparison is available.

The magnitude of this effect is such that it is expected to result in clinically relevant effects.

Activity shown in the TKI-pretreated ROS1+ NSCLC population is, as expected, lower and less durable than in the TKI-naïve patients but strengthened by updated results from a larger and more mature dataset with an ORR > 48% and a stable median DOR of 14.75 months. This is deemed clinically relevant although limited data are available for contextualization since no other ROS1-targeted TKI has an equivalent approved indication.

Since the number of patients with resistance mutations is relatively low in the studied TKI pretreated population (EXP-2, EXP-3, EXP-4), no certain estimation of ORR can be performed per cohort and

mutation type. However, it seems that repotrectinib has the potential to overcome resistance mutations developed after previous treatment with a ROS1 targeting TKI and provide similar response as for the overall pretreated population.

Despite limitations in study design and recruitment challenges in the ongoing phase 3 trial, TRIDENT-3, the study is expected to provide unique randomised data comparing repotrectinib with crizotinib. Furthermore, results on acquired resistance to repotrectinib is confirmed by the applicant to be provided when final data from TRIDENT-3 are available. Final data from TRIDENT-3 are of clinical relevance and will be submitted by the applicant as a Recommendation (**REC**).

NTRK positive solid tumours

Currently, the data provided in the NTRK positive solid tumour population is considered non-comprehensive.

The overall response rate could be considered clinically meaningful in the TKI-naïve and -pretreated setting of NTRK positive tumours, if confirmed by a more mature DoR. The interpretation of efficacy per tumour type is, however, hampered by the heterogeneous dataset, limited number of different histologies and small sample size in each tumour group. With ORRs ranging from 0 to 100%, no firm conclusion can be drawn regarding efficacy per tumour type. In a setting of rare tumours and rare gene alteration in common tumours, there is an unmet medical need, especially in the TKI-pretreated population.

In the setting of a CMA, the unmet medical need should be addressed to a similar or greater extent than what is understood for the already conditionally authorised products for the NTRK solid tumour indication. Although no direct comparison is available, the overall antitumour activity of repotrectinib in NTRK positive tumour in TKI-naive subjects, seems to be in line with that of entrectinib and larotrectinib. An important part of the unmet medical need is efficacy in brain metastases and response in tumour despite presence of resistance mutations. Very limited data are available in IC response in the NTRK population (n=9) and is not sufficient to conclude. Although some support is provided from the IC-responses in the ROS1 positive NSCLC population, a larger dataset in the NTRK+ solid tumour population will be provided through final data submission of TRIDENT-1 (**SOB**).

Patients with resistance mutations seem to have a similar response to repotrectinib as the overall pretreated cohort. However, the number of TKI-pretreated patients in EXP-6 with resistance mutations is small, and ORR per mutation type cannot be estimated. The applicant has proposed to report efficacy by baseline resistance mutation status as part of the broader NTRK data generation plan as a subgroup. Thus, this will be part of the SOB on reporting of results from TRIDENT-1 and CARE.

Efficacy data from the paediatric NTRK solid tumour population is limited to 13 patients of whom five are responders. A comprehensive assessment of the data is therefore not feasible. The NTRK indication in adolescents is primarily supported by extrapolation of pivotal adult data through PK exposure matching under the assumption of similarity of disease and response to treatment. The applicant will submit the final data from CARE as a specific obligation (**SOB**).

In the context of a CMA, the applicant has presented plans for further data collection across tumour types. The abbreviated SAP outlines the plan which is considered acceptable.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

In order 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) by Q1 2029.

In order 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 (CARE) by Q4 2030.

2.6.8. Clinical safety

The clinical safety data supporting this application are derived from the pivotal Phase 1/2 study TRIDENT-1, and the Phase 1/2 paediatric study CARE, supporting the use of repotrectinib in:

- adult subjects with locally advanced or metastatic ROS1-positive NSCLC
- adult and adolescent subjects (≥ 12 years of age) with NTRK-positive solid tumours

The primary safety analysis includes all subjects treated with at least 1 dose of repotrectinib in the TRIDENT-1 study (n=565), out of which 472 subjects were treated with the recommended dose (RP2D). Additional safety analyses were conducted in the following subpopulations: subjects with ROS1-positive NSCLC (n=367), subjects with NTRK-positive solid tumours (n=144), and "Other treated subjects" subjects with ROS1-positive non-NSCLC, and ALK-positive gene fusions, per protocol(n=54). The RP2D pools for ROS1+ NSCLC and NTRK + patients consist of 335 and 135 patients, respectively.

Safety analysis of the CARE study included 38 paediatric subjects with advanced or metastatic solid tumours, primary CNS tumours, or anaplastic large cell lymphoma (ALCL) with ALK, ROS1, or NTRK alterations who received at least 1 dose of repotrectinib. Thirty-four (34) subjects received the recommended dose (RP2D). Out of the total 38 subjects, 19 presented with NTRK-positive solid tumours, 8 of them being ≥ 12 years which corresponds to the applied indication. The other 11 out of 19 subjects with NTRK-positive tumours were < 12 years of age. The remaining 19 out of 38 subjects had advanced solid tumours with ALK or ROS1 gene fusions or other ALK/ROS1/NTRK aberrations (including amplifications and point mutations) or ALK gene fusion, 8 of them being of ≥ 12years of age, while 11 subjects were < 12 years of age.

The original DCO date for safety data was 19-Dec-2022. Since TRIDENT-1 and CARE studies were ongoing at that time, additional safety data were provided upon request, with a DCO date of 15-Oct-2023, representing an additional 10 months of safety data. For the CARE study, some parts have only been submitted with data from the initial DCO (certain laboratory values, SAE by PT). The safety overview is based on data from the latest DCO, unless otherwise specified.

2.6.8.1. Patient exposure

As of the original data cutoff date, 19-Dec-2022, 519 adult subjects and 26 paediatric subjects had received at least one dose of repotrectinib in the ongoing studies TRIDENT-1 and CARE, respectively. The updated safety dataset (data cutoff date 15-Oct-2023) includes safety data from 565 subjects in TRIDENT-1 and 38 paediatric subjects in CARE.

TRIDENT-1

In TRIDENT-1, the RP2D subpopulation comprises integrated data (pooled) for 472 subjects from Phase 1 and Phase 2 of the study who received the recommended dose of 160 mg QD for 14 days, followed by 160 mg BID. The median duration of treatment and follow-up of the overall safety population was 7.59 (range 0.0-71.2) months and 27.04 months (range 0.4-79.2), respectively. Relative dose intensity was 93.9 % in the overall population. Further details on exposure are given in Table 41, followed by key demographic characteristics in Table 42. Median treatment duration for the

RP2D pools for ROS1+NSCLC, NTRK+ tumours, and overall were 9.07, 7.56, and 8.90 months, respectively. Demographic characteristics in the total RP2D population, the RP2D ROS1+ NSCLC patients, and the RPD2D were comparable and comparable to the overall population.

Table 41. Extent of Exposure to Study Therapy - TRIDENT-1 Safety Analysis Set

	***ROS1*-positive NSCLC Subjects (N = 367)**	***NTRK*-positive Solid Tumour Subjects (N = 144)**	**Other Treated Subjects (N = 54)**	**Overall Population (N= 565)**
Treatment Duration (months)[a]				
Mean	12.71 (12.168)	10.68 (10.206)	7.43 (13.803)	11.69 (11.961)
Median	9.07	7.00	2.73	7.59
Min, Max	0.2, 71.2	0.0, 51.2	0.1, 70.1	0.0, 71.2
Subjects Treated by Cycle, n (%)[b]				
1	367 (100.0)	144 (100.0)	54 (100.0)	565 (100.0)
2	342 (93.2)	135 (93.8)	44 (81.5)	521 (92.2)
3	304 (82.8)	114 (79.2)	32 (59.3)	450 (79.6)
4	283 (77.1)	105 (72.9)	24 (44.4)	412 (72.9)
5	259 (70.6)	94 (65.3)	18 (33.3)	371 (65.7)
6	246 (67.0)	86 (59.7)	14 (25.9)	346 (61.2)
>6	226 (61.6)	78 (54.2)	12 (22.2)	316 (55.9)
>12	158 (43.1)	55 (38.2)	7 (13.0)	220 (38.9)
>15	129 (35.1)	46 (31.9)	6 (11.1)	181 (32.0)
>18	108 (29.4)	36 (25.0)	6 (11.1)	150 (26.5)
Number of Treatment Cycles[c]				
Mean (SD)	14.2 (13.24)	12.1 (11.08)	8.4 (15.01)	13.1 (13.01)
Median	10.0	8.0	3.0	9.0
Min, Max	1, 78	1, 56	1, 77	1, 78
Treated at RP2D, n(%)[d]				
Yes	290 (79.0)	112 (77.8)	2 (3.7)	404 (71.5)
No	45 (12.3)	21 (14.6)	0	66 (11.7)
NA	0	2 (1.4)	0	2 (0.4)
NA-Phase 1	32 (8.7)	9 (6.3)	52 (96.3)	93 (16.5)
Cumulative Dose on Study (mg)				
Mean	91443.38	71467.78	37991.11	81243.54
SD	93365.422	73805.735	76696.948	88667.783
Median	64240.00	42980.00	12040.00	47920.00
Min, Max	640.0, 610560.0	160.0, 370520.0	320.0, 400280.0	160.0, 610560.0
Relative Dose Intensity (%)[e]				
Mean (SD)	83.74	81.41	121.58	86.76
Median	93.30	84.60	100.00	93.90
Min, Max	(35.338)	(50.095)	(116.251)	(53.347)

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[a] Treatment duration (months) for repotrectinib is calculated as (date of last dose – date of first dose + 1)/ 30.4375. For subjects who are still on drug as of the data cut-off date, the data cut-off date is used as the date of last dose.

[b] A subject is treated during a cycle if they have been administered at least one dose within the specified cycle.

[c] Number of cycles is the duration of treatment divided by the length of a cycle (28 days) and then increased to the next integer.

[d] The RP2D is 160 mg QD for 14 days followed by 160 mg BID. NA = subjects were not on treatment for at least 14 days. NA-Phase 1 = subjects in Phase 1 did not have the option to titrate at day 14.

[e] Relative Dose Intensity (%) is defined as (cumulative dose on study (in mg) divided by expected cumulative dose on study) x 100 where expected cumulative dose is defined as the starting dose times number of days on treatment. The expected cumulative dose is adjusted for subjects who received a lead-in dose and for subjects starting at BID dosing who are required to take study drug QD on the first day.

Table 42. Key demographic characteristics: TRIDENT-1 Safety Analysis Set

Characteristic	*ROS1*-positive NSCLC Subjects (N = 367)	*NTRK*-positive Solid Tumour Subjects (N = 144)	Other Treated Subjects (N = 54)	Overall Population (N =565)
Phase, n (%)				
Phase 1	40 (10.9)	9 (6.3)	54 (100.0)	103 (18.2)
Phase 1a, 1b, and 1c	32 (8.7)	9 (6.3)	52 (96.3)	93 (16.5)
Midazolam Substudy	8 (2.2)	0	2 (3.7)	10 (1.8)
Phase 2	327 (89.1)	135 (93.8)	0	462 (81.8)
Age (years)[a]				
N	367	144	54	565
Mean (SD)	54.8 (11.99)	56.3 (15.84)	52.8 (14.24)	55.0 (13.30)
Median	56.0	59.0	56.5	56.0
Min, max	27, 93	18, 84	18, 75	18, 93
Age Group, n (%)				
≥ 18 to < 65	291 (79.3)	90 (62.5)	44 (81.5)	425 (75.2)
≥ 65 to < 75	58 (15.8)	38 (26.4)	9 (16.7)	105 (18.6)
≥ 75	18 (4.9)	16 (11.1)	1 (1.9)	35 (6.2)
Missing	0	0	0	0
Sex, n (%)				
Female	138 (37.6)	70 (48.6)	29 (53.7)	237 (41.9)
Male	229 (62.4)	74 (51.4)	25 (46.3)	328 (58.1)
Race, n (%)				
American Indian or Alaskan Native	1 (0.3)	0	0	2 (0.4)
Asian	170 (48.3)	48 (33.3)	23 (42.6)	250 (44.2)
Black or African American	9 (2.5)	4 (2.8)	2 (3.7)	15 (2.7)
Native Hawaiian or Other Pacific Islander	3 (0.8)	0	0	3 (0.5)
White	159 (43.3)	76 (52.8)	26 (48.1)	261 (46.2)
Other	0	1 (0.7)	3 (5.6)	4 (0.7)
Not reported	12 (3.3)	15 (10.4)	0	27 (4.8)
Unknown	3 (0.8)	0	0	3 (0.5)
Region,[b] **n (%)**				
US	98 (26.7)	40 (27.8)	37 (68.5)	175 (31.0)
Asia	149 (40.6)	38 (26.4)	17 (31.5)	204 (36.1)
Other (Europe and Australia)	120 (32.7)	66 (45.8)	0	186 (32.9)
Baseline ECOG performance status,[c] **n (%)**				
0	129 (35.1)	59 (41.0)	14 (25.9)	202 (35.8)
1	237 (64.6)	85 (59.0)	40 (74.1)	362 (64.1)
Missing	1 (0.3)	0	0	1 (0.2)
Smoking status, n (%)				
Current smoker	5 (1.4)	7 (4.9)	0	12 (2.1)
Former smoker	101 (27.5)	51 (35.4)	0	152 (26.9)
Never smoked	221 (60.2)	77 (53.5)	0	298 (52.7)
Not collected	40 (10.9)	9 (6.3)	54 (100.0)	103 (18.2)

[a] Age in years is calculated based on the number of years between the informed consent date and the birth date.
[b] Countries grouped to 'Other' include: Australia, Belgium, Canada, Germany, Denmark, Spain, France, United Kingdom, Hungary, Italy, Netherlands, Poland.
[c] ECOG Performance Status (0 = Fully Active to 5 = Dead) 15-Oct-2023 DCO

CARE

Out of the 38 paediatric subjects in CARE, 34 subjects received the RP2D. The median duration of treatment for the overall safety population was 6.127 (range 0.03-41.53) months. More details on the extent of exposure is given in Table 43, followed by key demographic characteristics in Table 44 and Table 45.

Table 43. Extent of Exposure - Full Analysis Set, CARE

	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Treatment Duration (months)[a]			
N	19	19	38
Mean	7.795	10.342	9.069
Standard Deviation	7.7065	11.0395	9.4788
Median	5.520	9.232	6.127
Min, Max	0.89, 32.89	0.03, 41.53	0.03, 41.53
Dose Modifications, n (%)[b]			
Reduced	0	1 (5.3)	1 (2.6)
Interrupted	10 (52.6)	8 (42.1)	18 (47.4)
Cumulative Dose of Study Treatment (mg)			
N	19	19	38
Mean	47797.895	62086.872	54942.383
Standard Deviation	46183.1459	78178.6824	63744.8184
Median	29721.600	19660.800	26140.800
Min, Max	3968.00,	140.00, 286340.00	140.00, 286340.00
Dose Intensity (mg/day)[c]			
N	19	19	38
Mean	203.149	187.012	195.080
Standard Deviation	86.5838	87.3761	86.1861
Median	239.167	188.381	193.547
Min, Max	48.99, 325.19	57.98, 314.54	48.99, 325.19
Subjects Treated by Cycle,[d] **n (%)**			
1	19 (100)	19 (100)	38 (100)
2	18 (94.7)	16 (84.2)	34 (89.5)
3	16 (84.2)	11 (57.9)	27 (71.1)
4	12 (63.2)	11 (57.9)	23 (60.5)
5	11 (57.9)	11 (57.9)	22 (57.9)
6	10 (52.6)	11 (57.9)	21 (55.3)
> 6	9 (47.4)	10 (52.6)	19 (50.0)
> 12	4 (21.1)	7 (36.8)	11 (28.9)

[a] Treatment duration (months) is calculated as (date of last dose - date of first dose + 1)/30.4375. For subjects who are still on drug as of the data cut-off date, the cut-off date is used.
[b] Subjects who report a reduced or interrupted dose are considered to have dose modified. Reduced dose and interrupted dose are not mutually exclusive; therefore, a subject who reports having had dose reduced and dose interrupted are counted for both categories.
[c] Dose Intensity is defined as cumulative dose on study divided by the number of days on treatment from first dose through last dose.
[d] A subject is considered to have been considered treated during a cycle if they have been administered at least one dose within the specified cycle.
Note: *NTRK* summary pools subjects with an *NTRK*1-*NTRK*3 genetic alteration. Other summary pools subjects with an ALK or *ROS1* genetic alteration. Percentages are based on the number of subjects in the Full Analysis Set.
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Table 44. Subject Demographics in CARE – Subjects under 12 Years

Parameter	NTRK (N=11)	Other (N=11)	Overall Total (N=22)
Age (years) [a]			
Mean	4.7	5.0	4.9
Standard Deviation	2.94	4.52	3.72
Median	4.0	5.0	4.5
Min, Max	1, 11	0, 11	0, 11
Age Group, n (%)			
Newborn: 0 to 28 days	0	0	0
Infant and Toddler: > 28 days to < 2 years	2 (18.2)	3 (27.3)	5 (22.7)
Child: 2 years to < 12 years	9 (81.8)	8 (72.7)	17 (77.3)

Parameter	NTRK (N=11)	Other (N=11)	Overall Total (N=22)
Sex, n (%)			
Female	6 (54.5)	7 (63.6)	13 (59.1)
Male	5 (45.5)	4 (36.4)	9 (40.9)
Race, n (%)			
Not Allowed by Local Law	0	0	0
American Indian or Alaskan Native	0	0	0
Asian	1 (9.1)	2 (18.2)	3 (13.6)
Black or African American	1 (9.1)	1 (9.1)	2 (9.1)
Native Hawaiian or Other Pacific Islander	0	0	0
White	9 (81.8)	6 (54.5)	15 (68.2)
Multiple	0	1 (9.1)	1 (4.5)
Missing	0	1 (9.1)	1 (4.5)
Ethnicity, n (%)			
Hispanic or Latino	5 (45.5)	1 (9.1)	6 (27.3)
Not Hispanic or Latino	6 (54.5)	10 (90.9)	16 (72.7)
Baseline Height (cm)			
n	11	11	22
Mean	109.66	106.54	108.10
Standard Deviation	22.287	33.352	27.727
Median	105.10	105.30	105.20
Min, Max	78.0, 155.4	65.1, 157.7	65.1, 157.7
Baseline Weight (kg)			
n	11	11	22
Mean	22.82	21.23	22.02
Standard Deviation	11.320	13.337	12.099
Median	20.30	19.40	19.85
Min, Max	11.1, 44.6	5.9, 39.2	5.9, 44.6
Baseline Body Mass Index (BMI) (kg/m2)			
n	11	11	22
Mean	18.41	16.84	17.62
Standard Deviation	5.665	2.380	4.316
Median	17.10	16.40	16.90
Min, Max	13.4, 34.2	13.4, 22.2	13.4, 34.2

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Note: NTRK summary pools subjects with an NTRK1-NTRK3 genetic alteration. Other summary pools subjects with an ALK or ROS1 genetic alteration. A baseline value is the last non-missing assessment prior to initial administration of study treatment. Percentages are based on the number of subjects in the Full Analysis Set.
For Karnofsky Performance Status Scale, the numeric scores refer to the following: 100 = Normal; 90 = Minor signs; 80 = Normal with effort; 70 = Cares for self; 60 = Occasional assistance; 50 = Considerable assistance; 40 = Disabled; 30 = Severely disabled; 20 = Very sick; 10 = Moribund. For Lansky Performance Score, the numeric scores refer to the following: 100 = Fully active, normal; 90 = Minor restrictions in strenuous physical activity; 80 = Active, but tired more quickly; 70 = Greater restriction of plan and less time spent in play activity; 60 = Up and around, but active play minimal; keeps busy by being involved in quieter activities; 50 = Lying around much of the day, but gets dressed; no active playing, participates in all quiet play and activities; 40 = Mainly in bed; participates in quiet activities 30 = Bed bound; needing assistance even for quiet play; 20 = Sleeping often; play entirely limited to very passive activities; 10 = Doesn't play; doesn't get out of bed.
[a] Age in years is calculated based on the number of years between the informed consent date and the birth date.

Table 45. Subject Demographics in CARE – Subjects 12 Years and above

Parameter	NTRK (N=8)	Other (N=8)	Overall Total (N=16)
Age (years) [a]			
Mean	15.6	14.9	15.3
Standard Deviation	3.46	2.53	2.96
Median	15.0	14.0	14.0
Min, Max	13, 24	13, 21	13, 24
Age Group, n (%)			
Adolescent: 12 to < 18 years	7 (87.5)	7 (87.5)	14 (87.5)
Adult: 18 to 25 years	1 (12.5)	1 (12.5)	2 (12.5)
Sex, n (%)			
Female	4 (50.0)	1 (12.5)	5 (31.3)
Male	4 (50.0)	7 (87.5)	11 (68.8)
Race, n (%)			
Not Allowed by Local Law	0	0	0

Parameter	NTRK (N=8)	Other (N=8)	Overall Total (N=16)
American Indian or Alaskan Native	0	0	0
Asian	2 (25.0)	3 (37.5)	5 (31.3)
Black or African American	0	1 (12.5)	1 (6.3)
Native Hawaiian or Other Pacific Islander	0	0	0
White	6 (75.0)	3 (37.5)	9 (56.3)
Multiple	0	0	0
Missing	0	1 (12.5)	1 (6.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (12.5)	0	1 (6.3)
Not Hispanic or Latino	7 (87.5)	7 (87.5)	14 (87.5)
Missing	0	1 (12.5)	1 (6.3)
Baseline Height (cm)			
n	8	8	16
Mean	166.08	169.58	167.83
Standard Deviation	13.092	11.433	12.010
Median	166.25	166.20	166.25
Min, Max	147.5, 188.2	161.9, 197.0	147.5, 197.0
Baseline Weight (kg)			
n	8	8	16
Mean	62.65	62.24	62.44
Standard Deviation	14.097	10.726	12.103
Median	63.60	66.15	64.05
Min, Max	42.0, 86.7	47.5, 76.7	42.0, 86.7
Baseline Body Mass Index (BMI) (kg/m2)			
n	8	8	16
Mean	22.50	21.85	22.18
Standard Deviation	2.881	3.508	3.119
Median	22.20	22.20	22.20
Min, Max	17.7, 27.2	16.4, 25.6	16.4, 27.2

15-Oct-2023 DCO
Note: NTRK summary pools subjects with an NTRK1-NTRK3 genetic alteration. Other summary pools subjects with an ALK or ROS1 genetic alteration. A baseline value is the last non-missing assessment prior to initial administration of study treatment. Percentages are based on the number of subjects in the Full Analysis Set.
For Karnofsky Performance Status Scale, the numeric scores refer to the following: 100 = Normal; 90 = Minor signs; 80 = Normal with effort; 70 = Cares for self; 60 = Occasional assistance; 50 = Considerable assistance; 40 = Disabled; 30 = Severely disabled; 20 = Very sick; 10 = Moribund. For Lansky Performance Score, the numeric scores refer to the following: 100 = Fully active, normal; 90 = Minor restrictions in strenuous physical activity; 80 = Active, but tired more quickly; 70 = Greater restriction of plan and less time spent in play activity; 60 = Up and around, but active play minimal; keeps busy by being involved in quieter activities; 50 = Lying around much of the day, but gets dressed; no active playing, participates in all quiet play and activities; 40 = Mainly in bed; participates in quiet activities 30 = Bed bound; needing assistance even for quiet play; 20 = Sleeping often; play entirely limited to very passive activities; 10 = Doesn't play; doesn't get out of bed.
[a] Age in years is calculated based on the number of years between the informed consent date and the birth date.

Disease characteristics and previous treatments

Details on key disease history is given in Table 46 and previous treatment is presented in Table 47.

Table 46. Key Disease History of Study Population - TRIDENT-1 Safety Analysis Set

	***ROS1*-positive NSCLC Subjects (N = 367)**	***NTRK*-positive Solid Tumour Subjects (N = 144)**	**Other Treated Subjects (N = 54)**	**Overall Population (N=565)**
Brain Metastasis per BICR,[a,b] n (%)				
Yes	116 (31.6)	30 (20.8)	16 (29.6)	162 (28.7)
No/ NA	251 (68.4)	114 (79.2)	38 (70.4)	403 (71.3)
Brain Metastasis per Investigator, [a] n (%)				
Yes	141 (38.4)	30 (20.8)	22 (40.7)	193 (34.2)
No	226 (61.6)	114 (79.2)	32 (59.3)	372 (65.8)
Time since Diagnosis (years)[c]				
N	367	144	54	565
Mean (SD)	2.20 (2.794)	4.74 (6.934)	3.84 (2.835)	3.00 (4.390)
Median	1.34	2.56	3.41	1.78

	ROS1-positive NSCLC Subjects (N = 367)	*NTRK*-positive Solid Tumour Subjects (N = 144)	Other Treated Subjects (N = 54)	Overall Population (N=565)
Min, Max	0.0, 26.5	0.0, 42.5	0.1, 13.2	0.0, 42.5
Stage at Diagnosis, n (%)				
I	12 (3.3)	11 (7.6)	4 (7.4)	27 (4.8)
II	13 (3.5)	17 (11.8)	1 (1.9)	31 (5.5)
III	30 (8.2)	22 (15.3)	3 (5.6)	55 (9.7)
IIIA	1 (0.3)	0 (0.0)	2 (3.7)	3 (0.5)
IIIB	23 (6.3)	6 (4.2)	2 (3.7)	31 (5.5)
IV	285 (77.7)	80 (55.6)	42 (77.8)	407 (72.0)
Missing	2 (0.5)	8 (5.6)	0 (0.0)	10 (1.8)
Unknown	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Stage at Study Entry,[d] n (%)				
III	7 (1.9)	5 (3.5)	0 (0.0)	12 (2.1)
IIIB	11 (3.0)	2 (1.4)	0 (0.0)	13 (2.3)
IV	349 (95.1)	136 (94.4)	54 (100.0)	539 (95.4)
Missing	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Resistance Mutation[e]				
Solvent Front	45 (12.3)	31 (21.5)	5 (9.3)	81 (14.3)
Gatekeeper	2 (0.5)	5 (3.5)	0 (0.0)	7 (1.2)
Activating	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.2)
Other	10 (2.7)	3 (2.1)	5 (9.3)	18 (3.2)

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[a] Brain metastasis present if target or non-target lesion selected in the brain at baseline

[b] No/ NA indicates subjects did not have measurable or non-measurable lesions per BICR or were not yet evaluated by BICR.

[c] Time since diagnosis in years is calculated based on the number of years from diagnosis to inform consent date.

[d] III/IIIB = Locally Advanced, IV = Metastatic.

[e] Subjects can be counted in more than one category.

Table 47. Key Treatment History – TRIDENT-1 Safety Analysis set

	ROS1+ NSCLC Subjects (N = 367)	*NTRK*+ Solid Tumour Subjects (N = 144)	Other Treated Subjects (N = 54)	Overall Population (N = 565)
Number of Lines Prior Systemic Therapy, n (%)				
Median (Min, Max)	1.00 (0.0, 8.0)	2.00 (0.0, 6.0)	3.00 (1.0, 12.0)	1.00 (0.0, 12.0)
0	88 (24.0)	19 (13.2)	0 (0.0)	107 (18.9)
1	136 (37.1)	45 (31.3)	8 (14.8)	189 (33.5)
2	98 (26.7)	43 (29.9)	16 (29.6)	157 (27.8)
≥3	45 (12.3)	37 (25.7)	30 (55.6)	112 (19.8)
Type of Prior Systemic Therapy,[a] n (%)				
TKI	246 (67.0)	86 (59.7)	42 (77.8)	374 (66.2)
Chemotherapy with/without Immunotherapy	128 (34.9)	88 (61.1)	45 (83.3)	261 (46.2)
Immunotherapy Alone	13 (3.5)	13 (9.0)	4 (7.4)	30 (5.3)
Other Targeted Therapy	24 (6.5)	35 (24.3)	17 (31.5)	76 (13.5)
Other Therapy	3 (0.8)	10 (6.9)	1 (1.9)	14 (2.5)
No Prior Therapy Taken	88 (24.0)	19 (13.2)	0 (0.0)	107 (18.9)
Prior Platinum-based Chemotherapy, n (%)				
Yes	127 (34.6)	54 (37.5)	43 (79.6)	224 (39.6)
No	240 (65.4)	90 (62.5)	11 (20.4)	341 (60.4)
Most Recent Prior Systemic Therapy Type,[a] n (%)				
TKI	216 (58.9)	77 (53.5)	31 (57.4)	324 (57.3)
Chemotherapy with/without Immunotherapy	61 (16.6)	36 (25.0)	18 (33.3)	115 (20.4)
Immunotherapy Alone	3 (0.8)	5 (3.5)	1 (1.9)	9 (1.6)
Other Targeted Therapy	11 (3.0)	13 (9.0)	6 (11.1)	30 (5.3)
Other Therapy	1 (0.3)	4 (2.8)	0 (0.0)	5 (0.9)
Missing	88 (24.0)	19 (13.2)	0 (0.0)	107 (18.9)

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2.6.8.2. Adverse events

Adverse events (AEs) reported on or after the first dose date through 28 days after last dose of study drug are considered treatment emergent. AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) v4.03 and coded to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) v25.0 for the 19-Dec-2022 DCO. For the 15-Oct-2023 DCO, AEs were coded to PT and SOC using MedDRA version 26.1.

Nearly all of the adult patients (99.5 %) in TRIDENT-1 experienced treatment-emergent adverse events (TEAE), which led to dose modification (reduction or interruption) in 57.2 % of patients and discontinuation in 10.8 % of the patients. In CARE, all paediatric patients experienced at least one TEAE, which led to discontinuation in two patients (5.3 %) and to dose modifications in 13 patients (34.2 %).

An overview of adverse events in TRIDENT-1 and CARE is summarized in Table 48 and Table 49, respectively.

Table 48. Overall Summary of Safety Analysis – TRIDENT-1

	ROS1+ NSCLC Subjects (N=367)	*NTRK*+ Solid Tumour Subjects (N=144)	Other Treated Subjects (N=54)	RP2D Safety Population (N=472)	Overall Population (N=565)
Subjects with TEAEs, n (%)					
All Subjects with TEAEs	365 (99.5)	143 (99.3)	54 (100.0)	469 (99.4)	562 (99.5)
Leading to Discontinuation of Study Drug	39 (10.6)	14 (9.7)	8 (14.8)	47 (10.0)	61 (10.8)
Leading to Dose Modifications	222 (60.5)	85 (59.0)	16 (29.6)	291 (61.7)	323 (57.2)
Leading to Dose Reduction	141 (38.4)	65 (45.1)	10 (18.5)	199 (42.2)	216 (38.2)
Leading to Drug Interruption	200 (54.5)	76 (52.8)	15 (27.8)	261 (55.3)	291 (51.5)
SAEs	153 (41.7)	56 (38.9)	21 (38.9)	186 (39.4)	230 (40.7)
Grade ≥ 3 TEAEs	213 (58.0)	83 (57.6)	27 (50.0)	269 (57.0)	323 (57.2)
Fatal TEAEs	25 (6.8)	8 (5.6)	2 (3.7)	28 (5.9)	35 (6.2)
Subjects with TRAEs, n (%)					
All Subjects with TRAEs	350 (95.4)	139 (96.5)	46 (85.2)	453 (96.0)	535 (94.7)
Leading to Discontinuation of Study Drug	17 (4.6)	5 (3.5)	1 (1.9)	20 (4.2)	23 (4.1)
Leading to Dose Modifications	157 (42.8)	74 (51.4)	9 (16.7)	222 (47.0)	240 (42.5)
Leading to Dose Reduction	123 (33.5)	63 (43.8)	9 (16.7)	179 (37.9)	195 (34.5)
Leading to Drug Interruption	128 (34.9)	61 (42.4)	8 (14.8)	182 (38.6)	197 (34.9)
Treatment-Related SAEs	29 (7.9)	18 (12.5)	1 (1.9)	45 (9.5)	48 (8.5)
Grade ≥3 TRAEs	107 (29.2)	49 (34.0)	6 (11.1)	150 (31.8)	162 (28.7)
Fatal TRAEs	1 (0.3)	1 (0.7)	0	2 (0.4)	2 (0.4)
Subjects with TEAEs by Maximum CTCAE Grade (n (%)					
Grade 1	26 (7.1)	17 (11.8)	5 (9.3)	39 (8.3)	48 (8.5)
Grade 2	126 (34.3)	43 (29.9)	22 (40.7)	161 (34.1)	191 (33.8)
Grade 3	158 (43.1)	66 (45.8)	21 (38.9)	204 (43.2)	245 (43.4)
Grade 4	30 (8.2)	9 (6.3)	4 (7.4)	37 (7.8)	43 (7.6)
Grade 5	25 (6.8)	8 (5.6)	2 (3.7)	28 (5.9)	35 (6.2)
Subjects with TRAEs by Maximum CTCAE Grade (n (%)					
Grade 1	85 (23.2)	31 (21.5)	20 (37.0)	100 (21.2)	136 (24.1)
Grade 2	158 (43.1)	59 (41.0)	20 (37.0)	203 (43.0)	237 (41.9)
Grade 3	99 (27.0)	44 (30.6)	6 (11.1)	137 (29.0)	149 (26.4)
Grade 4	7 (1.9)	4 (2.8)	0	11 (2.3)	11 (1.9)
Grade 5	1 (0.3)	1 (0.7)	0	2 (0.4)	2 (0.4)

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Table 49. CARE - Overall Summary of Adverse Events - Full Analysis Set

	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Subjects with TEAE, n (%)			
All Subjects with TEAE	19 (100)	19 (100)	38 (100)
All Subjects with Dose Limiting Toxicity (for Phase 1)	0	0	0
Leading to Discontinuation of Study Drug	0	2 (10.5)[a]	2 (5.3)[a]
Leading to Dose Modification	5 (26.3)	8 (42.1)	13 (34.2)
Leading to Dose Reduction	0	1 (5.3)	1 (2.6)
Leading to Drug Interruption	5 (26.3)	8 (42.1)	13 (34.2)
SAEs	8 (42.1)	6 (31.6)	14 (36.8)
Grade ≥3 TEAE	10 (52.6)	11 (57.9)	21 (55.3)
Fatal AE	3 (15.8)	0	3 (7.9)
Subjects with TRAEs, n (%)			
All Subjects with TRAE	17 (89.5)	15 (78.9)	32 (84.2)
Leading to Discontinuation of Study Drug	0	2 (10.5)[a]	2 (5.3)[a]

	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Leading to Dose Modification	1 (5.3)	4 (21.1)	5 (13.2)
Leading to Dose Reduction	0	1 (5.3)	1 (2.6)
Leading to Drug Interruption	1 (5.3)	4 (21.1)	5 (13.2)
Related SAEs	2 (10.5)	0	2 (5.3)
Grade ≥3 TRAE	4 (21.1)	4 (21.1)	8 (21.1)
Related Fatal AE	0	0	0
Subjects with TEAE by Maximum CTCAE Grade, n (%)			
Grade 1	4 (21.1)	3 (15.8)	7 (18.4)
Grade 2	5 (26.3)	5 (26.3)	10 (26.3)
Grade 3	5 (26.3)	7 (36.8)	12 (31.6)
Grade 4	2 (10.5)	4 (21.1)	6 (15.8)
Grade 5	3 (15.8)	0	3 (7.9)
Subjects with TRAE by Maximum CTCAE Grade, n (%)			
Grade 1	4 (21.1)	5 (26.3)	9 (23.7)
Grade 2	9 (47.4)	6 (31.6)	15 (39.5)
Grade 3	4 (21.1)	4 (21.1)	8 (21.1)
Grade 4	0	0	0
Grade 5	0	0	0

[a] Due to grade 3 anemia (Day 29), reason for treatment discontinuation for 1 subject was reported as radiographic disease progression (Day 28).

Note: *NTRK* summary pools subjects with an *NTRK*1-*NTRK*3 genetic alteration. Other summary pools subjects with an ALK or *ROS1* genetic alteration.

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

Adverse events occurring on or after the first dose date through 28 days after last dose of study drug are considered treatment-emergent. A subject is counted once for each type of event reported. For maximum grade, a subject is counted once based on the maximum grade identified for the specified event type. Leading to Dose Modification includes adverse events that led to dose reduction or dose interruption.

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Common adverse events

Treatment-emergent adverse events in TRIDENT-1

The most frequently reported TEAEs (any grade, in ≥ 10%) in the overall safety population are listed in Table 50.

Grade ≥3 TEAEs reported in ≥2 % of subjects are displayed in Table 51. There were few reported Grade 4 TEAEs and those reported in > 1 subject in the Overall safety population were dyspnoea (7 [1.2%] subjects), blood creatine phosphokinase increased (6 [1.1%] subjects), respiratory failure (4 [0.7%] subjects), hypoxia (3 [0.5%] subjects), hypoxia (3 [0.5%] subjects, sepsis (3 [0.5%] subjects), hypertriglyceridemia (2 [0.4%] subjects), neutrophil count decreased (2 [0.4%] subjects) and hyperuricaemia (2 [0.4%] subjects).

The most frequent PTs (all grades and Grade 3-4) were comparable between the RP2D (n=472) and the overall safety populations (n=565).

Table 50. Summary of Treatment-Emergent Adverse Events in ≥ 10% Subjects in Any Group by System Organ Class and Preferred Term - Safety Analysis Set in TRIDENT-1

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects (N=367)	*NTRK*+ Solid Tumour Subjects (N=144)	Other Treated Subjects (N=54)	Overall Population (N=565)
Subjects with at least one TEAE	**365 (99.5)**	**143 (99.3)**	**54 (100.0)**	**562 (99.5)**
Nervous system disorders	**329 (89.6)**	**132 (91.7)**	**49 (90.7)**	**510 (90.3)**
Dizziness	231 (62.9)	90 (62.5)	35 (64.8)	356 (63.0)
Dysgeusia	189 (51.5)	81 (56.3)	26 (48.1)	296 (52.4)
Paraesthesia	129 (35.1)	51 (35.4)	12 (22.2)	192 (34.0)
Ataxia	84 (22.9)	34 (23.6)	6 (11.1)	124 (21.9)

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects (N=367)	*NTRK*+ Solid Tumour Subjects (N=144)	Other Treated Subjects (N=54)	Overall Population (N=565)
Headache	74 (20.2)	28 (19.4)	11 (20.4)	113 (20.0)
Memory impairment	45 (12.3)	24 (16.7)	0	69 (12.2)
Neuralgia	47 (12.8)	16 (11.1)	0	63 (11.2)
Disturbance in attention	39 (10.6)	19 (13.2)	0	58 (10.3)
Somnolence	33 (9.0)	19 (13.2)	0	52 (9.2)
Gastrointestinal disorders	**265 (72.2)**	**101 (70.1)**	**40 (74.1)**	**406 (71.9)**
Constipation	148 (40.3)	59 (41.0)	15 (27.8)	222 (39.3)
Nausea	75 (20.4)	31 (21.5)	11 (20.4)	117 (20.7)
Vomiting	40 (10.9)	30 (20.8)	12 (22.2)	82 (14.5)
Diarrhea	49 (13.4)	33 (22.9)	3 (5.6)	85 (15.0)
Abdominal pain	24 (6.5)	10 (6.9)	7 (13.0)	41 (7.3)
General disorders and administration site conditions	**207 (56.4)**	**93 (64.6)**	**32 (59.3)**	**332 (58.8)**
Fatigue	80 (21.8)	42 (29.2)	18 (33.3)	140 (24.8)
Pyrexia	37 (10.1)	25 (17.4)	10 (18.5)	72 (12.7)
Oedema peripheral	37 (10.1)	25 (17.4)	4 (7.4)	66 (11.7)
Asthenia	31 (8.4)	18 (12.5)	3 (5.6)	52 (9.2)
Respiratory, thoracic and mediastinal disorders	**220 (59.9)**	**73 (50.7)**	**34 (63.0)**	**327 (57.9)**
Dyspnea	113 (30.8)	44 (30.6)	20 (37.0)	177 (31.3)
Cough	69 (18.8)	29 (20.1)	9 (16.7)	107 (18.9)
Investigations	**214 (58.3)**	**79 (54.9)**	**19 (35.2)**	**312 (55.2)**
Alanine aminotransferase increased	93 (25.3)	27 (18.8)	5 (9.3)	125 (22.1)
Aspartate aminotransferase increased	86 (23.4)	27 (18.8)	5 (9.3)	118 (20.9)
Blood creatine phosphokinase increased	69 (18.8)	29 (20.1)	1 (1.9)	99 (17.5)
Weight increased	59 (16.1)	21 (14.6)	3 (5.6)	83 (14.7)
White blood cell count decreased	38 (10.4)	12 (8.3)	1 (1.9)	51 (9.0)
Musculoskeletal and connective tissue disorders	**216 (58.9)**	**78 (54.2)**	**26 (48.1)**	**320 (56.6)**
Muscular weakness	85 (23.2)	28 (19.4)	9 (16.7)	122 (21.6)
Arthralgia	63 (17.2)	18 (12.5)	5 (9.3)	86 (15.2)
Myalgia	43 (11.7)	21 (14.6)	5 (9.3)	69 (12.2)
Pain in extremity	46 (12.5)	12 (8.3)	9 (16.7)	67 (11.9)
Back pain	36 (9.8)	17 (11.8)	4 (7.4)	57 (10.1)
Blood and lymphatic system disorders	**158 (43.1)**	**62 (43.1)**	**16 (29.6)**	**236 (41.8)**
Anemia	141 (38.4)	59 (41.0)	15 (27.8)	215 (38.1)
Infections and infestations	**154 (42.0)**	**66 (45.8)**	**18 (33.3)**	**238 (42.1)**
Pneumonia	40 (10.9)	14 (9.7)	4 (7.4)	58 (10.3)
Urinary tract infection	27 (7.4)	17 (11.8)	2 (3.7)	46 (8.1)
Upper respiratory tract infection	21 (5.7)	6 (4.2)	7 (13.0)	34 (6.0)
COVID-19	50 (13.6)	15 (10.4)	1 (1.9)	66 (11.7)
Metabolism and nutrition disorders	**118 (32.2)**	**62 (43.1)**	**16 (29.6)**	**196 (34.7)**
Decreased appetite	35 (9.5)	25 (17.4)	4 (7.4)	64 (11.3)

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Table 51. Treatment-emergent Adverse Events ≥ Grade 3 in ≥ 2% of Subjects by System Organ Class and Preferred Term - Safety Analysis Set - TRIDENT-1

System Organ Class Preferred Term	ROS1+NSCLC Subjects (N=367)	NTRK+Solid Tumor Subjects (N=144)	Other Treated Subjects (N=54)	Total (N=565)
Total Subjects With An Event	**133 (36.2)**	**49 (34.0)**	**14 (25.9)**	**196 (34.7)**
Respiratory, thoracic and mediastinal disorders	53 (14.4)	11 (7.6)	7 (13.0)	71 (12.6)
Dyspnoea	26 (7.1)	6 (4.2)	6 (11.1)	38 (6.7)
Pulmonary embolism	13 (3.5)	3 (2.1)	1 (1.9)	17 (3.0)
Hypoxia	13 (3.5)	1 (0.7)	0	14 (2.5)
Pleural effusion	11 (3.0)	1 (0.7)	1 (1.9)	13 (2.3)
Investigations	**44 (12.0)**	**14 (9.7)**	**2 (3.7)**	**60 (10.6)**
Blood creatine phosphokinase increased	14 (3.8)	4 (2.8)	1 (1.9)	19 (3.4)
Weight increased	15 (4.1)	2 (1.4)	1 (1.9)	18 (3.2)
Aspartate aminotransferase increased	9 (2.5)	6 (4.2)	0	15 (2.7)
Neutrophil count decreased	10 (2.7)	2 (1.4)	0	12 (2.1)
Blood and lymphatic system disorders	**28 (7.6)**	**16 (11.1)**	**6 (11.1)**	**50 (8.8)**
Anaemia	28 (7.6)	16 (11.1)	6 (11.1)	50 (8.8)
Infections and infestations	**21 (5.7)**	**10 (6.9)**	**1 (1.9)**	**32 (5.7)**
Pneumonia	21 (5.7)	10 (6.9)	1 (1.9)	32 (5.7)
Nervous system disorders	**16 (4.4)**	**11 (7.6)**	**2 (3.7)**	**29 (5.1)**
Dizziness	8 (2.2)	7 (4.9)	2 (3.7)	17 (3.0)
Syncope	10 (2.7)	6 (4.2)	0	16 (2.8)

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Treatment-emergent adverse events in CARE

All subjects in CARE experienced at least one TEAE (see Table 52 below).

TEAEs by SOC (>20 %) were: 'Gastrointestinal disorders' (76.3 %), 'Investigations' (65.8 %), 'Nervous system disorders' (57.9 %), 'General disorders and administration site conditions' (55.3 %), 'Metabolism and nutrition disorders' (52.6 %), 'Blood and lymphatic system disorders' (50.0 %), 'Infections and infestations' (47.4 %), 'Respiratory, thoracic and mediastinal disorders' (42.1 %), 'Skin and subcutaneous disorders' (34.2 %), 'Injury, poisoning and procedural complications' (34.2 %), 'Vascular disorders' (31.6 %), 'Musculoskeletal and connective tissue disorders' (28.9 %), 'Psychiatric disorders' (23.7 %), 'Cardiac disorders' (21.1 %), and 'Renal and urinary disorders' (21.1 %).

Reported Grade ≥ 3 TEAEs are displayed in Table 53.

Table 52. Most Common (≥ 10%) Treatment-Emergent Adverse Events by Preferred Term - Full Analysis Set (CARE)

Preferred Term	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Subjects with at Least One TEAE	**19 (100)**	**19 (100)**	**38 (100)**
Anaemia	9 (47.4)	10 (52.6)	19 (50.0)
Constipation	5 (26.3)	10 (52.6)	15 (39.5)
Fatigue	7 (36.8)	7 (36.8)	14 (36.8)
Headache	5 (26.3)	7 (36.8)	12 (31.6)
Nausea	4 (21.1)	7 (36.8)	11 (28.9)
Cough	3 (15.8)	7 (36.8)	10 (26.3)
Pyrexia	2 (10.5)	8 (42.1)	10 (26.3)
Weight increased	6 (31.6)	4 (21.1)	10 (26.3)

Preferred Term	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Aspartate aminotransferase increased	3 (15.8)	6 (31.6)	9 (23.7)
Dysgeusia	5 (26.3)	4 (21.1)	9 (23.7)
White blood cell count decreased	5 (26.3)	4 (21.1)	9 (23.7)
Dizziness	3 (15.8)	5 (26.3)	8 (21.1)
Neutrophil count decreased	3 (15.8)	5 (26.3)	8 (21.1)
Vomiting	2 (10.5)	6 (31.6)	8 (21.1)
Alanine aminotransferase increased	1 (5.3)	6 (31.6)	7 (18.4)
Diarrhoea	3 (15.8)	4 (21.1)	7 (18.4)
Hypertension	2 (10.5)	5 (26.3)	7 (18.4)
Lymphocyte count decreased	3 (15.8)	4 (21.1)	7 (18.4)
Abdominal pain	2 (10.5)	4 (21.1)	6 (15.8)
Blood creatine phosphokinase increased	2 (10.5)	4 (21.1)	6 (15.8)
Dyspnoea	1 (5.3)	5 (26.3)	6 (15.8)
Electrocardiogram QT prolonged	2 (10.5)	4 (21.1)	6 (15.8)
Hypermagnesaemia	2 (10.5)	4 (21.1)	6 (15.8)
Hypotension	0	6 (31.6)	6 (15.8)
Blood alkaline phosphatase increased	2 (10.5)	3 (15.8)	5 (13.2)
Decreased appetite	1 (5.3)	4 (21.1)	5 (13.2)
Hyperuricaemia	0	5 (26.3)	5 (13.2)
Hypokalaemia	2 (10.5)	3 (15.8)	5 (13.2)
Increased appetite	1 (5.3)	4 (21.1)	5 (13.2)
Paraesthesia	4 (21.1)	1 (5.3)	5 (13.2)
Sinus tachycardia	0	5 (26.3)	5 (13.2)
Urinary tract infection	2 (10.5)	3 (15.8)	5 (13.2)
Arthralgia	1 (5.3)	3 (15.8)	4 (10.5)
Back pain	1 (5.3)	3 (15.8)	4 (10.5)
Blood lactate dehydrogenase increased	1 (5.3)	3 (15.8)	4 (10.5)
COVID-19	2 (10.5)	2 (10.5)	4 (10.5)
Chills	1 (5.3)	3 (15.8)	4 (10.5)
Dermatitis acneiform	1 (5.3)	3 (15.8)	4 (10.5)
Gait disturbance	2 (10.5)	2 (10.5)	4 (10.5)
Hyperkalaemia	1 (5.3)	3 (15.8)	4 (10.5)
Hypernatraemia	1 (5.3)	3 (15.8)	4 (10.5)
Hypoalbuminaemia	1 (5.3)	3 (15.8)	4 (10.5)
Irritability	1 (5.3)	3 (15.8)	4 (10.5)
Lipase increased	2 (10.5)	2 (10.5)	4 (10.5)
Pain in extremity	0	4 (21.1)	4 (10.5)
Proteinuria	2 (10.5)	2 (10.5)	4 (10.5)
Somnolence	3 (15.8)	1 (5.3)	4 (10.5)
Tachypnoea	0	4 (21.1)	4 (10.5)
Upper respiratory tract infection	1 (5.3)	3 (15.8)	4 (10.5)

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Table 53. Treatment-emergent Adverse Events with Grade ≥ 3 by System Organ Class, Preferred Term and Maximum CTCAE Grade - CARE - Full Analysis Set

System Organ Class Preferred Term Grade	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Subjects with at Least One Grade >=3 TEAE	**10 (52.6)**	**11 (57.9)**	**21 (55.3)**
Investigations	**3 (15.8)**	**7 (36.8)**	**10 (26.3)**
Weight increased	3 (15.8)	3 (15.8)	6 (15.8)
Grade 3	3 (15.8)	3 (15.8)	6 (15.8)
Lipase increased	0	2 (10.5)	2 (5.3)
Grade 3	0	1 (5.3)	1 (2.6)
Grade 4	0	1 (5.3)	1 (2.6)

System Organ Class Preferred Term Grade	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Alanine aminotransferase increased	1 (5.3)	0	1 (2.6)
Grade 3	1 (5.3)	0	1 (2.6)
Amylase increased	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Aspartate aminotransferase increased	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Neutrophil count decreased	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Platelet count decreased	0	1 (5.3)	1 (2.6)
Grade 4	0	1 (5.3)	1 (2.6)
Blood and lymphatic system disorders	**2 (10.5)**	**4 (21.1)**	**6 (15.8)**
Anaemia	2 (10.5)	4 (21.1)	6 (15.8)
Grade 3	2 (10.5)	4 (21.1)	6 (15.8)
Infections and infestations	**2 (10.5)**	**4 (21.1)**	**6 (15.8)**
Sepsis	1 (5.3)	1 (5.3)	2 (5.3)
Grade 4	1 (5.3)	1 (5.3)	2 (5.3)
Bronchiolitis	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Enterovirus infection	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Influenza	1 (5.3)	0	1 (2.6)
Grade 3	1 (5.3)	0	1 (2.6)
Pneumonia	0	1 (5.3)	1 (2.6)
Grade 4	0	1 (5.3)	1 (2.6)
Rhinovirus infection	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Upper respiratory tract infection	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Urinary tract infection	1 (5.3)	0	1 (2.6)
Grade 3	1 (5.3)	0	1 (2.6)
Viral infection	1 (5.3)	0	1 (2.6)
Grade 3	1 (5.3)	0	1 (2.6)
Respiratory, thoracic and mediastinal disorders	**1 (5.3)**	**4 (21.1)**	**5 (13.2)**
Hypoxia	0	2 (10.5)	2 (5.3)
Grade 3	0	2 (10.5)	2 (5.3)
Asthma	1 (5.3)	0	1 (2.6)
Grade 4	1 (5.3)	0	1 (2.6)
Dyspnoea	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Obstructive sleep apnoea syndrome	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Pleural effusion	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Respiratory failure	1 (5.3)	0	1 (2.6)
Grade 4	1 (5.3)	0	1 (2.6)
Stridor	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Gastrointestinal disorders	**3 (15.8)**	**1 (5.3)**	**4 (10.5)**
Diarrhoea	1 (5.3)	1 (5.3)	2 (5.3)
Grade 3	1 (5.3)	1 (5.3)	2 (5.3)
Abdominal pain	1 (5.3)	0	1 (2.6)
Grade 3	1 (5.3)	0	1 (2.6)
Constipation	1 (5.3)	0	1 (2.6)
Grade 3	1 (5.3)	0	1 (2.6)
Ileus paralytic	1 (5.3)	0	1 (2.6)

System Organ Class Preferred Term Grade	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Grade 3	1 (5.3)	0	1 (2.6)
General disorders and administration site conditions	**2 (10.5)**	**1 (5.3)**	**3 (7.9)**
Disease progression	2 (10.5)	0	2 (5.3)
Grade 3	1 (5.3)	0	1 (2.6)
Grade 5	1 (5.3)	0	1 (2.6)
Fatigue	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Metabolism and nutrition disorders	**1 (5.3)**	**2 (10.5)**	**3 (7.9)**
Decreased appetite	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Hypokalaemia	1 (5.3)	0	1 (2.6)
Grade 3	1 (5.3)	0	1 (2.6)
Hyponatraemia	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Nervous system disorders	**2 (10.5)**	**1 (5.3)**	**3 (7.9)**
Brain compression	1 (5.3)	0	1 (2.6)
Grade 5	1 (5.3)	0	1 (2.6)
Encephalopathy	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Hemiparesis	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Hydrocephalus	1 (5.3)	0	1 (2.6)
Grade 3	1 (5.3)	0	1 (2.6)
Injury, poisoning and procedural complications	**1 (5.3)**	**1 (5.3)**	**2 (5.3)**
Fracture	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Stress fracture	1 (5.3)	0	1 (2.6)
Grade 3	1 (5.3)	0	1 (2.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (5.3)**	**1 (5.3)**	**2 (5.3)**
Glioma	1 (5.3)	0	1 (2.6)
Grade 5	1 (5.3)	0	1 (2.6)
Tumour pain	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)
Renal and urinary disorders	**0**	**1 (5.3)**	**1 (2.6)**
Acute kidney injury	0	1 (5.3)	1 (2.6)
Grade 3	0	1 (5.3)	1 (2.6)

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Treatment-related adverse events in TRIDENT-1

Nearly all subjects (94.7%) in TRIDENT-1 experienced at least one TRAE. The most common TRAEs (any grade occurring in ≥ 10% in any population) are summarized in Table 54. Grade ≥3 TRAEs were reported in 162 patients in the overall population (28.7 %). TRAEs with grade ≥3 reported in ≥ 2 % of subjects are listed in

Table 54. Most Common (≥ 10% in any Population) Treatment-related Adverse Events by System Organ Class and Preferred Term and Maximum CTCAE Grade in TRIDENT-1 Safety Analysis

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Subjects with at least one TRAE	**350 (95.4)**	**139 (96.5)**	**46 (85.2)**	**535 (94.7)**
Nervous system disorders	**302 (85.8)**	**127 (88.2)**	**40 (74.1)**	**483 (85.5)**
Dizziness	302 (85.8)	83 (57.6)	30 (55.6)	324 (57.3)
Dysgeusia	199 (56.5)	78 (54.2)	26 (48.1)	283 (50.1)
Paraesthesia	172 (48.9)	44 (30.6)	10 (18.5)	168 (29.7)
Ataxia	107 (30.4)	33 (22.9)	6 (11.1)	119 (21.1)
Memory impairment	69 (19.6)	16 (11.1)	0	56 (9.9)
Headache	38 (10.4)	14 (9.7)	1 (1.9)	53 (9.4)
Neuralgia	38 (10.4)	13 (9.0)	0	51 (9.0)
Disturbance in attention	31 (8.4)	15 (10.4)	0	46 (8.1)
Gastrointestinal disorders	**192 (52.3)**	**77 (53.5)**	**24 (44.4)**	**293 (51.9)**
Constipation	99 (27.0)	39 (27.1)	8 (14.8)	146 (25.8)
Nausea	43 (11.7)	18 (12.5)	7 (13.0)	68 (12.0)
Diarrhoea	23 (6.3)	19 (13.2)	1 (1.9)	43 (7.6)
Investigations	**168 (45.8)**	**63 (43.8)**	**9 (16.7)**	**240 (42.5)**
Alanine aminotransferase increased	72 (19.6)	20 (13.9)	5 (9.3)	97 (17.2)
Aspartate aminotransferase increased	72 (19.6)	21 (14.6)	5 (9.3)	98 (17.3)
Blood creatine phosphokinase increased	64 (17.4)	25 (17.4)	0	89 (15.8)
Weight increased	43 (11.7)	16 (11.1)	2 (3.7)	61 (10.8)
General disorders and administration site conditions	**122 (33.2)**	**57 (39.6)**	**15 (27.8)**	**194 (34.3)**
Fatigue	53 (14.4)	28 (19.4)	12 (22.2)	93 (16.5)
Musculoskeletal and connective tissue disorders	**123 (33.5)**	**44 (30.6)**	**10 (18.5)**	**177 (31.3)**
Muscular weakness	58 (15.8)	23 (16.0)	4 (7.4)	85 (15.0)
Myalgia	30 (8.2)	15 (10.4)	2 (3.7)	47 (8.3)
Blood and lymphatic system disorders	**109 (29.7)**	**45 (31.3)**	**8 (14.8)**	**162 (28.7)**
Anaemia	98 (26.7)	43 (29.9)	7 (13.0)	148 (26.2)
Respiratory, thoracic and mediastinal disorders	**67 (18.3)**	**27 (18.8)**	**7 (13.0)**	**101 (17.9)**
Dyspnoea	36 (9.8)	16 (11.1)	4 (7.4)	56 (9.9)
Skin and subcutaneous tissue disorders	**56 (15.3)**	**24 (16.7)**	**4 (7.4)**	**84 (14.9)**
Metabolism and nutrition disorders	**49 (13.4)**	**34 (23.6)**	**4 (7.4)**	**87 (15.4)**
Decreased appetite	14 (3.8)	14 (9.7)	2 (3.7)	30 (5.3)

Table 55. Treatment-related Adverse Events ≥ Grade 3 in ≥ 2% of Subjects by System Organ Class and Preferred Term - Safety Analysis Set - TRIDENT-1 (DCO 15-Oct-2023)

System Organ Class Preferred Term	ROS1+NSCLC Subjects (N=367)	NTRK+Solid Tumor Subjects (N=144)	Other Treated Subjects (N=54)	Total (N=565)
Total Subjects With An Event	**39 (10.6)**	**22 (15.3)**	**4 (7.4)**	**65 (11.5)**
Investigations	**21 (5.7)**	**6 (4.2)**	**0**	**27 (4.8)**
Blood creatine phosphokinase increased	13 (3.5)	4 (2.8)	0	17 (3.0)
Weight increased	10 (2.7)	2 (1.4)	0	12 (2.1)
Blood and lymphatic system disorders	**11 (3.0)**	**9 (6.3)**	**2 (3.7)**	**22 (3.9)**

System Organ Class Preferred Term	ROS1+NSCLC Subjects (N=367)	NTRK+Solid Tumor Subjects (N=144)	Other Treated Subjects (N=54)	Total (N=565)
Anaemia	11 (3.0)	9 (6.3)	2 (3.7)	22 (3.9)
Nervous system disorders	**8 (2.2)**	**7 (4.9)**	**2 (3.7)**	**17 (3.0)**
Dizziness	8 (2.2)	7 (4.9)	2 (3.7)	17 (3.0)

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Treatment-related adverse events in CARE

Most subjects (84.2%) in CARE experienced at least one TRAE. The most common TRAEs (any grade occurring in ≥ 10% in any population) are summarized in Table 56. Treatment-related AEs with grade ≥3 were reported in 21.1 % of patients and are summarized in Table 57. There were no reported grade ≥4 TRAEs in CARE.

Table 56. Most Common (≥ 10%) Treatment-Related Adverse Events by Preferred Term - Full Analysis Set (CARE)

Preferred Term	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Subjects with at Least One Treatment-related TEAE	**17 (89.5)**	**15 (78.9)**	**32 (84.2)**
Anaemia	5 (26.3)	7 (36.8)	12 (31.6)
Fatigue	6 (31.6)	5 (26.3)	11 (28.9)
Dysgeusia	5 (26.3)	4 (21.1)	9 (23.7)
White blood cell count decreased	5 (26.3)	4 (21.1)	9 (23.7)
Constipation	2 (10.5)	6 (31.6)	8 (21.1)
Dizziness	3 (15.8)	5 (26.3)	8 (21.1)
Nausea	3 (15.8)	5 (26.3)	8 (21.1)
Weight increased	4 (21.1)	4 (21.1)	8 (21.1)
Lymphocyte count decreased	3 (15.8)	4 (21.1)	7 (18.4)
Neutrophil count decreased	3 (15.8)	4 (21.1)	7 (18.4)
Electrocardiogram QT prolonged	2 (10.5)	4 (21.1)	6 (15.8)
Increased appetite	1 (5.3)	4 (21.1)	5 (13.2)
Paraesthesia	4 (21.1)	1 (5.3)	5 (13.2)
Aspartate aminotransferase increased	1 (5.3)	3 (15.8)	4 (10.5)
Blood creatine phosphokinase increased	1 (5.3)	3 (15.8)	4 (10.5)
Hypertension	0	4 (21.1)	4 (10.5)
Hyperuricaemia	0	4 (21.1)	4 (10.5)
Pain in extremity	0	4 (21.1)	4 (10.5)

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Table 57. Treatment-related Adverse Events with Grade ≥ 3 by System Organ Class, Preferred Term and Maximum CTCAE Grade - CARE - Full Analysis Set

Medical concept Preferred term	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Subjects with at Least One Grade >=3 TRAE	**4 (21.1)**	**4 (21.1)**	**8 (21.1)**
Investigations	**2 (10.5)**	**3 (15.8)**	**5 (13.2)**
Weight increased	2 (10.5)	2 (10.5)	4 (10.5)
Amylase increased	0	1 (5.3)	1 (2.6)
Platelet count decreased	0	1 (5.3)	1 (2.6)
Blood and lymphatic system disorders	**0**	**2 (10.5)**	**2 (5.3)**
Anaemia	0	2 (10.5)	2 (5.3)
General disorders and administration site conditions	**0**	**1 (5.3)**	**1 (2.6)**
Fatigue	0	1 (5.3)	1 (2.6)
Injury, poisoning and procedural complications	**1 (5.3)**	**0**	**1 (2.6)**
Stress fracture	1 (5.3)	0	1 (2.6)
Metabolism and nutrition disorders	**1 (5.3)**	**0**	**1 (2.6)**

Medical concept Preferred term	NTRK (N=19)	Other (N=19)	Overall Total (N=38)
Hypokalaemia	1 (5.3)	0	1 (2.6)

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Adverse drug reactions proposed in the SmPC

The applicant referred to the SmPC guideline and the EMA guideline on the evaluation of anticancer medicinal products in. Frequency categories are based on the frequencies of all-causality AEs from the overall pools in TRIDENT-1 (n = 565) and CARE (n = 38).

ADRs were determined with the following considerations:

- TEAEs were assessed quantitatively and qualitatively as having a possible causal drug-event relationship
- TEAEs that were assessed as related to alternative aetiologies were excluded
- PT grouped/cluster terms representing medical concepts were used when applicable to better inform the prescriber with useful information about the drug
- Lab AEs were included as ADR if evidence supported a possible causal association

The following ADRs reported in TRIDENT-1 (Table 58) and CARE (Table 59) are proposed to be included in the SmPC.

Table 58. Adverse reactions occurring in adult patients treated with Augtyro clinical trial (N = 565) listed in the SmPC as proposed by the applicant

		% All Grades	% ≥ 3 Grades
Infections and infestations			
Very common	pneumonia	10.3	5.7
Blood and lymphatic system disorders			
Very common	anaemia	38.1	8.8
Metabolism and nutrition disorders			
Common	hyperuricaemia[a]	5.0	0.7
Nervous system disorders			
Very common	dizziness[b]	65.5	3.2
	ataxia[c]	29.0	0.5
	cognitive disorders[d]	22.3	1.2
	paraesthesia[e],	39.1	0.7
	peripheral sensory neuropathy[f]	20.2	1.1
	sleep disorders[g]	17.3	0.2
	headache	20.0	0.4
	dysgeusia[h]	56.5	0
Eye disorders			
Very common	vision disorders[i]	14.2	0.5
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea	31.3	6.7
	cough	18.9	0.2
Common	pneumonitis[j]	3.2	0.9
	pleural effusion	7.1	2.3
Gastrointestinal disorders			
Very common	nausea	20.7	1.2

		% All Grades	% ≥ 3 Grades
	vomiting	14.5	1.1
	constipation	39.3	0.2
	diarrhoea	15.0	0.9
Common	abdominal pain	7.3	0.5
Musculoskeletal and connective tissue disorders			
Very common	muscular weakness	21.6	1.9
	pain in extremity	11.9	0.4
	arthralgia	15.2	0.4
	myalgia	12.2	0.5
	back pain	10.1	0.5
Common	skeletal fractures[k]	3.5	0.5
General disorders and administration site conditions			
Very common	pyrexia	12.7	0.7
	fatigue	24.8	1.2
	decreased appetite	11.3	0.4
	oedema peripheral	11.7	0
Investigations			
Very common	blood creatine phosphokinase increased	17.5	3.4
	weight increased	14.7	3.2
	alanine aminotransferase increased	22.1	1.9
	aspartate aminotransferase increased	20.9	2.7
Common	lymphocyte count decreased	4.6	1.6
	white blood cell count decreased	9.0	0.9
	neutrophil count decreased	8.0	2.1
	gamma-glutamyltransferase increased	6.7	1.2
	blood alkaline phosphatase increased	8.3	1.1
Injury, poisoning and procedural complications			
Common	fall	4.6	0.5

[a] Hyperuricaemia (hyperuricaemia, increased blood uric acid)
[b]Dizziness (dizziness, vertigo, dizziness postural, dizziness exertional, vertigo positional)
[c] Ataxia (ataxia, gait disturbance, balance disorder, cerebellar ataxia, coordination abnormal, nystagmus)
[d] Cognitive disorders (memory impairment, disturbance in attention, cognitive disorder, confusional state, delirium, amnesia, attention deficit hyperactivity disorder, aphasia, altered state of consciousness, depressed level of consciousness, bradyphrenia, delusion, dysgraphia, hallucination, intellectual disability, mental disorder, mental status changes, neurological decompensation)
[e] Paraesthesia (paraesthesia, hypoaesthesia, dysaesthesia, burning sensation, anaesthesia, formication)
[f] Peripheral sensory neuropathy (neuralgia, neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, polyneuropathy)
[g] Sleep disorders (somnolence, insomnia, hypersomnia, sleep apnoea syndrome, sleep disorder, abnormal dreams, narcolepsy, obstructive sleep apnoea syndrome, snoring)
[h] Dysgeusia (dysgeusia, taste disorder, ageusia, sensory disturbance, allodynia, hypogeusia, sensory loss)
[i] Vision disorders (vision blurred, visual impairment, dry eye, photophobia, visual field defect, conjunctivitis, diplopia, eye pain, periorbital oedema, asthenopia, cataract, eye haematoma, photosensitivity reaction, visual acuity reduced, vitreous floaters, blepharospasm, cataract nuclear, colour blindness, eye infection, eye oedema, eye swelling, eyelid disorder, eyelid injury, eyelids pruritus, glaucoma, iridocyclitis, myopia, night blindness, ophthalmic herpes zoster, orbital oedema)
[j] Pneumonitis (pneumonitis, interstetial lung disease)
[k] Skeletal fractures (foot fracture, rib fracture, pathological fracture, acetabulum fracture, ankle fracture, femur fracture, fibula fracture, spinal compression fracture, sternal fracture, upper limb fracture)

Table 59. Adverse reactions occurring in paediatric patients treated with Augtyro clinical trial (N = 38) listed in the SmPC as proposed by the applicant

		% All Grades	% ≥ 3 Grades
Infections and infestations			
Common	pneumonia	5.3	2.6
Blood and lymphatic system disorders			
Very common	anaemia	50.0	15.8
Metabolism and nutrition disorders			
Very common	increased appetite	13.2	0
	hyperkalaemia	10.5	0
	hyperuricaemia[a]	15.8	0
Nervous system disorders			
Very common	dizziness	21.1	0
	ataxia[b]	15.8	0
	cognitive disorders[c]	10.5	0
	paraesthesia	13.2	0
	sleep disorders[d]	18.4	2.6
	headache	31.6	0
	dysgeusia[e]	26.3	0
Common	peripheral sensory neuropathy[f]	5.3	0
Eye disorders			
Very common	vision disorders[g]	10.5	0
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea	15.8	2.6
	cough	26.3	0
Common	pleural effusion	5.3	2.6
Gastrointestinal disorders			
Very common	nausea	28.9	0
	vomiting	21.1	0
	constipation	39.5	2.6
	diarrhoea	18.4	5.3
Common	paraesthesia oral	7.9	0
Musculoskeletal and connective tissue disorders			
Very common	skeletal fractures[h]	18.4	5.3
	arthralgia	10.5	0
Common	myalgia	7.9	0
	muscular weakness	7.9	0
General disorders and administration site conditions			
Very common	pyrexia	26.3	0
	fatigue	36.8	2.6
	abdominal pain	15.8	2.6
Investigations			
Very common	blood creatine phosphokinase increased	15.8	0
	weight increased	26.3	15.8
	lymphocyte count decreased	18.4	0
	white blood cell count decreased	23.7	0
	neutrophil count decreased	21.1	2.6

		% All Grades	% ≥ 3 Grades
	aspartate aminotransferase increased	23.7	2.6
	blood alkaline phosphatase increased	13.2	0
Injury, poisoning and procedural complications			
Common	fall	7.9	0

[a] Hyperuricaemia (hyperuricaemia, increased blood uric acid)
[b] Ataxia (gait disturbance, ataxia)
[c] Cognitive disorders (aphasia, confusional state, memory impairment, attention deficit, hyperactivity disorder, depressed level of consciousness)
[d] Sleep disorders (somnolence, insomnia, obstructive sleep apnoea syndrome)
[e] Dysgeusia (dysgeusia, allodynia)
[f] Peripheral sensory neuropathy (peripheral sensory neuropathy, peripheral motor neuropathy)
[g] Vision disorders (vision blurred, eye pain, hemianopia homonymous, photophobia, visual impairment)
[h] Skeletal fractures (ankle fracture, foot fracture, stress fracture, fibula fracture, fracture, tibia fracture)
* Frequencies include data from two adult patients

2.6.8.3. Serious adverse events, deaths, and other significant events

Adverse events of special interest

Selection of medical concepts as adverse events of interest (AESI) were based on expected pharmacological effects related to the mechanism of action, class effects of similar TKIs, and observed toxicities from preclinical and clinical studies.

Repotrectinib has been shown to inhibit the neurotrophin receptor tyrosine kinases TRKA, TRKB, and TRKC in both biochemical and cellular potency assays. TRKs are known to play key roles in sensory neuron development and differentiation. AEs that have been attributed to TRK inhibition are associated with decreased proprioception and cerebellar dysfunction. Nervous system disorders including dizziness, dysgeusia, paresthesia, peripheral sensory neuropathy, and ataxia are events of special interest.

Investigations on other events of special interest for muscular weakness, paraesthesia, peripheral sensory neuropathy, cognitive disorders, sleep disorders, vision disorders, pneumonitis, hepatic enzyme elevation, QTc prolongation and skeletal fractures were conducted based on medical concepts with grouped PT terms (i.e., similar clinical and symptom presentation) to assess clinical relevance in subjects administered repotrectinib.

AESIs in TRIDENT-1

Most patients experienced at least one AESI (94.7 %), and the most reported AESIs were overall consistent across the safety populations and mirror the most common TEAE. An overview of AESIs reported in > 2 subjects are provided in Table 60, below. The most frequently reported AESIs were primarily CNS effects which is consistent with those reported with TRK inhibition.

Table 60. Treatment-Emergent Adverse Events of Special Interest in > 2 Subjects by Medical Concept and Preferred Term in TRIDENT-1 Safety Analysis

Medical Concept Preferred Term	***ROS1*+ NSCLC Subjects N = 367**	***NTRK*+ Solid Tumour Subjects N = 144**	**Other Treated Subjects N = 54**	**Overall Population N = 565**
Subjects with at least one AESI	349 (95.1)	136 (94.4)	**50 (92.6)**	535 (94.7)
Ataxia	**109 (29.7)**	**47 (32.6)**	**8 (14.8)**	**164 (29.0)**
Ataxia	84 (22.9)	34 (23.6)	6 (11.1)	124 (21.9)
Gait disturbance	17 (4.6)	10 (6.9)	4 (7.4)	31 (5.5)
Balance disorder	13 (3.5)	8 (5.6)	0	21 (3.7)
Cognitive Disorders	**84 (22.9)**	**35 (24.3)**	**7 (13.0)**	**126 (22.3)**
Memory impairment	45 (12.3)	24 (16.7)	0	69 (12.2)
Disturbance in attention	39 (10.6)	19 (13.2)	0	58 (10.3)
Cognitive disorder	24 (6.5)	10 (6.9)	1 (1.9)	35 (6.2)

Medical Concept Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Confusional state	7 (1.9)	2 (1.4)	3 (5.6)	12 (2.1)
Delirium	4 (1.1)	1 (0.7)	2 (3.7)	7 (1.2)
Amnesia	5 (1.4)	0	0	5 (0.9)
Attention deficit hyperactivity disorder	4 (1.1)	0	0	4 (0.7)
Aphasia	1 (0.3)	2 (1.4)	1 (1.9)	4 (0.7)
Depressed level of consciousness	1 (0.3)	1 (0.7)	1 (1.9)	3 (0.5)
Dizziness	**241 (65.7)**	**94 (65.3)**	**35 (64.8)**	**370 (65.5)**
Dizziness	231 (62.9)	90 (62.5)	35 (64.8)	356 (63.0)
Vertigo	15 (4.1)	4 (2.8)	0	19 (3.4)
Dizziness postural	5 (1.4)	1 (0.7)	2 (3.7)	8 (1.4)
Dysgeusia	**206 (56.1)**	**87 (60.4)**	**26 (48.1)**	**319 (56.5)**
Dysgeusia	189 (51.5)	81 (56.3)	26 (48.1)	296 (52.4)
Taste disorder	13 (3.5)	5 (3.5)	0	18 (3.2)
Ageusia	4 (1.1)	2 (1.4)	0	6 (1.1)
Sensory disturbance	3 (0.8)	0	0	3 (0.5)
Hepatic Enzyme Elevation	**112 (30.5)**	**35 (24.3)**	**5 (9.3)**	**152 (26.9)**
Alanine aminotransferase increased	93 (25.3)	27 (18.8)	5 (9.3)	125 (22.1)
Aspartate aminotransferase increased	86 (23.4)	27 (18.8)	5 (9.3)	118 (20.9)
Hypertransaminasaemia	3 (0.8)	1 (0.7)	0	4 (0.7)
Mood Disorders	**25 (6.8)**	**8 (5.6)**	**4 (7.4)**	**37 (6.5)**
Anxiety	12 (3.3)	2 (1.4)	4 (7.4)	18 (3.2)
Depression	6 (1.6)	3 (2.1)	0	9 (1.6)
Irritability	3 (0.8)	2 (1.4)	0	5 (0.9)
Depressed mood	3 (0.8)	1 (0.7)	0	4 (0.7)
Muscular Weakness	**85 (23.2)**	**28 (19.4)**	**9 (16.7)**	**122 (21.6)**
Muscular weakness	85 (23.2)	28 (19.4)	9 (16.7)	122 (21.6)
Paraesthesia	**152 (41.4)**	**55 (38.2)**	**14 (25.9)**	**221 (39.1)**
Paraesthesia	129 (35.1)	51 (35.4)	12 (22.2)	192 (34.0)
Hypoaesthesia	17 (4.6)	3 (2.1)	0	20 (3.5)
Hyperaesthesia	11 (3.0)	3 (2.1)	1 (1.9)	15 (2.7)
Dysaesthesia	7 (1.9)	2 (1.4)	1 (1.9)	10 (1.8)
Burning sensation	5 (1.4)	0	0	5 (0.9)
Peripheral Sensory Neuropathy	**77 (21.0)**	**28 (19.4)**	**9 (16.7)**	**114 (20.2)**
Neuralgia	47 (12.8)	16 (11.1)	0	63 (11.2)
Neuropathy peripheral	14 (3.8)	6 (4.2)	5 (9.3)	25 (4.4)
Peripheral sensory neuropathy	19 (5.2)	7 (4.9)	4 (7.4)	30 (5.3)
Peripheral motor neuropathy	3 (0.8)	2 (1.4)	0	5 (0.9)
Pneumonitis	**13 (3.5)**	**4 (2.8)**	**1 (1.9)**	**18 (3.2)**
Pneumonitis	13 (3.5)	3 (2.1)	1 (1.9)	17 (3.0)
QT Prolongation	**4 (1.1)**	**1 (0.7)**	**0**	**5 (0.9)**
Electrocardiogram QT prolonged	4 (1.1)	1 (0.7)	0	5 (0.9)
Skeletal Fractures	**14 (3.8)**	**4 (2.8)**	**2 (3.7)**	**20 (3.5)**
Foot fracture	3 (0.8)	2 (1.4)	1 (1.9)	6 (1.1)
Rib fracture	3 (0.8)	0	0	3 (0.5)
Sleep Disorders	**65 (17.7)**	**31 (21.5)**	**2 (3.7)**	**98 (17.3)**
Somnolence	33 (9.0)	19 (13.2)	0	52 (9.2)
Insomnia	23 (6.3)	10 (6.9)	1 (1.9)	34 (6.0)
Hypersomnia	5 (1.4)	2 (1.4)	0	7 (1.2)
Sleep apnoea syndrome	5 (1.4)	0	1 (1.9)	6 (1.1)
Sleep disorder	2 (0.5)	1 (0.7)	0	3 (0.5)
Vision Disorders	**50 (13.6)**	**26 (18.1)**	**4 (7.4)**	**80 (14.2)**
Vision blurred	16 (4.4)	6 (4.2)	1 (1.9)	23 (4.1)
Visual impairment	8 (2.2)	4 (2.8)	1 (1.9)	13 (2.3)
Dry eye	6 (1.6)	3 (2.1)	0	9 (1.6)
Photophobia	2 (0.5)	3 (2.1)	1 (1.9)	6 (1.1)
Visual field defect	3 (0.8)	1 (0.7)	0	4 (0.7)
Conjunctivitis	3 (0.8)	0	0	3 (0.5)
Diplopia	2 (0.5)	1 (0.7)	0	3 (0.5)

Medical Concept Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Eye pain	3 (0.8)	1 (0.7)	0	4 (0.7)
Periorbital oedema	2 (0.5)	1 (0.7)	0	3 (0.5)

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Serious AESIs were reported for 34 (6.0%) of subjects in the Overall safety population (Table 61), with most individual event PTs reported at low incidences (< 1% of subjects) with the exceptions of muscular weakness and pneumonitis (6 [1.1%] subjects, each). There was one reported AESI with a fatal outcome (skeletal fracture).

Table 61 - Treatment-Emergent Serious Adverse Events of Special Interest by Medical Concept and Preferred Term (Safety Analysis Set) (TRIDENT-1)

Medical Concept Preferred Term	ROS1+ NSCLC Subjects (N=367)	NTRK+ Solid Tumor Subjects (N=144)	Other Treated Subjects (N=54)	Total (N=565)
Subjects with at Least One Serious TEAE of Special Interest	22 (6.0)	9 (6.3)	3 (5.6)	34 (6.0)
Ataxia	2 (0.5)	0	0	2 (0.4)
Ataxia	2 (0.5)	0	0	2 (0.4)
Cognitive Disorders	3 (0.8)	3 (2.1)	2 (3.7)	8 (1.4)
Delirium	1 (0.3)	1 (0.7)	0	2 (0.4)
Depressed level of consciousness	0	1 (0.7)	1 (1.9)	2 (0.4)
Altered state of consciousness	1 (0.3)	0	0	1 (0.2)
Aphasia	0	0	1 (1.9)	1 (0.2)
Confusional state	1 (0.3)	0	0	1 (0.2)
Neurological decompensation	0	1 (0.7)	0	1 (0.2)
Dizziness	3 (0.8)	2 (1.4)	0	5 (0.9)
Dizziness	3 (0.8)	2 (1.4)	0	5 (0.9)
Mood Disorders	1 (0.3)	0	0	1 (0.2)
Mania	1 (0.3)	0	0	1 (0.2)
Muscular Weakness	3 (0.8)	2 (1.4)	1 (1.9)	6 (1.1)
Muscular weakness	3 (0.8)	2 (1.4)	1 (1.9)	6 (1.1)
Peripheral Sensory Neuropathy	1 (0.3)	0	0	1 (0.2)
Peripheral motor neuropathy	1 (0.3)	0	0	1 (0.2)
Pneumonitis	5 (1.4)	1 (0.7)	0	6 (1.1)
Pneumonitis	5 (1.4)	1 (0.7)	0	6 (1.1)
Skeletal Fractures	5 (1.4)	1 (0.7)	0	6 (1.1)
Ankle fracture	1 (0.3)	0	0	1 (0.2)
Femur fracture	1 (0.3)	0	0	1 (0.2)
Fibula fracture	0	1 (0.7)	0	1 (0.2)
Skeletal Fractures (cont'd)				
Pathological fracture	1 (0.3)	0	0	1 (0.2)
Rib fracture	1 (0.3)	0	0	1 (0.2)
Spinal compression fracture	1 (0.3)	0	0	1 (0.2)
Vision Disorders	1 (0.3)	1 (0.7)	0	2 (0.4)
Ophthalmic herpes zoster	0	1 (0.7)	0	1 (0.2)
Visual impairment	1 (0.3)	0	0	1 (0.2)

Abbreviations: TEAE = Treatment-Emergent Adverse Event.
NTRK+ Solid Tumor Subjects includes expansion cohorts EXP-5 and EXP-6. Other treated subjects includes subjects with ROS1+ non-NSCLC, ALK+ gene fusions, and any gene fusions with discordant results between local FISH test and central laboratory test. Percentages are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 26.1. Adverse events occurring on or after the first dose date through 28 days after last dose of study drug are considered treatment emergent. If a subject reported one or more adverse event, subject is counted once at each level reported. Medical Concepts are as described in the SAP based on cross-functional review of higher level terms and preferred terms. Medical concepts are sorted alphabetically and the preferred terms are sorted in order of descending total frequency.

The median time to first event onset for the most frequently reported AESIs (≥ 10% of subjects) in the Overall safety population was typically within the first month of study treatment, irrespective of

causality. Time to first onset of treatment-related AESIs are presented in Table 62 and for treatment-emergent AESIs is presented in

Table 63.

Table 62. Time to First Onset (Days) of Treatment-related Adverse Events of Special Interest Within Each Medical Concept (TRIDENT-1)

Medical Concept Value	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Ataxia, n(%)	**109 (29.7)**	**45 (31.3)**	**7 (13.0)**	**154 (27.3)**
Median	20.5	15.0	12.0	17.5
Min, Max	1, 511	1, 1121	1, 389	1, 1121
Cognitive Disorders, n(%)	**66 (18.0)**	**25 (17.4)**	**1 (1.9)**	**92 (16.3)**
Median	38.0	43.0	11.0	38.0
Min, Max	1, 511	8, 367	11, 11	1, 511
Dizziness, n(%)	**222 (60.5)**	**86 (59.7)**	**30 (55.6)**	**338 (59.8)**
Median	7.0	7.0	4.0	6.5
Min, Max	1, 1150	1, 477	1, 141	1, 1150
Dysgeusia, n(%)	**195 (53.1)**	**83 (57.6)**	**26 (48.1)**	**304 (53.8)**
Median	8.0	8.0	10.5	8.0
Min, Max	1, 589	1, 195	1, 43	1, 589
Hepatic Enzyme Elevation, n(%)	**92 (25.1)**	**24 (16.7)**	**5 (9.3)**	**121 (21.4)**
Median	15.0	25.5	16.0	21.0
Min, Max	1, 1065	8, 589	7, 23	1, 1065
Mood Disorders, n(%)	**11 (3.0)**	**5 (3.5)**	**1 (1.9)**	**17 (3.0)**
Median	43.0	22.0	10.0	26.0
Min, Max	4, 1192	15, 442	10, 10	4, 1192
Muscular Weakness, n(%)	**58 (15.8)**	**23 (16.0)**	**4 (7.4)**	**85 (15.0)**
Median	42.5	37.0	30.0	37.0
Min, Max	2, 1233	1, 841	17, 533	1, 1233
Paraesthesia, n(%)	**134 (36.5)**	**47 (32.6)**	**12 (22.2)**	**193 (34.2)**
Median	13.0	15.0	11.5	13.0
Min, Max	1, 827	1, 532	2, 17	1, 827
Peripheral Sensory Neuropathy, n(%)	**66 (18.0)**	**21 (14.6)**	**8 (14.8)**	**95 (16.8)**
Median	11.0	29.0	7.0	15.0
Min, Max	1, 839	8, 225	2, 37	1, 839
Pneumonitis, n(%)	**10 (2.7)**	**4 (2.8)**	**0 (0.0)**	**14 (2.5)**
Median	38.0	202.0	-	45.0
Min, Max	18, 356	34, 281	-	18, 356
QT Prolongation, n(%)	**1 (0.3)**	**1 (0.7)**	**0 (0.0)**	**2 (0.4)**
Median	29.0	28.0	-	28.5
Min, Max	29, 29	28, 28	-	28, 29
Sleep Disorders, n(%)	**0 (0.0)**	**1 (0.7)**	**1 (1.9)**	**1 (0.2)**
Median	-	59.0	10.0	59.0
Min, Max	-	59, 59	10, 10	59, 59
Vision Disorders, n(%)	**38 (10.4)**	**19 (13.2)**	**0 (0.0)**	**58 (10.3)**
Median	18.5	19.0	-	18.0
Min, Max	1, 869	3, 420	-	1, 869

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Table 63 - Time to First Onset (Days) of Treatment-emergent Adverse Events of Special Interest Within Each Medical Concept (TRIDENT-1)

Medical Concept Value	ROS1+ NSCLC Subjects (N = 367)	NTRK+ Solid Tumor Subjects (N = 144)	Other Treated Subjects (N = 54)	Total (N = 565)
Ataxia, n(%)	109 (29.7)	47 (32.6)	8 (14.8)	164 (29.0)
Median	21.0	14.0	16.0	16.5
Min, Max	1, 589	1, 1121	1, 332	1, 1121
Cognitive Disorders, n(%)	84 (22.9)	35 (24.3)	7 (13.0)	126 (22.3)
Median	38.0	29.0	15.0	37.0
Min, Max	1, 752	1, 562	4, 120	1, 752
Dizziness, n(%)	241 (65.7)	94 (65.3)	35 (64.8)	370 (65.5)
Median	7.0	7.5	4.0	7.0
Min, Max	1, 760	1, 581	1, 141	1, 760
Dysgeusia, n(%)	206 (56.1)	87 (60.4)	26 (48.1)	319 (56.5)
Median	8.0	8.0	10.5	8.0
Min, Max	1, 427	1, 562	1, 43	1, 562
Hepatic Enzyme Elevation, n(%)	112 (30.5)	35 (24.3)	5 (9.3)	152 (26.9)
Median	15.0	29.0	16.0	19.0
Min, Max	1, 1065	1, 589	7, 23	1, 1065
Mood Disorders, n(%)	25 (6.8)	8 (5.6)	4 (7.4)	37 (6.5)
Median	50.0	42.5	81.5	57.0
Min, Max	4, 1213	8, 442	10, 126	4, 1213
Muscular Weakness, n(%)	85 (23.2)	28 (19.4)	9 (16.7)	122 (21.6)
Median	43.0	36.0	19.0	39.0
Min, Max	1, 1233	1, 990	3, 533	1, 1233
Paraesthesia, n(%)	152 (41.4)	55 (38.2)	14 (25.9)	221 (39.1)
Median	13.5	15.0	12.0	14.0
Min, Max	1, 907	1, 532	2, 1905	1, 1905
Peripheral Sensory Neuropathy, n(%)	77 (21.0)	28 (19.4)	9 (16.7)	114 (20.2)
Median	15.0	29.5	8.0	15.0
Min, Max	1, 839	1, 503	2, 37	1, 839
Pneumonitis, n(%)	13 (3.5)	4 (2.8)	1 (1.9)	18 (3.2)
Median	48.0	202.0	106.0	56.0
Min, Max	18, 356	34, 281	106, 106	18, 356
QT Prolongation, n(%)	4 (1.1)	1 (0.7)	0 (0.0)	5 (0.9)
Median	22.0	28.0		28.0
Min, Max	14, 251	28, 28		14, 251
Skeletal Fractures, n(%)	14 (3.8)	4 (2.8)	2 (3.7)	20 (3.5)
Median	127.5	195.5	375.0	171.5
Min, Max	10, 921	59, 751	51, 699	10, 921
Sleep Disorders, n(%)	65 (17.7)	31 (21.5)	2 (3.7)	98 (17.3)
Median	26.0	22.0	16.0	22.5
Min, Max	1, 869	1, 562	10, 22	1, 869
Vision Disorders, n(%)	50 (13.6)	26 (18.1)	4 (7.4)	80 (14.2)
Median	57.0	41.5	45.0	53.0
Min, Max	1, 646	3, 715	8, 150	1, 715

NTRK+ Solid Tumor Subjects includes expansion cohorts EXP-5 and EXP-6. Other treated subjects includes subjects with ROS1+ non-NSCLC, ALK+ gene fusions, and any gene fusions with discordant results between local FISH test and central laboratory test. Percentages are based on the number of subjects in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 26.1. Medical Concepts are as described in the SAP based on cross-functional review of higher level terms and preferred terms.
Cross Reference: ADAE, ADSL

AESIs in CARE

The most frequently reported (> 10%) Treatment Emergent Adverse Events of Special Interest by medical concept included dysgeusia and hepatic enzyme elevation (26.3% each), dizziness (21.1%), sleep disorders and skeletal fractures (18.4% each), ataxia, mood disorders and QT prolongation (15.8% each; all reported events of QT prolonged were nonserious, low grade, did not require dose modifications, and QTcF for all patients was reported within normal range), paraesthesia (13.2%), and vision disorders and cognitive disorders (10.5% each). AESIs by medical concept with a >10% increase in frequency since the 19-Dec-2022 DCO were skeletal fractures (7.7% to 18.4%) and hepatic enzyme elevation (15.4% to 26.3%).

- Skeletal fractures: 7 (18.4%) patients were reported with TEAEs, including the PTs of ankle fracture (3 [7.9%] patients), fibula fracture (2 [5.3%] patients), foot fracture, fracture, stress fracture, tibia fracture (each in 1 [2.6%] patient). Of these, the majority were reported as low grade by the Investigator.

The most frequently reported (> 10%) treatment-related AESIs by medical concepts included dysgeusia (10/38, 26.3%), dizziness (8/38, 21.1%), QT prolongation (6/38, 15.8%), paraesthesia, ataxia, and hepatic enzyme elevation (5/38, 13.2% each), and skeletal fractures (4/38, 10.5%), as shown in Table 64.

Table 64. Treatment Related Adverse Events of Special Interest by Medical Concept and Preferred Term - Full Analysis Set (CARE)

Medical Concept Preferred Term	NTRK N=19	Other N=19	Overall Total N=38
Ataxia	**2 (10.5)**	**3 (15.8)**	**5 (13.2)**
Gait disturbance	2 (10.5)	1 (5.3)	3 (7.9)
Ataxia	0	2 (10.5)	2 (5.3)
Cognitive Disorders	**0**	**1 (5.3)**	**1 (2.6)**
Confusional state	0	1 (5.3)	1 (2.6)
Memory impairment	0	1 (5.3)	1 (2.6)
Dizziness	**3 (15.8)**	**5 (26.3)**	**8 (21.1)**
Dizziness	3 (15.8)	5 (26.3)	8 (21.1)
Dysgeusia	**5 (26.3)**	**5 (26.3)**	**10 (26.3)**
Dysgeusia	5 (26.3)	4 (21.1)	9 (23.7)
Allodynia	0	1 (5.3)	1 (2.6)
Hepatic Enzyme Elevation	**1 (5.3)**	**4 (21.1)**	**5 (13.2)**
Aspartate aminotransferase increased	1 (5.3)	3 (15.8)	4 (10.5)
Alanine aminotransferase increased	0	3 (15.8)	3 (7.9)
Mood Disorders	**0**	**1 (5.3)**	**1 (2.6)**
Irritability	0	1 (5.3)	1 (2.6)
Muscular Weakness	**1 (5.3)**	**0**	**1 (2.6)**
Muscular weakness	1 (5.3)	0	1 (2.6)
Paraesthesia	**4 (21.1)**	**1 (5.3)**	**5 (13.2)**
Paraesthesia	4 (21.1)	1 (5.3)	5 (13.2)
Peripheral Sensory Neuropathy	**2 (10.5)**	**0**	**2 (5.3)**
Peripheral motor neuropathy	1 (5.3)	0	2 (2.6)
Peripheral sensory neuropathy	1 (5.3)	0	1 (2.6)
Qt Prolongation	**2 (10.5)**	**4 (21.1)**	**6 (15.8)**
Electrocardiogram QT prolonged	2 (10.5)	4 (21.1)	6 (15.8)
Skeletal Fractures	**1 (5.3)**	**3 (15.8)**	**4 (10.5)**
Ankle fracture	0	2 (10.5)	2 (5.3)
Fibula fracture	0	1 (5.3)	1 (2.6)
Foot fracture	0	1 (5.3)	1 (2.6)
Stress fracture	1 (5.3)	0	1 (2.6)
Tibia fracture	0	1 (5.3)	1 (2.6)
Sleep Disorders	**2 (10.5)**	**1 (5.3)**	**3 (7.9)**
Somnolence	2 (10.5)	1 (5.3)	3 (7.9)
Insomnia	0	1 (5.3)	1 (2.6)
Vision Disorders	**1**	**2 (10.5)**	**3 (7.9)**
Hemianopia homonymous	1 (5.3)	0	1 (2.6)
Vision blurred	0	1 (5.3)	1 (2.6)
Visual impairment	0	1 (5.3)	1 (2.6)

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Note: NTRK summary pools subjects with an NTRK1-NTRK3 genetic alteration. Other summary pools subjects with an ALK or ROS1 genetic alteration. Percentages are based on the number of subjects in the Full Analysis Set.

Discussion of selected AESIs

The numbers presented refer to data from TRIDENT-1, with some additions from CARE where relevant. This is specified.

Dizziness is the most reported AESI in adults (65.5 %), as well as the most common overall TRAE. However, most cases are lower grade with only grade 3 events reported in 3.2 % adult subjects. Some adult patients required dose reduction (11.5 %) and/or temporary interruptions (10.3 %), but no subjects discontinued treatment due to dizziness. Median TTO was 7 days. Resolution occurred in 187 patients (50.5%) with a median time to resolution of 40.0 weeks (range: 0.1 weeks to 323.6+ weeks). The incidence of reported dizziness is lower in children and adolescents (21.1 %), but data are strictly limited in this group.

Ataxia (including ataxia, gait disturbances, balance disorder, cerebellar ataxia, and coordination abnormal) was reported in 29.0% (164/565) of adult patients; Grade 3 ataxia was reported in 0.5% (3/565) of patients. The median time to onset was 17 days (range: 1 day to 3.1 years). Resolution occurred in 85 patients (51.8%) with a median time to resolution of 28.4 weeks (range: 0.4+ weeks to 257.6+ weeks). Dose reduction was required in 7.6% (43/565) of patients, 5.0% (28/565) required dose interruptions and 0.2% (1/565) discontinued due to ataxia.

Cognitive disorders were reported in 22.3% (126/565) of adult patients. Cognitive disorders included memory impairment (12.2%), disturbance in attention (10.3%), cognitive disorder (6.2%), confusional state (2.1%), delirium (1.2%), amnesia (0.9%), attention deficit hyperactivity disorder, aphasia (0.7% each), depressed level of consciousness (0.5%), altered state of consciousness, neurological decompensation (0.4% each), bradyphrenia, delusion, dysgraphia, hallucinations, intellectual disability, mental disorder, and mental status change (0.2% each); Grade 3 cognitive disorders were reported in 1.2% (7/565) of patients. The median time to onset of cognitive disorders was 37 days (range: 1 day to 2.1 years). Resolution occurred in 56 patients (44.4%) with a median time to resolution of 69.3 weeks (range: 0.1 weeks to 235.7+ weeks). Dose reduction was required in 1.9% (11/565) of patients, 1.6% (9/565) required dose interruption and 0.9% (5/565) of patients discontinued repotrectinib due to cognitive adverse reactions.

Skeletal fractures were more commonly reported in paediatric patients (7/38, 18.4 %) than in adults (20/565, 3.5 %). For adults, one of the events was considered treatment-related by the Investigator (0.2%), and there were two patients with grade 3 events (0.4 %). Most adult patients reported with a fracture had an underlying risk factor that included a history of bone metastases, hypophosphatemia, osteoporosis, osteoarthritis, prior fractures, unwitnessed falls, visual impairment, and adverse events of relevance on study (e.g., dizziness, cognitive disorders, ataxia, and falls) that preceded the skeletal fracture. For paediatric patients , grade 3 fractures were reported in 5.3 % (2/38). Overall, four of the seven events (all grade) were considered related to treatment (10.5 %), and one case was a grade 3 stress fracture. The risk of skeletal fractures appears larger in children, which is consistent with data reported for the class. Additionally, repotrectinib causes dizziness in many patients, which increases the risk of fractures caused by fall, especially in patients with risk factors for fractures. Median time to onset was 5.6 months in adult (range:10 days to 2.5 years) and 4.2 months in paediatric patients (range: 25 days to 16.9 months), respectively. Resolution occurred in 50 % of adult patients and 57.1 % of paediatric patients, with corresponding times to resolution of 40 weeks (TRIDENT-1, range 0.1 weeks to 220.9+ weeks) and between 10 days to 6.7 months (CARE). Dose interruption was required in 0.7 % in TRIDENT-1 and 10.5 % in CARE. One adult (0.2 %) and one paediatric patient (2.6 %) discontinued treatment due to skeletal fractures.

Pneumonitis as a medical concept was selected as an AESI (including pneumonitis and ILD) and was reported in 18 adult patients (3.2 %), with grade 3 events in 5 patients (0.9 %). The median time to onset was 56 days (18 days to 11.7 months). Resolution occurred in 12 patients (66.7%) with median time to resolution 7.4 weeks (range: 0.6 weeks to 67.7 weeks). Dose interruption was required in 1.4% (8/565) of patients, 0.5% (3/565) of patients required dose reduction, and 0.9% (5/565) of patients permanently discontinued due to ILD/pneumonitis. No cases with ILD/pneumonitis were reported in CARE.

Hepatotoxicity: In TRIDENT-1 increased alanine transaminase (ALT) occurred in 22.1% (125/565) patients, increased aspartate aminotransferase (AST) occurred in 20.9% (118/565), including Grade 3 increased ALT in 1.8% (10/565) and increased AST in 2.5% (14/565). The median time to onset was 19 days (range: 1 day to 2.9 years). Resolution occurred in 120 patients (78.9%) with median time to resolution 5 weeks (0.7+ weeks to 92.0+ weeks). Dose interruption was required in 3% (17/565) of patients, 1.2% (7/565) of patients required dose reduction. Vision disorders: In the adult population, vision changes occurred in 14.2 % (80/565) of patients, including Grade 3 vision disorder in 0.5% (3/565). Vision disorders included blurred vision (4.1%), visual impairment (2.3%), dry eye (1.6%). Resolution occurred in 34 patients (42.5%) with a range of time to resolution of 0.1 weeks to 226.9+ weeks. Dose interruption was required in 1.2% (7/565) of patients, 0.2% (1/565) of patients required dose reduction, and 0.2% (1/565) of patients permanently discontinued treatment due to vision disorders.

Muscle weakness with or without creatine phosphokinase (CPK) elevation was reported. In TRIDENT-1 weakness occurred in 21.6% (122/565) of patients, with Grade 3 in 1.9% (11/565). Median time to onset of muscle weakness was 39 days (range: 1 day to 3.4 years). Resolution occurred in 49 patients (40.2%) with median time to resolution 86.6 weeks (0.3 weeks to 236.6+ weeks). Dose interruption was required in 5.5% (31/565) of patients, 4.8% (27/565) of patients required dose reduction, and 0.9% (5/565) of patients permanently discontinued due to muscle weakness.

Median time to onset of dyspnoea was 43 days (range: 1 day to 2.1 years). Resolution occurred in 75 patients (42.4%) with median time to resolution 35.6 weeks (range: 0.1 weeks to 269.1+ weeks).

Serious adverse events

The proportion of patients who experienced at least one treatment-emergent serious adverse event (SAE) is overall comparable across analysis populations, and between adult (40.7 %) (Table 65) and paediatric patients (36.8 %.). Data in children and adolescents is very limited, there were 14 patients reported with SAEs (36.8 %) as of the new data cutoff, compared to 11 patients (42.3 %) from the initial cut-off, when no SAEs reported in > 1 subjects (19-Dec-2022 DCO, see Table 66).

Table 65. Treatment-Emergent Serious Adverse Events in > 2 Subjects by System Organ Class and Preferred Term in TRIDENT-1 Safety Analysis

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Subjects with at Least One SAE	**153 (41.7)**	**56 (38.9)**	**21 (38.9)**	**230 (40.7)**
Grade 1	1 (0.3)	1 (0.7)	1 (1.9)	3 (0.5)
Grade 2	20 (5.4)	7 (4.9)	3 (5.6)	30 (5.3)
Grade 3	90 (24.5)	35 (24.3)	12 (22.2)	137 (24.2)
Grade 4	17 (4.6)	5 (3.5)	3 (5.6)	25 (4.4)
Grade 5	25 (6.8)	8 (5.6)	2 (3.7)	35 (6.2)
Respiratory, thoracic and mediastinal disorders	**52 (14.2)**	**12 (8.3)**	**9 (16.7)**	**73 (12.9)**
Dyspnoea	13 (3.5)	3 (2.1)	4 (7.4)	20 (3.5)

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Pleural effusion	14 (3.8)	2 (1.4)	1 (1.9)	17 (3.0)
Hypoxia	10 (2.7)	0	1 (1.9)	11 (1.9)
Pulmonary embolism	7 (1.9)	2 (1.4)	1 (1.9)	10 (1.8)
Pneumonitis	5 (1.4)	1 (0.7)	0	6 (1.1)
Respiratory failure	4 (1.1)	2 (1.4)	1 (1.9)	7 (1.2)
Infections and infestations	**48 (13.1)**	**23 (16.0)**	**6 (11.1)**	**77 (13.6)**
Pneumonia	22 (6.0)	11 (7.6)	2 (3.7)	35 (6.2)
COVID-19	5 (1.4)	2 (1.4)	1 (1.9)	8 (1.4)
Sepsis	5 (1.4)	2 (1.4)	0	7 (1.2)
Urinary tract infection	1 (0.3)	1 (0.7)	2 (3.7)	4 (0.7)
COVID-19 pneumonia	1 (0.3)	2 (1.4)	0	3 (0.5)
Pneumonia aspiration	3 (0.8)	0	0	3 (0.5)
Nervous system disorders	**22 (6.0)**	**9 (6.3)**	**5 (9.3)**	**36 (6.4)**
Syncope	3 (0.8)	3 (2.1)	0	6 (1.1)
Dizziness	3 (0.8)	2 (1.4)	0	5 (0.9)
Cerebrovascular accident	3 (0.8)	0	1 (1.9)	4 (0.7)
General disorders and administration site conditions	**16 (4.4)**	**8 (5.6)**	**2 (3.7)**	**26 (4.6)**
Pyrexia	4 (1.1)	3 (2.1)	0	7 (1.2)
Death	6 (1.6)	0	0	6 (1.1)
Sudden death	2 (0.5)	0	1 (1.9)	3 (0.5)
Cardiac disorders	**16 (4.4)**	**4 (2.8)**	**1 (1.9)**	**21 (3.7)**
Pericardial effusion	7 (1.9)	0	0	7 (1.2)
Cardiac arrest	4 (1.1)	1 (0.7)	1 (1.9)	6 (1.1)
Gastrointestinal disorders	**8 (2.2)**	**7 (4.9)**	**3 (5.6)**	**18 (3.2)**
Abdominal pain	2 (0.5)	2 (1.4)	0	4 (0.7)
Colitis	2 (0.5)	1 (0.7)	0	3 (0.5)
Nausea	2 (0.5)	0	1 (1.9)	3 (0.5)
Musculoskeletal and connective tissue disorders	**14 (3.8)**	**5 (3.5)**	**2 (3.7)**	**21 (3.7)**
Muscular weakness	3 (0.8)	2 (1.4)	1 (1.9)	6 (1.1)
Back pain	2 (0.5)	1 (0.7)	0	3 (0.5)
Blood and lymphatic system disorders	**7 (1.9)**	**2 (1.4)**	**1 (1.9)**	**10 (1.8)**
Anaemia	3 (0.8)	2 (1.4)	1 (1.9)	6 (1.1)
Injury, poisoning and procedural complications	**11 (3.0)**	**2 (1.4)**	**0**	**13 (2.3)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6 (1.6)**	**2 (1.4)**	**1 (1.9)**	**9 (1.6)**
Vascular disorders	**5 (1.4)**	**2 (1.4)**	**0**	**8 (1.4)**
Metabolism and nutrition disorders	**5 (1.4)**	**1 (0.7)**	**1 (1.9)**	**7 (1.2)**
Hyponatraemia	3 (0.8)	0	0	3 (0.5)
Renal and urinary disorders	**5 (1.4)**	**0**	**1 (1.9)**	**6 (1.1)**
Hepatobiliary disorders	**4 (1.1)**	**1 (0.7)**	**1 (1.9)**	**6 (1.1)**
Investigations	**2 (0.5)**	**1 (0.7)**	**1 (1.9)**	**4 (0.7)**
Psychiatric disorders	**3 (0.8)**	**1 (0.7)**	**0**	**4 (0.7)**

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Table 66: Serious Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum CTCAE Grade; Full Analysis Set (CARE) 19-Dec-2022 DCO

System Organ Class Preferred Term	NTRK (N=16)	Other (N=10)	Overall Total (N=26)
Subjects with at Least One Serious TEAE	**7 (43.8)**	**4 (40.0)**	**11 (42.3)**
Infections and infestations	**2 (12.5)**	**3 (30.0)**	**5 (19.2)**
Bronchiolitis (Grade 1)	0	1 (10.0)	1 (3.8)
Enterovirus infection (Grade 1)	0	1 (10.0)	1 (3.8)
Norovirus infection (Grade 1)	0	1 (10.0)	1 (3.8)
Pneumonia (Grade 4)	0	1 (10.0)	1 (3.8)
Rhinovirus infection (Grade 1)	0	1 (10.0)	1 (3.8)
Upper respiratory tract infection (Grade 3)	0	1 (10.0)	1 (3.8)
Urinary tract infection (Grade 2)	1 (6.3)	0	1 (3.8)
Viral infection (Grade 3)	1 (6.3)	0	1 (3.8)
General disorders and administration site conditions	**2 (12.5)**	**1 (10.0)**	**3 (11.5)**
Disease progression (Grade 3)	1 (6.3)	0	1 (3.8)
Disease progression (Grade 5)	1 (6.3)	0	1 (3.8)
Pyrexia (Grade 1)	0	1 (10.0)	1 (3.8)
Nervous system disorders	**2 (12.5)**	**1 (10.0)**	**3 (11.5)**
Brain compression (Grade 5)	1 (6.3)	0	1 (3.8)
Dizziness (Grade 2)	1 (6.3)	0	1 (3.8)
Encephalopathy (Grade 3)	0	1 (10.0)	1 (3.8)
Hemiparesis (Grade 3)	0	1 (10.0)	1 (3.8)
Hydrocephalus (Grade 3)	1 (6.3)	0	1 (3.8)
Cardiac disorders	**0**	**1 (10.0)**	**1 (3.8)**
Bradycardia (Grade 1)	0	1 (10.0)	1 (3.8)
Gastrointestinal disorders	**1 (6.3)**	**0**	**1 (3.8)**
Abdominal pain (Grade 3)	1 (6.3)	0	1 (3.8)
Injury, poisoning and procedural complications	**1 (6.3)**	**0**	**1 (3.8)**
Stress fracture (Grade 3)	1 (6.3)	0	1 (3.8)
Musculoskeletal and connective tissue disorders	**1 (6.3)**	**0**	**1 (3.8)**
Back pain (Grade 2)	1 (6.3)	0	1 (3.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (6.3)**	**0**	**1 (3.8)**
Glioma (Grade 5)	1 (6.3)	0	1 (3.8)
Respiratory, thoracic and mediastinal disorders	**0**	**1 (10.0)**	**1 (3.8)**
Hypoxia	0	1 (10.0)	1 (3.8)

SAEs considered treatment-related and reported in > 1 subject in TRIDENT-1 are shown in Table 67. In CARE, 2 events (5.3 %) were considered treatment-related.

Table 67. Treatment-related Serious Adverse Events in > 1 Subjects by System Organ Class and Preferred Term in TRIDENT-1 Safety Analysis

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Subjects with at Least One Serious TRAE	**29 (7.9)**	**18 (12.5)**	**1 (1.9)**	**48 (8.5)**
Grade 2	6 (1.6)	5 (3.5)	0	11 (1.9)
Grade 3	20 (5.4)	10 (6.9)	1 (1.9)	31 (5.5)
Grade 4	2 (0.5)	2 (1.4)	0	4 (0.7)
Respiratory, thoracic and mediastinal disorders	**12 (3.3)**	**5 (3.5)**	**1 (1.9)**	**18 (3.2)**
Pneumonitis	4 (1.1)	1 (0.7)	0	5 (0.9)
Pleural effusion	2 (0.5)	0	1 (1.9)	3 (0.5)
Dyspnoea	1 (0.3)	1 (0.7)	0	2 (0.4)
Respiratory failure	2 (0.5)	0	0	2 (0.4)
Nervous system disorders	**6 (1.6)**	**3 (2.8)**	**0**	**10 (1.8)**
Dizziness	3 (0.8)	2 (1.4)	0	5 (0.9)
Cardiac disorders	**3 (0.8)**	**1 (0.7)**	**0**	**4 (0.7)**
Pericardial effusion	3 (0.8)	0	0	3 (0.5)
General disorders and administration site conditions	**2 (0.5)**	**2 (1.4)**	**0**	**4 (0.7)**
Infections and infestations	**2 (0.5)**	**2 (1.4)**	**0**	**4 (0.7)**
Pneumonia	1 (0.3)	2 (1.4)	0	3 (0.5)
Musculoskeletal and connective tissue disorders	**2 (0.5)**	**2 (1.4)**	**0**	**4 (0.7)**
Muscular weakness	2 (0.5)	2 (1.4)	0	4 (0.7)
Blood and lymphatic system disorders	**2 (0.5)**	**1 (0.7)**	**0**	**3 (0.5)**
Anaemia	2 (0.5)	1 (0.7)	0	3 (0.5)
Gastrointestinal disorders	**0**	**2 (1.4)**	**0**	**2 (0.4)**
Injury, poisoning and procedural complications	**2 (0.5)**	**0**	**0**	**2 (0.4)**

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Dyspnoea as a SAE was reported in 20 adult patients (3.5 %), which were considered treatment-related in 2 patients (0.4 %). Overall, dyspnoea is very commonly reported as an AE (177/565, 31.3 %), with grade 3 in 38 patients (6.7 %). The majority of cases are attributed to other factors, with 56 (9.9 %) considered treatment-related. Median time to onset of dyspnoea was 43 days (range: 1 day to 2.1 years). Resolution occurred in 75 patients (42.4%) with median time to resolution 35.6 weeks (range: 0.1 weeks to 269.1+ weeks). Dose reduction was required in 1.6% (9/565) of patients, 6.5% (37/565) required dose interruptions and 1.1% (6/565) of patients were required to discontinue due to dyspnoea.

Deaths

In total 219 patients (38.8 %) died in the TRIDENT-1 study, mainly because of disease progression. TEAEs with fatal outcome occurred in 35 patients (6.2 %) and are listed in Table 68. There were 2 reported TEAEs (sudden death and cardio-respiratory arrest) with a fatal outcome assessed as treatment-related by the Investigator.

Table 68. Treatment-Emergent Adverse Events with a Fatal Outcome by System Organ Class and Preferred Term TRIDENT-1 Safety Analysis

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Subjects with at least one TEAE	**25 (6.8)**	**8 (5.6)**	**2 (3.7)**	**35 (6.2)**
Cardiac disorders	**6 (1.6)**	**2 (1.4)**	**1 (1.9)**	**9 (1.6)**
Cardiac arrest	3 (0.8)	1 (0.7)	1 (1.9)	5 (0.9)
Cardiac failure	1 (0.3)	0	0	1 (0.2)
Cardio-respiratory arrest	1 (0.3)	1 (0.7)	0	2 (0.4)
Acute myocardial infarction	1 (0.3)	0	0	1 (0.2)
General disorders and administration site conditions	**8 (2.2)**	**1 (0.7)**	**1 (1.9)**	**10 (1.8)**
Death	6 (1.6)	0	0	6 (1.1)
Sudden death	2 (0.5)	0	1 (1.9)	3 (0.5)
Sudden cardiac death	0	1 (0.7)	0	1 (0.2)
Infections and infestations	**4 (1.1)**	**3 (2.1)**	**0**	**7 (1.2)**
Pneumonia	1 (0.3)	2 (1.4)	0	3 (0.5)
Pneumonia aspiration	2 (0.5)	0	0	2 (0.4)
COVID-19 pneumonia	1 (0.3)	0	0	1 (0.2)
Sepsis	0	1 (0.9)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**5 (1.4)**	**1 (0.7)**	**0**	**6 (1.1)**
Dyspnoea	2 (0.5)	0	0	2 (0.4)
Hypoxia	2 (0.5)	0	0	2 (0.4)
Respiratory failure	1 (0.3)	1 (0.7)	0	2 (0.4)
Blood and lymphatic system disorders	**1 (0.3)**	**0**	**0**	**1 (0.2)**
Disseminated intravascular coagulation	1 (0.3)	0	0	1 (0.2)
Injury, poisoning and procedural complications	**1 (0.3**)	**0**	**0**	**1 (0.2)**
Femur fracture	1 (0.3)	0	0	1 (0.2)
Nervous system disorders	**0**	**1 (0.7)**	**0**	**1 (0.2)**
Tremor	0	1 (0.7)	0	1 (0.2)

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The deaths related to respiratory disorders occurred are numerically lower in the NSCLC compared to the NTRK group, (1.4 % vs 0.7 %), which can be explained by the underlying condition.

TEAEs with fatal outcome were reported in 3 (7.9%) subjects in CARE, including 1 subject < 12 years old and 2 subjects ≥ 12 years old. All 3 deaths were reported as disease progression events not related to study drug.

2.6.8.4. Laboratory findings

Haematology

Both all grade and high-grade decreases in haemoglobin, lymphocytes, leukocytes, and neutrophils were commonly reported in adults, as shown in Table 69.

Table 69. Hematology Parameters: Abnormalities in ≥ 20% of Subjects Worsening from Baseline (Safety Analysis Set)

Laboratory Abnormality Finding	Overall Population N = 565 Denominator[a]	All Grades	Grade 3 or 4
Hemoglobin (Low)[b]	554	439 (79.2)	52 (9.4)
Lymphocytes (Low)[b]	552	267 (48.4)	74 (13.4)
Leukocytes (Low)[b]	553	214 (38.7)	23 (4.2)
Neutrophils (Low)[b]	549	182 (33.2)	48 (8.7)

a Denominator, the number of patients who have both baseline and postbaseline results for each analyte
b Refers to the low (or high) end of the parameter graded with CTCAE version 4.03.
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Data from the paediatric group (CARE, 19-Dec-2022 DCO) showed that compared with baseline grade, post-baseline toxicity worst grade remained at < Grade 3, with the exceptions of haemoglobin [low] (4/26, 15.4%), lymphocytes [low] (3/26, 11.5%), platelets [low] (2/26, 7.7%), and neutrophils [low] (1/26, 3.8%) Toxicity shifts from Grade 0 at baseline to Grade 3 or 4 post-baseline were reported for platelets [low]: 1 (3.8%).

Clinical chemistry

Laboratory abnormalities from the overall adult population are presented in Table 70. The most frequently affected clinical parameter was CK (62.9 %), which is consistent with the catabolic state of many cancer patients. This is included as an ADR in the product information.

Shifts in liver parameters (GGT: 51.5 %, AST: 41.4 %, ALT: 39.3 %, ALP: 31.8 %) were common. One subject met criteria for Hy's law but presented with plausible alternate aetiology (Male 18 years with metastatic renal carcinoma and worsening liver metastasis).

Regarding other parameters, the rather common high-grade shifts of urate (increased, all grade: 22.6 %, grade 3 and 4: 11.2%), and phosphate (decreased, all grade: 27.9 %, grade 3 and 4: 7.5 %) are noticeable, as are high creatinine (37.6 %) and reduced GFR (26.1 %). There were no events of treatment-related renal failure, and only one reported case of treatment related renal impairment (0.2 %) in the overall adult safety populations.

Table 70. Laboratory Abnormalities (≥ 20% Subjects) Worsening from Baseline

Parameter	Overall Population N = 565 Denominator[a]	All Grades	Grade 3 or 4
Creatine Kinase, High[b]	450	283 (62.9)	33 (7.3)
Gamma Glutamyl Transferase, High[c]	233	120 (51.5)	31 (13.3)
Aspartate Aminotransferase, High[de]	561	232 (41.4)	15 (2.7)
Alanine Aminotransferase, High[f]	563	221 (39.3)	18 (3.2)
Sodium, High[g]	564	204 (36.2)	3 (0.5)
Glucose, High[h]	562	176 (31.3)	12 (2.1)
Cholesterol, High[i]	13	4 (30.8)	0 (0.0)
Alkaline Phosphatase, High[j]	563	179 (31.8)	14 (2.5)
Phosphate, Low[k]	559	156 (27.9)	42 (7.5)
Creatinine, High[l]	564	212 (37.6)	4 (0.7)
Glomerular Filtration Rate, Low[m]	318	83 (26.1)	7 (2.2)
Urate, High[n]	561	127 (22.6)	63 (11.2)
Potassium, High[o]	564	126 (22.3)	7 (1.2)

[a] Denominator is the number of patients who have both baseline and postbaseline results for each analyte
[b] Refers to the low (or high) end of the parameter graded with CTCAE version 4.03.
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Data from CARE (19-Dec-2022 DCO) showed that compared with baseline, post-baseline toxicity worst grade remained at Grade 0 for most parameters, with the exception(s) of calcium [low] (1/26, 3.8%) and calcium [high] (1/26, 3.8%). No toxicity shifts from Grade 0 at baseline to Grade 3 or 4 post-baseline were reported. There were no reported cases of DILI or Hy's Law.

Vital signs

No meaningful changes in vital signs were detected by the applicant.

An analysis of vital signs by visit show that median change in diastolic blood pressure from baseline to end of treatment was – 4.0 (n = 565, interval -30, 32). The corresponding change in systolic blood pressure was -3.0 (interval -56, 45). Outlier analysis show that systolic and diastolic elevations (19.1 %/16.8 %) were more common than reductions (7.3 %/9.9 %). Hypotension and orthostatic hypotension were reported as TEAE in 3.0 %/2.7 % and as TRAE in 1.9 %/1.9 % of adults, respectively. Hypertension was reported as TEAE in 3.0 % and TRAE in 0.7 % of patients in TRIDENT-1. Thus, there is no clear trend to indicate how repotrectinib affects blood pressure.

There was no median change in pulse rate, respiratory rate or temperature from baseline to end of treatment (n = 565). Decreases or increases in pulse (bpm) meeting outlier values were reported in 2.7% and 18.4% of subjects, respectively; outlier values for temperature (°C) were reported in < 5% of subjects. In CARE (19-Dec-2022 DCO), no clinically meaningful changes in vital signs (e.g., blood pressure, temperature, pulse) were reported at any post-baseline visit. Most vital sign measurements did not meet outlier criteria.

For weight, there is a median increase of 1.1 kg (n = 185, interval -12.5, 21.9) from baseline to end of treatment. However, in earlier cycles there is a larger median weight gain. The mechanisms behind weight increase are unclear, but this is addressed sufficiently in the product information.

Electrocardiogram – QTc

Concentration-QTcF model analysis is addressed in the clinical pharmacology section.

Long QT interval and risk factors for QTc prolongation were exclusion criteria for both TRIDENT-1 and CARE. According to the study protocols, triplicate 12-lead ECGs were performed. For QTc prolongation

(> 500 msec), the ECG should be manually verified. Study drug is interrupted until QTc interval < 500 msec and then resumed at a lower dose.

In TRIDENT-1, the outlier analysis by central read showed that 2 patients had a worst post-baseline QTc > 500 ms (0.4 %) and 6 patients (1.1 %) had a maximum increase from baseline > 60 ms, as shown in Table 71. A cardiac safety analysis based triplicate ECGs matched with repotrectinib concentration data from Phase 1a (N = 43), Phase 1c (N = 21) and Phase 2 (N = 334) of the TRIDENT-1 study based showed no clinically significant effects.

Table 71. Electrocardiogram Results by Central Read: Outlier Analysis for QTcF in TRIDENT-1 Safety Analysis

QTcF Interval (msec) Outlier Definition	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
QTcF Interval (msec), n (%)				
Worst Post-baseline QTc < 450	334 (91.0)	133 (92.4)	47 (87.0)	514 (91.0)
450 ≤ Worst Post-baseline QTc ≤ 480	29 (7.9)	8 (5.6)	6 (11.1)	43 (7.6)
480 < Worst Post-baseline QTc ≤ 500	2 (0.5)	1 (0.7)	0	3 (0.5)
Worst Post-baseline QTc > 500	1 (0.3)	1 (0.7)	0	2 (0.4)
Missing	1 (0.3)	1 (0.7)	1 (1.9)	3 (0.5)
Maximum Increase from Baseline < 30	289 (78.7)	114 (79.2)	43 (79.6)	446 (78.9)
30 ≤ Maximum Increase from Baseline ≤ 60	70 (19.1)	29 (20.1)	10 (18.5)	109 (19.3)
Maximum Increase from Baseline > 60	6 (1.6)	0	0	6 (1.1)
Missing	2 (0.5)	1 (0.7)	1 (1.9)	4 (0.7)

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From adverse events reporting, electrocardiogram QT prolonged was reported as in 5 patients (0.9 %), 4 events were considered grade 1 (0.8 %) and 1 event grade 2 (0.2 %). Four of the five events occurred in NSCLC patients (1.1 %), the last in the NTRK+ group (0.7 %, grade 1). Two of the cases were deemed as treatment-related (0.4 %), both of which were grade 1. Four of the events were reported in Asia (2.1 %), including the grade 2 event. No events of QTc prolongation leading to discontinuation or dose modification were reported.

In CARE, there were no patients with a worst post-baseline QTc > 500 ms or a maximum increase from baseline > 60 ms (Table 72).

Table 72. Electrocardiogram Results by Central Read: Outlier Analysis for QTcF in CARE Full Analysis Set

QTcF Interval (msec) Outlier Definition	NTRK N = 19	Other N = 19	Overall Total N = 38
QTcF Interval (msec), n (%)			
Worst Post-baseline QTc < 450	18 (94.7)	19 (100)	37 (97.4)
450 ≤ Worst Post-baseline QTc ≤ 480	0	0	0
480 < Worst Post-baseline QTc ≤ 500	0	0	0
Worst Post-baseline QTc > 500	0	0	0
Missing	1 (5.3)	0	1 (2.6)
Maximum Increase from Baseline < 30	16 (84.2)	13 (68.4)	29 (76.3)
30 ≤ Maximum Increase from Baseline ≤ 60	2 (10.5)	6 (31.6)	8 (21.1)
Maximum Increase from Baseline > 60	0	0	0
Missing	1 (5.3)	0	1 (2.6)

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However, from adverse event reporting there were 6 patients with electrocardiogram increased (15.8 %), all of them considered related to treatment. Five of the events were considered grade 1, one event was considered grade 2. Two events were reported in children < 12 years (2/22 = 9.1 %), and four events were reported in children from 12 years (4/16 = 25 %), two were in the NTRK adolescent group (2/8 = 25 %). QTc prolongation did not lead to discontinuation or dose modifications in CARE. QT values corrected with Fridericia's formula (QTcF) were within the normal range for these patients.

Left Ventricular Ejection Fraction

One case with a maximum decrease in LVEF from baseline ≥20 % was reported in the adult population (TRIDENT-1), which was attributed to an underlying condition of heart failure. The patient (female 26 years) had an LVEF of 70 % at enrolment, which worsened to 41 % (cycle 13 day 1), but later increased again to 65 % (Cycle 19 Day 1).

In CARE there were no reports with a decrease in LVEF from baseline ≥ 20 % (19-Dec-2022 DCO). Further, there were no reports of cardiac failure as AE in CARE. In TRIDENT-1, there were three reports of cardiac failure as TEAE (0.5 %): grade 2, grade 3, and grade 5 respectively, but none of these were considered related to treatment.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

In the present application, paediatric patients are not considered a special population, as the separate clinical study CARE includes this group. Safety data from this group are discussed throughout and compared to data in adults.

Age (adult population)

SAEs and TEAEs leading to discontinuation were more commonly reported in higher age groups, which are common for this kind of treatment. Patients over 75 years of age are especially susceptible to more serious adverse events (62.9% vs 37.2 % in 18-65 Y and 47.6 % in 65-75 Y), and discontinuation is more often required (22.9 % vs 8.5 % in 18-65 Y and 16.2 % in 65-75 Y).

Sex

The presented analysis of differences in the safety profiles between biological sex show that Grade ≥ 3 TEAEs was higher in males versus females with 63.3% vs. 52.7% of subjects, which is not further discussed. No other marked differences were seen.

Race and region

No marked differences were reported in subgroups of 'race': White and Asian according to the applicant.

In the Overall safety population, there was a ≥ 10% difference for the incidence of subjects who required a dose reduction in Asia (43.6%) versus Other regions (39.8%) (which included EU countries) and the US population (30.3%). Fewer subjects were reported with SAEs from the Asian (33.3%) and Other regions (40.9%) versus the US (49.1%). For Grade ≥ 3 TEAEs, more events were reported for subjects from the US (59.4%) and Other regions (61.8%) versus Asian regions (51.0%). There is no obvious trend that the reported safety profiles differ importantly across regions.

Baseline brain metastasis

The analysis and discussion presented by the applicant show no apparent meaningful differences in the manifestation of CNS-related adverse events in patients with brain metastasis at baseline (n = 193) compared to patients without (n = 372).

The most frequently reported CNS-related treatment-emergent AESIs for all subjects in the overall safety population diagnosed with brain metastases at baseline were: dizziness (60.6%), dysgeusia (48.7%), and paraesthesia (32.6%), which is comparable to the overall population. No relevant differences were noted in a stratified analysis by cancer type and brain metastasis.

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Interactions are discussed in the clinical pharmacology section.

2.6.8.9. Discontinuation due to adverse events

Discontinuation and dose modifications in TRIDENT-1 (adult population)

The number of patients who had to discontinue treatment due to an AE is 10.8 % (n = 61), which is considered acceptable. The occurrence is consistent across the overall safety population, NSCLC subjects, and NTRK+ solid tumours, as shown in the overview of in Table 73. For 'other subjects' the incidence is higher (14.8 %).

Table 73. Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug in > 2 Subjects by System Organ Class and Preferred Term in TRIDENT-1 Safety Analysis

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Subjects with TEAEs leading to discontinuation of study drug	**39 (10.6)**	**14 (9.7)**	**8 (14.8)**	**61 (10.8)**
Grade 1	2 (0.5)	0	0	2 (0.4)
Grade 2	7 (1.9)	4 (2.8)	4 (7.4)	15 (2.7)
Grade 3	18 (4.9)	4 (2.8)	3 (5.6)	25 (4.4)
Grade 4	3 (0.8)	2 (1.4)	0	5 (0.9)
Grade 5	9 (2.5)	4 (2.8)	1 (1.9)	14 (2.5)
Respiratory, thoracic and mediastinal disorders	**15 (4.1)**	**4 (2.8)**	**2 (3.7)**	**21 (3.7)**
Dyspnoea	5 (1.4)	1 (0.7)	0	6 (1.1)
Pneumonitis	4 (1.1)	1 (0.7)	0	5 (0.9)
Pleural effusion	2 (0.5)	0	1 (1.9)	3 (0.5)
Nervous system disorders	**5 (1.4)**	**3 (2.1)**	**1 (1.9)**	**9 (1.6)**
General disorders and administration site conditions	**2 (0.5)**	**2 (1.4)**	**1 (1.9)**	**5 (0.9)**
Cardiac disorders	**5 (1.4)**	**1 (0.7)**	**0**	**6 (1.1)**
Infections and infestations	**3 (0.8)**	**1 (0.7)**	**0**	**4 (0.7)**
Metabolism and nutrition disorders	**1 (0.3)**	**1 (0.7)**	**1 (1.9)**	**3 (0.5)**
Musculoskeletal and connective tissue disorders	**4 (1.1)**	**1 (0.7)**	**0**	**5 (0.9)**
Muscular weakness	4 (1.1)	1 (0.7)	0	5 (0.9)
Injury, poisoning and procedural complications	**2 (0.5)**	**2 (1.4)**	**0**	**4 (0.7)**

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AESIs leading to discontinuation of study drug were reported in 19 (3.4%) subjects and considered related to treatment in 13 (2.3%) subjects (overall population). Treatment-emergent AESIs leading to discontinuation of study drug in the Overall safety population were reported in single subjects except for pneumonitis (n = 5 (0.9%)), muscular weakness (n = 5 (0.9%)), depressed level of consciousness (n = 2 (0.4%)), and neurological decompensation (n = 2 (0.4%)).

All TRAEs leading to discontinuation were ≤ Grade 3 severity. Of these, only pneumonitis (n = 5), muscular weakness (n = 5), and pleural effusion (n = 2) were reported in > 1 subject in the Overall safety analysis set.

TEAEs leading to dose reduction (38.2 %) and temporary interruptions (51.5 %) were commonly reported, as shown in Table 74 and Table 75, respectively. Median exposure in TRIDENT-1 was 93.9 %, which indicates that reductions and interruptions were short and the events acceptably manageable.

Dose reductions involve administering multiple 40 mg capsules, which are of relatively large size. (Please refer to the section on Quality Aspects).

The pattern is overall comparable across safety populations, but the proportion of subjects requiring dose reductions is higher in the NTRK+ solid tumour pool (45.1 %) compared to NSCLC patients (38.4 %) and the overall population (38.2 %). The difference is most pronounced for dizziness, which leads to dose reductions in 16.7 % in the NTRK pool compared to 9.8 % in NSCLC.

Dizziness is also more commonly reported as a cause of treatment interruption in NTRK+ patients (15.3 % vs 7.9 %). On the contrary, dyspnoea leads more frequently to treatment interruption (7.4 % vs 4.2 %) in NSCLC patients compared to the NTRK+ solid tumour group. This is not unexpected given the nature of the underlying indications.

Table 74. Treatment-Emergent Adverse Events Leading to Dose Reduction of Study Drug in > 2 Subjects by System Organ Class and Preferred Term in TRIDENT-1 Safety Analysis

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Subjects with TEAEs leading to dose reduction of study drug	**141 (38.4)**	**65 (45.1)**	**10 (18.5)**	**216 (38.2)**
Grade 1	18 (4.9)	10 (6.9)	1 (1.9)	29 (5.1)
Grade 2	75 (20.4)	34 (23.6)	7 (13.0)	116 (20.5)
Grade 3	44 (12.0)	19 (13.2)	2 (3.7)	65 (11.5)
Grade 4	4 (1.1)	2 (1.4)	0	6 (1.1)
Nervous system disorders	**73 (19.9)**	**40 (27.8)**	**6 (11.1)**	**119 (21.1)**
Dizziness	36 (9.8)	24 (16.7)	3 (5.6)	63 (11.2)
Ataxia	20 (5.4)	12 (8.3)	2 (3.7)	34 (6.0)
Paraesthesia	7 (1.9)	3 (2.1)	0	10 (1.8)
Balance disorder	3 (0.8)	1 (0.7)	0	4 (0.7)
Disturbance in attention	1 (0.3)	2 (1.4)	0	3 (0.5)
Dysgeusia	2 (0.6)	0	1 (1.9)	3 (0.5)
Memory impairment	3 (0.9)	0	0	3 (0.5)
Neuropathy peripheral	2 (0.6)	1 (0.7)	0	3 (0.5)
Investigations	**19 (5.4)**	**8 (5.6)**	**0**	**30 (5.3)**
Blood creatine phosphokinase increased	9 (2.6)	4 (2.8)	0	14 (2.5)
Alanine aminotransferase increased	2 (0.6)	3 (2.1)	0	7 (1.2)
Aspartate aminotransferase increased	2 (0.5)	1 (0.7)	0	3 (0.5)
Blood creatinine increased	3 (0.8)	0	0	3 (0.5)
Gamma-glutamyltransferase increased	1 (0.3)	2 (1.4)	0	3 (0.5)
Musculoskeletal and connective tissue disorders	**20 (5.4)**	**11 (7.6)**	**3 (5.6)**	**34 (6.0)**
Muscular weakness	18 (4.9)	7 (4.9)	2 (3.7)	27 (4.8)
Respiratory, thoracic and mediastinal disorders	**22 (6.0)**	**5 (3.5)**	**1 (1.9)**	**28 (5.0)**
Dyspnoea	6 (1.6)	2 (1.4)	1 (1.9)	9 (1.6)
Pleural effusion	3 (0.8)	1 (0.7)	0	4 (0.7)
Hypoxia	3 (0.8)	0	0	3 (0.5)
Pneumonitis	3 (0.8)	0	0	3 (0.5)
General disorders and administration site conditions	**9 (2.5)**	**6 (4.2)**	**2 (3.7)**	**17 (3.0)**
Fatigue	3 (0.8)	3 (2.1)	1 (1.9)	7 (1.2)
Gait disturbance	4 (1.1)	0	0	4 (0.7)
Gastrointestinal disorders	**2 (0.5)**	**5 (3.5)**	**0**	**7 (1.2)**
Psychiatric disorders	**6 (1.6)**	**0**	**0**	**6 (1.1)**
Blood and lymphatic system disorders	**3 (0.8)**	**2 (1.4)**	**0**	**5 (0.9)**
Anaemia	2 (0.5)	1 (0.7)	0	3 (0.5)
Infections and infestations	**8 (2.2)**	**1 (0.7)**	**0**	**9 (1.6)**
Ear and labyrinth disorders	2 (0.5)	1 (0.7)	0	3 (0.5)
Vertigo	2 (0.5)	1 (0.7)	0	3 (0.5)
Metabolism and nutrition disorders	2 (0.5)	1 (0.7)	0	

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
				3 (0.5)

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Table 75. Treatment-Emergent Adverse Events Leading to Dose Interruption of Study Drug in > 2 Subjects by System Organ Class and Preferred Term in TRIDENT-1 Safety Analysis

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Subjects with TEAEs leading to dose interruption of study drug	**200 (54.5)**	**76 (52.8)**	**15 (27.8)**	**291 (51.5)**
Grade 1	12 (3.3)	3 (2.1)	2 (3.7)	17 (3.0)
Grade 2	57 (15.5)	23 (16.0)	7 (13.0)	87 (15.4)
Grade 3	108 (29.4)	45 (31.3)	5 (9.3)	158 (28.0)
Grade 4	17 (4.6)	4 (2.8)	1 (1.9)	22 (3.9)
Grade 5	6 (1.6)	1 (0.7)	0	7 (1.2)
Nervous system disorders	**59 (16.1)**	**35 (24.3)**	**7 (13.0)**	**101 (17.9)**
Dizziness	29 (7.9)	22 (15.3)	5 (9.3)	56 (9.9)
Ataxia	13 (3.5)	6 (4.2)	2 (3.7)	21 (3.7)
Paraesthesia	4 (1.1)	2 (1.4)	0	6 (1.1)
Somnolence	1 (0.3)	4 (2.8)	0	5 (0.9)
Dysgeusia	3 (0.8)	0	0	5 (0.9)
Neuropathy peripheral	2 (0.5)	1 (0.7)	0	3 (0.5)
Syncope	2 (0.5)	1 (0.7)	0	3 (0.5)
Respiratory, thoracic and mediastinal disorders	**61 (16.6)**	**13 (9.0)**	**5 (9.3)**	**79 (14.0)**
Dyspnoea	27 (7.4)	6 (4.2)	4 (7.4)	37 (6.5)
Pleural effusion	9 (2.5)	1 (0.7)	0	10 (1.8)
Hypoxia	8 (2.2)	0	0	8 (1.4)
Pneumonitis	8 (2.2)	0	0	8 (1.4)
Pulmonary embolism	3 (0.8)	2 (1.4)	0	5 (0.9)
Respiratory failure	2 (0.5)	1 (0.7)	1 (1.9)	4 (0.7)
Acute respiratory failure	3 (0.8)	0	0	3 (0.5)
Cough	1 (0.3)	2 (1.4)	0	3 (0.5)
Productive cough	1(0.3)	2 (1.4)	0	3 (0.5)
Infections and infestations	**45 (12.3)**	**21 (14.6)**	**1 (1.9)**	**68 (12.0)**
Pneumonia	15 (4.1)	6 (4.2)	1 (1.9)	22 (3.9)
COVID-19	15 (4.1)	6 (4.2)	0	22 (3.9)
Urinary tract infection	2 (0.5)	1 (0.7)	0	3 (0.5)
Upper respiratory tract infection	3 (0.8)	0	0	3 (0.5)
Investigations	**38 (10.4)**	**16 (11.1)**	**0**	**54 (9.6)**
Blood creatine phosphokinase increased	14 (3.8)	3 (2.1)	0	17 (3.0)
Alanine aminotransferase increased	9 (2.5)	3 (2.1)	0	12 (2.1)
Aspartate aminotransferase increased	6 (1.6)	5 (3.5)	0	11 (1.9)
Neutrophil count decreased	7 (1.9)	2 (1.4)	0	9 (1.6)
Gamma-glutamyltransferase increased	3 (0.8)	3 (2.1)	0	6 (1.1)
White blood cell count decreased	3 (0.8)	1 (0.7)	0	4 (0.7)
Musculoskeletal and connective tissue disorders	**32 (8.7)**	**16 (11.1)**	**1 (1.9)**	**49 (8.7)**
Muscular weakness	22 (6.0)	8 (5.6)	1 (1.9)	31 (5.5)
Myalgia	3 (0.8)	2 (1.4)	0	5 (0.9)
Back pain	2 (0.5)	1 (0.7)	0	3 (0.5)
General disorders and administration site conditions	**19 (5.2)**	**12 (8.3)**	**2 (3.7)**	**33 (5.8)**
Fatigue	5 (1.4)	4 (2.8)	1 (1.9)	10 (1.8)

System Organ Class Preferred Term	*ROS1*+ NSCLC Subjects N = 367	*NTRK*+ Solid Tumour Subjects N = 144	Other Treated Subjects N = 54	Overall Population N = 565
Pyrexia	4 (1.1)	4 (2.8)	0	8 (1.4)
Asthenia	5 (1.4)	0	0	5 (0.9)
Gait disturbance	3 (0.8)	0	0	3 (0.5)
Gastrointestinal disorders	**18 (4.9)**	**14 (9.7)**	**2 (3.7)**	**34 (6.0)**
Vomiting	7 (1.9)	4 (2.8)	0	11 (1.9)
Nausea	3 (0.8)	2 (1.4)	1 (1.9)	6 (1.1)
Diarrhoea	2 (0.5)	3 (2.1)	0	5 (0.9)
Abdominal pain	3 (0.8)	1 (0.7)	0	4 (0.7)
Colitis	2 (0.5)	1 (0.7)	0	3 (0.5)
Blood and lymphatic system disorders	**12 (3.3)**	**9 (6.3)**	**1 (1.9)**	**22 (3.9)**
Anaemia	8 (2.2)	8 (5.6)	1 (1.9)	17 (3.0)
Neutropenia	2 (0.5)	1 (0.7)	0	3 (0.5)
Metabolism and nutrition disorders	**7 (1.9)**	**6 (4.2)**	**0**	**13 (2.3)**
Hyponatraemia	3 (0.8)	2 (1.4)	0	5 (0.9)
Decreased appetite	1 (0.3)	1 (0.7)	0	2 (0.4)
Hypophosphataemia	1 (0.3)	2 (1.4)	0	3 (0.5)
Psychiatric disorders	**8 (2.2)**	**0**	**0**	**8 (1.4)**
Confusional state	3 (0.8)	0	0	3 (0.5)
Injury, poisoning and procedural complications	**7 (1.9)**	**2 (1.4)**	**0**	**9 (1.6)**
Cardiac disorders	**10 (2.7)**	**0**	**0**	**10 (1.8)**
Pericardial effusion	6 (1.6)	0	0	6 (1.1)
Hepatobiliary disorders	**3 (0.8)**	**2 (1.4)**	**0**	**5 (0.9)**
Eye disorders	**4 (1.1)**	**1 (0.7)**	**0**	**5 (0.9)**
Renal and urinary disorders	**3 (0.8)**	**2 (1.4)**	**0**	**5 (0.9)**
Vascular disorders	**3 (0.8)**	**0**	**1 (1.9)**	**4 (0.7)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.3)**	**1 (0.7)**	**1 (1.9)**	**3 (0.5)**

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Discontinuation and dose modifications in CARE (paediatric population)

Data from CARE on discontinuation and treatment modification is very limited. Two patients (5.3 %) discontinued due to a treatment-related AE in CARE, of which one was grade 3 anaemia and one with a grade 2 fracture of the tibia. One patient had a dose reduction, and 13 patients (34.2 %) had drug interruptions due to a TEAE, five of which (13.2 %) were deemed related to treatment. The TEAEs leading to dose modification that were not considered TRAEs were: encephalopathy, hemiparesis, hydrocephalus, dental caries, COVID-19, platelet count decreased, and dehydration.

2.6.8.10. Post marketing experience

Repotrectinib received marketing approval in the US under the trade name Augtyro for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC (approved 15-Nov-2023) and for the treatment of adult and paediatric patients 12 years and older with solid tumours that have a NTRK gene fusion, are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and that have progressed following treatment or have no satisfactory alternative therapy (approved 13-Jun-2024). Total cumulative post-marketing patient exposure to repotrectinib through 14 May 2024 was estimated to be 5,025 patients.

2.6.9. Discussion on clinical safety

The present MAA is seeking approval of repotrectinib as monotherapy for the treatment of ROS1-positive NSCLC in adults and NTRK-positive solid tumours in adults and adolescents (≥ 12 years of age). Safety data from the **clinical development programme** include patients from the uncontrolled pivotal phase 1/2 TRIDENT-1 and the uncontrolled paediatric phase 1/2 study CARE. Both studies are ongoing.

Data from TRIDENT-1 are presented with two CSRs; one for the phase 1 and one for phase 2, whereas data from the CARE study are presented in an 'Ad Hoc Report'. Safety data from two data cutoff dates of 19 Dec 2022 and 15 Oct 2023 were submitted, the latter representing an additional 10 months of safety data which were overall consistent with the data from the initial DCO. The safety discussion is based on the latest data cutoff, unless otherwise specified.

The **safety databases** supporting the claimed indications consist of subjects who received at least one dose of repotrectinib: 565 adult patients and 38 paediatric patients. Data from TRIDENT-1 and CARE were not pooled due to differences in the study populations and are therefore presented separately. It is specified in the different sections of the discussion whether data are from TRIDENT-1 and/or CARE. Data from CARE are compared to TRIDENT-1 where possible.

In addition to the overall adult population (n = 565) in TRIDENT-1, **safety analysis subsets** with adults are presented based on molecular targets/indications: ROS1+ NSCLC subjects (n = 367), NTRK+ solid tumour subjects (n = 144), as well as a "other treated subject" group (n = 54), which are outside of the claimed indication. Data from subjects assigned into groups who have received the recommended phase 2 dose (RP2D overall population, n = 472) were included. Further subgroups include TKI naïve patients (EXP-1, n = 113) and TKI pretreated patients (EXP-4, n = 104).

Key demographic characteristics are overall comparable across the different adult analysis populations. Median age is 56 years (range 18-93), with 58.1 % of participants being male. The study sites are equally distributed between the US, Europe/Australia, and Asia.

Given the high prevalence of lung cancer, the NSCLC database is considered limited, although acceptable. Considering the rarity of NTRK positive solid tumours, the sample-size of this subgroup from TRIDENT-1 can in principle be acceptable, supported by safety data from the overall pool.

In CARE (n=38), there are 19 subjects treated for NTRK positive solid tumours, while the remaining subjects are treated for other types of cancer. Of the 19 subjects only 8 patients are ≥ 12 years, which corresponds to patients included in the claimed indication. In total, there are 16 patients ≥ 12 years, and 22 < 12 years. Data supporting the indication in adolescents are very limited. Characterisation of a reliable safety profile based on 8 subjects is considered unfeasible and is thus based on the overall group (n = 38), which is still very small and in addition heterogenous regarding age, weight, dose received (34 dosed at RP2D), developmental status/maturity, and cancer type. Corroborating the safety profile in the paediatric population with data from adults, preclinical studies, and exposure-safety analysis are thus important.

Median relative **dose intensity** in adults was 94 % of recommended dosage, and this is acceptably consistent across analysis subgroups (85-100 %). This indicates acceptable treatment compliance. Median dose intensity varied more in CARE (49-325 mg/day), which is explainable by differences in weight and dosing.

At the time of the latest data cut-off, approximately half of the patients had received treatment for more than 6 months, 55.9 % (n = 316) in TRIDENT-1 and 50 % (n = 19) in CARE. Median **exposure time** was 7.59/8.90 and 6.127 months in TRIDENT-1 (overall/RP2D) and CARE, respectively. At DCO,

164 patients (29 %) in TRIDENT-1 and 16 patients (42.1 %) in CARE were ongoing, and the median follow-up time was 27.04 and 14.62 months for TRIDENT-1 and CARE, respectively. This is still considered limited, but the update of safety data did not provide any new signals regarding long-term toxicity. An **important limitation** is the size of the analysis populations, which allows only for detection of common adverse events in adults and very common adverse events in children/adolescents. The uncontrolled design of the clinical studies is another concern, complicating differentiation of drug-related AEs from symptoms of the underlying conditions and imposing uncertainties regarding the characterisation of the safety profile.

Almost all subjects experienced at least 1 treatment-emergent **adverse event** (TEAE): overall adult population 99.5 %, overall paediatric population 100 %. Most patients (TRIDENT-1: 94.7 %, CARE: 84.2 %) had at least one adverse event that was considered related to treatment (TRAE), and the majority of patients had a grade ≥3 TEAE/TRAE (TRIDENT-1: 57.2%/28.7%, CARE: 55.3%/21.1%) or serious adverse events (TEAE/TRAE: TRIDENT-1: 40.7%/8.5%, CARE: 36.8%/5.3%). Discontinuation due to AEs occurred in 10.8 % in TRIDENT-1 and 5.3% in CARE, which is considered relatively low for cancer treatment.

Comparison of results between CARE and TRIDENT-1 is confined by the limited number of paediatric patients but they appear overall comparable. The safety profile was generally consistent between < 12 year old and ≥ 12 year old paediatric subjects, but data in these two age groups are too limited to draw firm conclusions.

The overall adverse events experience is mostly consistent across the **analysis subgroups** in TRIDENT-1 relevant for the applied indication (adult). Comparing the NTRK+ pool to the ROS1 NSCLC pool, some numbers (TRAEs) are numerically higher (SAE: 12.5% / 7.9 %, grade ≥3 AE: 34.0 % /29.2 %, TRAEs leading to dose reduction: 43.8 %/33.5 %), which may indicate differences in susceptibility towards more serious TRAEs across patient populations.

There are no relevant differences in the overall occurrence of adverse events in the RP2D population compared to the overall population; TEAEs (99.4 % vs 99.5 %), TRAEs (96.0 % vs 94.7 %), treatment-related SAEs (9.5 % vs 8.5 %), treatment-related grade ≥3 AEs (31.8 % vs 28.7 %), treatment-related fatal AEs (0.4 %, each), TRAEs leading to discontinuation (4.2 % vs 4.1 %) or dose modifications (47.0 % vs 42.5 %). Further, the applicant has shown that ADR frequencies are similar across these two pools. Given the larger size of the overall population, this has been chosen for the characterization of safety in the SmPC, as this pool provides a better basis for detecting more severe and/or less common AEs.

The most common TEAEs are comparable across the subgroups EXP-1 (n = 113, TKI naïve) and EXP-4 (n = 104, TKI pretreated). TEAEs (%) leading to discontinuation (14.2 vs 10.6), dose modifications (70.8 vs 58.7) as well as SAE (44.2 vs 34.6), grade ≥3 TEAEs (63.7 vs 48.1) and fatal TEAEs (7.1 vs 2.9) are all higher in the EXP-1 vs EXP-4 group. Possible explanations may be the longer exposure time in EXP-1 (15 months) compared to EXP-4 (8.9 months), or tolerance based on previous TKI-exposure.

Given the mechanism of action, TEAEs in 'Nervous system disorders' are expected, and this is the most frequently reported **TEAE by SOC** (TRIDENT-1/CARE, numbers in %: 90.3/57.9), followed by 'Gastrointestinal disorders' (71.9/76.3), 'General disorders and administration site conditions' (58.8/55.3), 'Respiratory, thoracic and mediastinal disorders' (57.9/42.1), 'Musculoskeletal and connective tissue disorders' (56.6/28.9), 'Investigations' (55.2/65.8), 'Infections and infestations' (42.1/47.4), 'Blood and lymphatic system disorders' (41.8/50.0), and 'Metabolism and nutrition disorders' (34.7/52.6). In the sub-populations of NTRK+ and ROS1 NSCLC (TRIDENT) the SOC frequencies are generally comparable, although for NTRK+ tumours the SOCs 'General disorders' (64.6

% vs 56.4 %), and 'Metabolism and nutrition disorders' (43.1 % vs 32.2 %) were higher. These differences may be related to the diseases in question.

The **most commonly reported TEAE by PT** were (TRIDENT-1/CARE, numbers in %): dizziness (63.0/21.1), dysgeusia (52.4/23.7), constipation (39.3/39.5), anaemia (38.1/50), paraesthesia (34.0/13.2), dyspnoea (31.3/15.8), fatigue (24.8/36.8), ALT increased (22.1/18.4), ataxia (21.9/5.3), muscular weakness (21.6/7.9), AST increased (20.9/23.7) nausea (20.7/28.9), and headache (20.0/31.6). The pattern of the most common adverse events is overall comparable across the NTRK+, ROS1 NSCLC, and overall populations in TRIDENT-1. The most reported AEs as PTs are mainly consistent between CARE and TRIDENT-1, but the frequencies are different, most likely due to the lower number of patients in the CARE study. All ADRs included for the adult population are considered potentially relevant for the paediatric population, which is also stated in the product information.

The most frequent (> 2 %) treatment-emergent **serious adverse events** in adults (TRIDENT-1) were: pneumonia (6.2 %), dyspnoea (3.5 %), and pleural effusion (3.0 %). SAEs were only considered treatment-related in 8.5 % of adult subjects, with pneumonitis and dizziness (0.9 % each) being the most frequent. The most common TEAE **≥ grade 3** generally mirror SAEs (pneumonia: 5.7 %, dyspnoea 6.7 %), with the addition of anaemia as the most reported ≥ grade 3 TEAE by PT (8.8 %). Data in children and adolescents are very limited, and only two SAEs (5.3%) were considered related to treatment (including one case of stress fracture). The most commonly reported grade ≥3 TEAE in the paediatric population were anaemia and weight increase (6/38, 15.8 % each).

The number of patients who had to **discontinue treatment** due to an AE in TRIDENT-1 is 10.8 % (n = 61), which is consistent across the overall safety population, NSCLC subjects, and NTRK+ solid tumours. The most frequently reported SOC leading to discontinuation was Respiratory, thoracic, and mediastinal disorders (overall, n = 21, 3.7 %). Dyspnoea (n = 6, 1.1 %), pneumonitis (n = 5, 0.9 %), and muscular weakness (n = 5, 0.9 %) were the most commonly reported PTs leading to discontinuation, and pleural effusion was reported in 3 patients (0.5 %).

TEAEs leading to **dose reduction** (38.2 %) and **temporary interruptions** (51.5 %) were commonly reported in adults. An overall high median exposure (93.9 %) indicates that reductions and interruptions were short and the events acceptably manageable. Dizziness (11.2 %) and ataxia (6.0 %) were the most common TEAEs leading to dose reductions. Dizziness (9.9 %), dyspnoea (6.5 %), and muscular weakness (5.5 %) were the most frequent TEAEs causing dose interruptions.

Fewer patients discontinued due to an AE in CARE (5.3 %) compared to TRIDENT-1, which were only reported in two paediatric subjects: one with grade 3 anaemia and one with grade 2 fracture. One patient had a dose reduction, and 13 subjects (34.2 %) were reported with TEAEs leading to dose interruption, of which 5 (13.2 %) were considered treatment-related.

In light of the severity of the intended indications, a high grade of morbidity in studied patient groups is expected. In total 219 patients (38.8 %) died in the TRIDENT-1 study, mainly because of disease progression. **TEAEs leading to death** were reported in 3 patients (7.9 % %) in CARE, all of which were attributed to disease progression and not considered related to treatment. In the overall adult population (TRIDENT-1), there were 35 patients with a TEAE with fatal outcome (6.2 %). Two fatal AEs were considered related by the investigators (sudden death and cardiorespiratory arrest), but not by the applicant who highlights that the patients presented with multiple risk factors and extensive medical history, and the TTO was 10 and 11 months, respectively.

The selection of medical concepts as **adverse events of special interest** (AESI) was based on expected pharmacological effects related to the mechanism of action, class effects of similar TKIs, and observed toxicities from preclinical and clinical studies. The selection of medical concepts as AESIs is rational.

Most adult patients experienced at least one AESI (94.7 %), primarily CNS effects which is consistent with TRK inhibition and in general mirror the most commonly reported adverse events. The following AESIs selected for further analysis occurred frequently (adult vs paediatric population): ataxia (29.0 % vs 15.8 %), cognitive disorders (22.3 % vs 10.5 %), dizziness (65.5 % vs 21.1 %), dysgeusia (56.5 % vs 26.3 %), hepatic enzyme elevation (26.9 % vs 26.3 %), mood disorders (6.5 % vs 15.8 %), muscular weakness (21.6 % vs 7.9 %), paraesthesia (39.1 % vs 13.2 %), pneumonitis (3.2 % vs 0 %), peripheral sensory neuropathy (20.2 % vs 5.3 %), QT prolongation (0.9 % vs 15.8 %), skeletal fractures (3.5 % vs 18.4 %), sleep disorders (17.3 % vs 18.4 %), and vision disorders (14.2 % vs 10.5 %). While several AESIs are more frequently reported for the adult population, it is noteworthy that skeletal fractures and QTc prolongation have a significantly higher occurrence in the paediatric patient group.

Time to onset of the reported AESIs was generally within the first month after treatment (based on data from TRIDENT-1).

Serious AESIs were less common (adults: 6.0 %), with muscular weakness, and pneumonitis (1.1% each) being the only terms reported in ≥ 1 %. AESIs leading to discontinuation of study drug were reported in 19 (3.4%) adult subjects, with pneumonitis (0.9%), cognitive disorders (0.8%), and muscular weakness (0.9%) as only AESI PTs reported in > 2 subjects.

CNS-related adverse events are very commonly reported in repotrectinib-treated patients and are therefore addressed with a warning in the SmPC 4.4, alongside descriptions of the AESIs dizziness, ataxia, and cognitive disorders in section 4.8.

Dizziness is the most reported AESI in adults (65.5 %), as well as the most common overall TRAE. However, most cases are lower grade with only grade 3 events reported in 3.2 % adult subjects. Some adult patients required dose reduction and/or temporary interruptions, but no subjects discontinued treatment due to dizziness. The incidence of reported dizziness is lower in children and adolescents, but data are strictly limited in this group. While dizziness is troublesome to patients, the toxicity is generally manageable. The risk of **skeletal fractures** appears substantially larger in children (DCO Oct 2023: 18.4 %, up from 7.7 % DCO Dec 2022) than adults (3.5 %), which is consistent with data reported for the treatment class. The large increase in reported incidence in children from the previous DCO may reflect that this adverse event has a longer TTO. For adults, most patients had underlying factors, and only 1 of the 20 cases was considered treatment-related. For children, the events included PTs of ankle fracture (3 [7.9%] patients), fibula fracture (2 [5.3%] patients), foot fracture, fracture, stress fracture, tibia fracture (each in 1 [2.6%] patient). Four events were considered treatment-related (10.5 %). There is one adult subject reported with a grade 3 femur fracture with a fatal outcome following a fall at home, this was not considered treatment-related. Patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures should be promptly evaluated (see sections 4.4 and 4.8 of the SmPC). **ILD/Pneumonitis** was not reported in CARE, but in 18 adult patients in TRIDENT-1 (3.2 %), with grade 3 events in 5 patients (0.9 %). Dose interruption was required in 1.4%, and 0.5% required dose reduction. ILD/pneumonitis was one the most reported events leading to discontinuation (0.9 %). To address the risk, a warning in the SmPC 4.4. and a description in section 4.8 has been included.

Other selected adverse events that are addressed specifically with descriptions in the SmPC 4.8 to raise awareness are **muscular weakness** and **vision disorders,** in addition to **dyspnoea.**

AEs in **Infections** and Infestations are commonly reported (TRIDENT-1: 42.1%, CARE: 47.4%), including serious cases (TRIDENT-1: 13.6 %). Infections are not unexpected in this patient population, and the events were mainly not considered treatment-related (TRIDENT-1: All-grade: 3.2 %, SAE: 0.7%). No life-threatening or fatal events were reported as related to the study drug, and no non-

clinical data suggest that repotrectinib increases the risk of infection. However, pneumonia has been included as an ADR (TRIDENT-1: 10.3 %, CARE: 5.3 %).

Shifts in **haematologic** parameters were frequently measured, as shown by data from TRIDENT-1 with both all grade and high grade (grade 3, 4) decrease in haemoglobin (79.2 %/9.4%), lymphocytes (48.4 %/13.4 %), leukocytes (38.7 %/4.2 %), and neutrophils (33.2 %/8.7 %) often reported. TKIs are in general associated with haematological toxicity, and haematological adverse events occurred in 47 % of patients in TRIDENT-1 and 55 % of paediatric patients in CARE.

The most frequently affected **clinical chemistry** parameter was CK (adults: 62.9 %), which is consistent with the catabolic state of many cancer patients. Liver parameters were frequently increased (data from TRIDENT-1: GGT: 51.5 %, AST: 41.4 %, ALT: 39.3 %, ALP: 31.8 %), which are included as ADRs. Liver function tests including ALT, AST and bilirubin should be monitored as clinically indicated (see sections 4.4 and 4.8 of the SmPC).

High-grade shifts of urate (increased, all grade: 22.6 %, grade 3 and 4: 11.2%) in the adult population are noticeable, and hyperuricemia is included as an ADR.

Regarding **vital signs**, there was no median change in pulse rate, respiratory rate, or baseline in CARE or TRIDENT-1. In the adult population, analysis of changes in blood pressure showed that systolic and diastolic elevations (19.1 %/16.8 %) were more common than reductions (7.3 %/9.9 %), and there is no clear trend to indicate if repotrectinib affects blood pressure. Weight increase is a common in both the adult (14.7 %) and paediatric (26.3 %) populations.

Electrocardiogram results (outlier analysis) showed that 2 patients had a worst post-baseline QTc > 500 ms (0.4 %) and 6 patients (1.1 %) had a maximum increase from baseline > 60 ms in TRIDENT-1. From adverse events reporting, electrocardiogram QT prolonged was reported in 5 adult patients (0.9 %), 4 events were considered grade 1 (0.7 %) and 1 event grade 2 (0.2 %). In CARE, there were no patients with a worst post-baseline QTc > 500 ms or a maximum increase from baseline > 60 ms detected in the outlier analysis by central read. However, from adverse event reporting there were 6 patients with electrocardiogram increased (15.8 %), all of them considered related to treatment. Five of the events were considered grade 1, one event was considered grade 2. It was explained that QTc prolongation reported as AE was based on Bazzett's formula, whereas there were no cases that reported the AE of QTcF (Fridericia formula) prolongation, which is the recommended formula for correcting QT measurements. Therefore, this AE is not included in the list of adverse reactions in the SmPC.

An analysis of **safety in special populations** (in TRIDENT-1) divided by age, biological sex, race and region, and by baseline brain metastasis has been presented. For this assessment, paediatric patients are not considered a special population.

Toxicity appears more pronounced in **higher age** groups, especially in patients over 75 years of age, where SAEs (62.9 % vs 37.2 % in 18-65 Y and 47.6 % in 65-75 Y), and TEAEs leading to discontinuation (22.9 % vs 8.5 % in 18-65 Y and 16.2 % in 65-75 Y) are more commonly reported. The most common serious adverse reactions in patients ≥ 65 years of age were pneumonia, dyspnoea, and pleural effusion (see section 4.8 of the SmPC).

No marked differences in the safety profiles between **biological sex** were noted, apart from a somewhat higher incidence of grade ≥ 3 TEAEs in males (63.3 % vs 52.7 %).

There were no notable differences in reported adverse events between subgroups of **'race'**: White and Asian. Dose reductions were more prevalent in Asia (43.6 %) compared to 39.8 % in other regions (including the EU) and 30.3 % in the US. SAEs and grade ≥3 AEs were more commonly reported in the US (SAE: 49.1 %, grade ≥3 AE: 59.4 %) than in Asia (SAE: 33.3 % and grade ≥3 AE: 51.0 %) and

other regions (SAE: 40.9 % and grade ≥3 AE: 61.8 %). Thus, there is no obvious trend that the reported safety profiles differ importantly across **regions**.

As several AESIs are related to CNS-effects or cognitive function, evaluation of AESIs by **baseline brain metastasis** was performed. No apparent meaningful differences in the manifestation of CNS-related adverse events in patients with brain metastasis at baseline (n = 193) compared to patients without (n = 372), e.g. illustrated by similar occurrence of dizziness (60.6 % vs 65.5 % in the overall population).

Repotrectinib is both a substrate and inducer of CYP3A4 and is therefore prone to **drug interactions**. Strong CYP3A4-inhibition causes a 6-fold increase in AUC. The safety profile of such exposure is not established, but increased occurrence and severity of adverse events can be expected, which constitutes a concern. Coadministration with strong CYP3A4 inhibitors and CYP3A4 sensitive substrates should be avoided, and a warning in the SmPC to addressing this risk is included.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

A Conditional Marketing Authorisation (CMA) is applied for in adult and adolescent patients with NTRK-positive solid tumours. The currently available safety data (TRIDENT-1) in adults within indication is limited to 144 subjects. As for the adolescent population in CARE, data is very scarce, with only 8 subjects having NTRK-positive solid tumours and being ≥ 12 years of age. In addition to the small sample sizes, the treatment period and follow-up time are restricted for both the adult and adolescent populations.

The applicant states that additional comprehensive data from TRIDENT-1 and CARE will allow for conversion to full approval and presents a proposed plan for additional data generation. According to the plan, efficacy will be reported in a total of approximately 230 adult and paediatric subjects with NTRK-positive solid tumours across the TRIDENT-1 and CARE studies, while safety results from all treated subjects (n > 600) across the repotrectinib program, including those with NTRK alterations, on TRIDENT-1 and CARE will be reported. The last subject enrolled will be followed for a minimum of 12 months from onset of response. Existing subjects from the MAA will be followed for at least 24 months from onset of response for long-term characterisation of efficacy and safety.

From a clinical safety perspective, the estimated total dataset of 600 patients with a minimum follow-up time of 12-24 months is considered acceptable for the adult indication.

Regarding the paediatric population, even when additional subjects are recruited to the study CARE, the patient pool will still be limited. Paediatric patients undergo growth and development, and a minimum follow-up of 12-24 months is considered too short to properly uncover potential developmental impairment caused by repotrectinib. Thus, uncertainties regarding detection of adverse events specific to this patient group remain. Therefore, post-marketing surveillance will be important to further establish the paediatric safety profile.

The following measures are necessary to address the missing safety data in the context of a conditional MA:

- Submission of safety data collected according to the proposed plan for additional data generation.
    - Regarding the plan for generation of additional safety data, the applicant has provided additional details describing that approximately 75 subjects are expected to be enrolled in CARE, with at least 40-43 NTRK+ paediatric patients. Enrolment is challenged by the rarity

of the conditions and the availability of other approved agents (larotrectinib and entrectinib). The protocol does not have specific targets for tumour types or enrolment targets for specific age groups. Therefore, it is difficult to estimate the number of patients by age range (< 12 years, ≥ 12 years), which is acknowledged. Provision of final data from CARE is suggested as a SOB. Final study report from CARE is expected in 2035, but interim analysis will be submitted from Nov 2025.

2.6.10. Conclusions on clinical safety

The uncontrolled study design, small sample size and limited follow-time impose uncertainties regarding the conclusions on the safety profile, in particular with respect to detection of less common adverse events and characterisation of long-term safety. In context of the severity and rarity of the conditions, the safety database is considered acceptable.

Based on the provided data, the overall safety profile of repotrectinib for the claimed indications in adult patients appears to be manageable.

The paediatric population is strictly limited with only 38 patients, but the safety profile appears overall comparable to that in adults. However, only 8 out of totally 38 subjects are representative of the indication applied for, resulting in uncertainties and prohibiting any firm conclusions for this group. Therefore, generating additional safety data from the clinical study CARE and through post-marketing surveillance will be important.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA.

In order 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 (CARE) by Q4 2030.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP as shown in Table 76.

Table 76. Summary of safety concerns in the RMP

Summary of safety concerns	
Important identified risks	Skeletal fractures
Important potential risks	None
Missing information	Safety in long term use

2.7.1.1. Discussion on safety specification

Data on treatment with repotrectinib for more than 12 months is only available in a limited number of adult and paediatric patients, and safety in long-term use cannot be determined at present. Inclusion of **safety in long-term use** as missing information is endorsed.

The risk of **skeletal fractures**, applicable to both adults and paediatric patients, is more pronounced in children. Data from the paediatric population is highly limited, which limits the conclusions drawn on adverse event occurrence in children and imposes uncertainties on the characterisation of this risk. Skeletal fractures are therefore included as an important identified risk.

2.7.1.2. Conclusions on the safety specification

Having considered the data in the safety specification, the rapporteur agrees that the safety concerns listed by the applicant are appropriate.

2.7.2. Pharmacovigilance plan

2.7.2.1. Routine pharmacovigilance activities

No other routine pharmacovigilance activities beyond ADR reporting and signal detection are deemed necessary.

2.7.2.2. *Summary of additional PhV activities*

Table 77. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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				

No additional pharmacovigilance activities are warranted.

2.7.3. Plans for post-authorisation efficacy studies

2.7.3.1. Summary of Post authorisation efficacy development plan

Table 78. Part IV.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 uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
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 antitumor activity study of repotrectinib in pediatric and young adult subjects with advanced or metastatic malignancies harboring ALK, ROS1, or NTRK1-3 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 Antitumour Activity Study of repotrectinib in Paediatric and Young Adult Subjects with Advanced or Metastatic Malignancies Harboring ALK, ROS1, or NTRK1 3 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 ALK, ROS1, or NTRK1-3 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)

Final data from the CARE and TRIDENT-1 study are requested as specific obligations. Subsequently, the applicant included both studies in Part IV under 'Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances'.

2.7.3.2. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

2.7.4. Risk minimisation measures

2.7.4.1. Routine Risk Minimisation Measures

Routine risk minimisation measures include routine risk communication through SmPC and PIL, as well as recommendations including specific clinical measure to address the risk. No other routine risk minimisation measures were deemed necessary by the PRAC for the currently proposed safety concerns.

2.7.4.2. Summary of additional risk minimisation measures

No additional risk minimisation measures are proposed. The PRAC was of the opinion that routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product in the proposed indications.

Table 79 Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Skeletal fractures	**Routine risk minimisation 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 minimisation 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

2.7.4.3. Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

2.7.5. Summary of the risk management plan

The public summary of the RMP does not require revision.

2.7.6. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD). The IBD is 15.11.2023. The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Augtyro (Repotrectinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

Agreed indication:

Repotrectinib as monotherapy for the treatment of adult patients with ROS1-positive locally advanced or metastatic 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 NTRK gene fusion, and

- who have received a prior NTRK inhibitor, or

- have not received a prior NTRK inhibitor and when treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted (see sections 4.4 and 5.1).

3.1.2. Available therapies and unmet medical need

ROS1 positive advanced NSCLC

Two medicines are currently authorised in the EU for ROS1-positive NSCLC:

- Crizotinib (Xalkori) was authorised in EU (EoI EMEA/H/C/002489/II/0039) on 25 August 2016 for the treatment of adult patients with ROS1-postive advanced NSCLC. The approval was based on data from 53 patients in a SAT. The patients were previously pretreated with chemotherapy. After a median follow-up of 62.6 months, ORR was 72% (95%CI 58, 83; CR 11%), median DOR 24.7 months (95%CI 15.2, 45.3) [Xalkori SmPC]. Clinical data on intracranial activity was not described; crizotinib seems to penetrate poorly the blood-brain barrier[19].

- Entrectinib (Rozlytrek), a second-generation inhibitor of several receptor tyrosine kinases (TKI), was authorised in EU on 31 July 2020 (EMEA/H/C/004936/0000) for the same advanced NSCLC ROS1 positive population not previously treated with ROS1 inhibitors. The approval was based on a pooled dataset form 3 SATs, including a total of 94 patients. Updated data from 161 patients post-approval with a median duration of follow-up of approximately 16 months, showed: ORR 67.1% (59.25, 74.27) and 12-month durable response at 63% (53, 73). Intracranial responses were seen in 19 of 24 [79.2% (95%CI: 57.8, 92.9)] patients with brain metastasis at baseline. [Rozlytrek SmPC].

Although initial responses to ROS1 inhibitors are good, up to 50% of the patients develop ROS1 mutations that mediate resistance to crizotinib and entrectinib, leading to treatment failure.[20] It is still uncertain whether re-challenging with another ROS1 inhibitor is beneficial in 2nd line or later[21], and none of the available ROS1-inhibitors in 1st line are approved for use after initial TKI.

Pemetrexed-based chemotherapy is viewed as the standard of care after initial treatment with a ROS1-TKI according to European guidelines.[22] The response rates for pemetrexed-based chemotherapy are

[19] Daniel B. Costa et al. CFS concentration of the ALK inhibitor crizotinib. J Clin Oncol, 2011
[20] Gainor JF, Tseng D, Yoda S, et al. Patterns of Metastatic Spread and Mechanisms of Resistance to Crizotinib in ROS1-Positive Non-Small-Cell Lung Cancer. JCO Precis Oncol 2017;2017
[21] Miguel Garcia-Pardo et al. ROS-1NSCLC therapy resistance mechanism (Review Article). Precision Cancer Medicine, 2021
[22] Planchard D. et al. Metastatic non-small lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol, 2018.

shown to be around 50% in 1st line, and approximately 25% in 2nd line treatment, based on retrospective data.[23]

NTRK fusion positive solid tumours

Two medicines are currently authorised in the EU for the treatment of NTRK fusion positive solid tumours:

- Larotrectinib (Vitrakvi), an NTRK inhibitor was granted a Conditional Marketing Authorisation by the European Commission on 19 September 2019 (EMEA/H/C/004919/0000) to, for the treatment of adult and paediatric patients with solid tumours that display a NTRK gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment option. The approval was based on a pooled analyses set (n=277) which included 28 patients < 18 years. CNS primary tumours was excluded from the primary analysis. Estimated ORR was 67% (95%CI: 61,72) and median DoR 43,3 months [Vitrakvi SmPC].

- Entrectinib (Rozlytrek) was granted a conditionally approval in EU at the same time as the MA in ROS1 positive NSCLC was given (2020), for the treatment of adults and paediatric patients from 12 years of age with solid tumours expressing NTRK gene fusion with the same wording of indication as for larotrectinib. The approval was based on of data from 3 SATs, including 150 patients with advanced NTRK fusion positive solid tumour not priorly treated with a TRK-inhibitor. The overall median duration of follow-up was 30.6 months. The estimated ORR is 61.3% (95% CI: 53.0, 69.2) with a median DoR of 20 months (13.2, 31.1). Intracranial responses were seen in 9 out of 13 (69.2%) patients with brain metastases at baseline. Efficacy in adolescents (≥ 12 years) was based on efficacy and pharmacology.

3.1.3. Main clinical studies

The main evidence of efficacy for both indications is TRIDENT-1, an ongoing Phase 1/2, open-label, single-arm, multi-centre, first-in-human study of the safety, tolerability, PK, pharmacokinetics, and anti-tumour activity of repotrectinib as a single agent in patients with advanced solid tumours harbouring ALK, ROS1 or NTRK1-3 rearrangements (Figure 8). All patients included in the primary analysis received at least one dose of repotrectinib and had measurable disease at baseline by BICR (RECIST v.1.1). Participants in EXP-1 and EXP-5 were naïve to prior TKI, whereas the subjects in EXP-2, EXP-3, EXP-4 and EXP-6 were pretreated with ROS1 inhibitor and TRK inhibitor, respectively.

Two datasets are presented: one for ROS1 positive NSCLC [n=257 (156 efficacy evaluable), divided into four separate cohorts] and one for NTRK positive solid tumour [n= 104 (79 efficacy evaluable), divided into two cohorts]. Participants in the efficacy evaluable dataset in both populations had at least 6 months of follow-up after the first post-baseline response evaluation.

The CSR is based on Phase 2 data in ROS1 + NSCLC population and these data are considered pivotal. Data for the NTRK positive population is presented in a CSR addendum at a later DCO. In addition, in the clinical overview the applicant has provided pooled analyses per cohort of Phase 2 and eligible patients from Phase 1 at the later DCO (adding a small number of patients), which is considered supportive evidence of efficacy.

To support the proposed indication for NTRK positive solid tumours in adolescents (≥ 12 years), the applicant has provided interim data from an ongoing uncontrolled open-label Phase 1/2 study in young adults (≤ 25 years), adolescents and paediatric patients (CARE). Data from totally 26 patients (wherein 16 with NTRK fusions) is provided, including 6 efficacy evaluable participants.

[23] Limin Zhang et al. Efficacy of crizotinib and pemetrexed-based chemotherapy in Chinese NSCLC patients with ROS1 rearrangement. Oncotarget, 2016

3.2. Favourable effects

ROS1 positive advanced NSCLC

The 121 TKI-naïve subjects with ROS1 positive NSCLC (EXP-1), achieved an ORR by BICR of 76.9% (95%CI: 68.3, 84.0), with 15 CRs (12.4%). The median DoR is 33.61 (25.46, NE). Median time to response (TTR) was 1.8 months (range: 1.5, 7.4).

In the 107 TKI-pretreated subjects (EXP-4), the ORR is estimated to be 48.6% (95%CI:38.8, 58.5) with 8 CRs (7.5%). The median DoR reached 14.75months (7.6, NE). Median TTR was 1.84 months (range; 1.6, 22.1).

The IC-ORR by BICR (based on 14 subjects) was 85.7% (95% CI:57.2, 98.2) in EXP-1. In EXP-4, the IC-ORR by BICR (based on 23 subjects) was 43.5% (95% CI:23.2, 65.5).

NTRK positive advanced solid tumours

In 51 TKI-naïve subjects with NTRK-positive solid tumours (EXP-5), an ORR by BICR of 58.8% (95%CI:44.2, 72.4) was reached with 8 CRs (15.7%). Objective responses (CR or PR) were seen across 6 different tumour types (NSCLC, salivary gland cancer, thyroid cancer, sarcoma, head and neck cancer and peripheral nerve sheath tumour). Median DoR is not reached (NE, NE). Medan TTR was 1.82 (range: 1.6, 7.3).

In 69 TKI-pretreated subjects with NTRK-positive solid tumours (EXP-6), an ORR by BICR of 47.8% (95%CI: 35.6, 60.2) was reached with 2 CRs. Objective responses (CR or PR) were seen in 10 different tumour types (secretory breast cancer, glioblastoma, NSCLC, CRC, neuroendocrine tumour, salivary gland cancer, thyroid cancer, sarcoma, cholangiocarcinoma, peripheral nerve sheath tumour). Median DoR was 9.76 months (7.36, 12.98). Median TTR was 1.87 months (range: 1.7, 3.7).

Thirteen (13) paediatric patients (5 TKI-naïve, 8 TKI-pretreated) with NTRK positive solid tumours were evaluated for efficacy in the CARE study. Five achieved a confirmed objective response by BICR: 1 CR (soft tissue sarcoma) and 2 PRs among TKI-naïve 2 PRs among TKI-pretreated.

3.3. Uncertainties and limitations about favourable effects

Applicable to both indications

Due to the single-arm design of the pivotal study, the risk of bias and more particularly the selection of patients, cannot be eliminated. Time to event endpoints such as OS and PFS cannot be contextualised in uncontrolled trials and the drug effect cannot be isolated.

Data on intracranial activity (IC) is limited. Approximately half of the participants with brain metastasis at baseline were not included in the analyses of IC-ORR due to not measurable metastases by BIRC. In the expanded dataset, approximately 24% (15/62) of the evaluated patients (ROS1+ NSCLC and NTRK+ solid tumours) with measurable baseline IC metastases had received radiation therapy or other CNS intervention within 60 days before inclusion (SAP amendment during study conduct).

The applicant regards the IC-ORR data from TRIDENT-3 as supportive. However, results from TRIDENT-3 are not proposed as a specific obligation for this CMA because that trial does not enrol patients with NTRK-positive solid tumours.

Although the data indicate that both ROS1+ and NTRK+ patients respond to repotrectinib treatment despite resistance mutations, the numbers of patients are quite small, and it is not possible to estimate ORR per type of baseline resistance mutation. For further confirmation of efficacy in patients with

different resistance mutations, the applicant will report efficacy by baseline resistance mutation status as part of the broader NTRK data generation plan for the CMA for NTRK positive patients.

NTRK positive solid tumours

Due to the limited efficacy data, the extent to which tumour origin impacts efficacy is in need of further clarification. The number of patients per tumour type is small and the confidence intervals are generally wide, making efficacy estimates generally imprecise and hampering the possibility to draw conclusions regarding efficacy in each tumour type; the ORR is highly variable ranging from 0 (TKI-naïve breast cancer, CRC and oesophageal cancer + TKI pretreated pancreatic cancer) to 100% (TKI-naïve salivary gland cancer and thyroid cancer). This uncertainty is stated in the SmPC (see section 4.4). The final results from TRIDENT-1, requested as a Specific Obligation will allow more precise estimate of the response rate within a larger number of tumour types.

DoR is still immature in the TKI-naïve cohort (EXP-6); median DoR is not reached. Additional follow-up to allow estimation of the DoR from the TRIDENT-1 study will be provided as part of the Specific Obligation.

Very limited efficacy data in paediatric patients with NTRK positive solid tumours is available. Among the 13 efficacy evaluable patients, five had confirmed responses. Efficacy estimates are associated with great uncertainty and a comprehensive assessment of the data is not feasible. The NTRK indication in adolescents relies on extrapolation of adult efficacy data through PK exposure matching under the assumption of similarity of disease and response to treatment. Additional data with increased number of patients for the CARE study will be provided as Specific Obligation.

3.4. Unfavourable effects

Characterisation of the safety profile is founded on databases consisting of 565 adult patients from TRIDENT-1 and 38 paediatric patients from CARE who received at least one dose of repotrectinib. Data from TRIDENT-1 and CARE are not pooled due to differences in the patient populations. Of note, the original DCO date for safety data was 19-Dec-2022 (n= 519 and n=26 for TRIDENT and CARE, respectively). Additional safety data with a DCO date of 15-Oct-2023 were provided for both the adult and paediatric populations.

Almost all subjects experienced at least one treatment-emergent adverse event (TEAE): overall adult population 99.5 %, overall paediatric population 100 %. Most patients (TRIDENT-1: 94.7 %, CARE: 84.2 %) had at least one adverse event that was considered related to treatment, and the majority of patients had a grade ≥3 TEAE (TRIDENT-1: 57.2 %, CARE: 55.3%) or a serious adverse event (SAE, TRIDENT-1: 40.7%, CARE: 36.8%). Time-to-onset of AEs was, where reported, generally within the first month after treatment.

Adverse events could mostly be handled through dose reductions (TRIDENT-1: 38.2%) and temporary interruptions (TRIDENT-1: 51.5%). The rate of AEs leading to discontinuation was 10.8 % and 5.3 % in the overall adult and paediatric populations, respectively.

Different analysis subgroups have been identified by the applicant, and data stratified by molecular alteration in adults are presented and discussed (NTRK+ n=144, ROS1+ n=367, patients outside claimed indication n=54). Results from the NTRK+ and ROS1+ groups are generally comparable to the overall population.

Given the mechanism of action, TEAEs in 'Nervous system disorders' are expected, and this is the most frequently reported TEAE by SOC (TRIDENT-1/CARE, numbers in %: 90.3/57.9), followed by 'Gastrointestinal disorders' (71.9/76.3), 'General disorders and administration site conditions'

(58.8/55.3), 'Respiratory, thoracic and mediastinal disorders' (57.9/42.1), 'Investigations' (55.2/65.8), 'Musculoskeletal and connective tissue disorders' (56.6/28.9), 'Infections and infestations' (42.1/47.4), 'Blood and lymphatic system disorders' (41.8/50.0), and 'Metabolism and nutrition disorders' (34.7/52.6). The most common TEAEs by PT were: dizziness (63.0/21.1), dysgeusia (52.4/23.7), constipation (39.3/39.5), anaemia (38.1/50.0), paraesthesia (34.0/13.2), dyspnoea (31.3/15.8), fatigue (24.8/36.8), ALT increased (22.1/18.4), ataxia (21.9/5.3), muscular weakness (21.6/7.9), AST increased (20.9/18.4), nausea (20.7/28.9), and headache (20.0/31.6).

The most frequent (> 2 %) SAEs in adults were: pneumonia (6.2 %), dyspnoea (3.5 %), and pleural effusion (3.0 %).

As repotrectinib is both a substrate and inducer of CYP3A4, there is a pronounced risk of drug-drug-interactions, which constitutes a safety concern.

3.5. Uncertainties and limitations about unfavourable effects

The size of the adult analysis population is limited, allowing only for detection of common adverse events, but is considered acceptable in context of the rarity and gravity of the diseases. The uncontrolled study design complicates differentiation of drug-related AEs from symptoms of the underlying conditions, thereby introducing uncertainties regarding the characterisation of the safety profile. In addition, evaluation of long-term safety is still confined by the limited follow-up time. Additional follow-up on safety from study TRIDENT-1 will be provided as part of the Specific Obligation.

The paediatric population is strictly limited with a mere 38 subjects, and only 8 of these correspond to the intended patient group (≥12 years with NTRK+ tumours). Firm conclusions on the safety profile in adolescents can presently not be drawn. While the sparse data presented appear overall comparable to those in adults, it is important to collect additional data post marketing. Additional safety data in adolescent will be collected in the context of the CARE study, listed as Specific Obligation. Of note, adolescents are more prone to skeletal fractures, which is addressed in the product information and RMP.

3.6. Effects table

Table 80. Effects Table for repotrectinib for the treatment of adult patients with *ROS1*-positive locally advanced or metastatic NSCLC and for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a *NTRK* gene fusion

Cohort	Effect	Short Description	Unit	Treatment	Uncertainties/ Strength of evidence	References
Favourable Effects						
ROS1-positive advanced NSCLC						
EXP-1 N=121 **TKI naïve ROS1+ NSCLC**	ORR	Overall response rate	N (%) 95%CI	93 (76.9) 68.3, 84.0	Single arm trial, exploratory study. Indication sought for ROS1+ NSCLC. Short follow up. Enrolment ongoing.	3.3.4.2
	DoR	Median duration of response	Months 95%CI	33.61 25.5, NE		
EXP-4 N=107	ORR	Overall response rate	N (%) 95%CI	52 (48.6) 38.8, 58.5		3.3.4.2

Cohort	Effect	Short Description	Unit	Treatment	Uncertainties/ Strength of evidence	References
TKI pretreated ROS1+ NSCLC	DoR	Median duration of response	Months 95%CI	14.75 7.6, NE	CSR DCO 15-Oct-2023	
NTRK positive solid tumours						
EXP-5 N=51 **TKI naïve NTRK+ solid tumour**	ORR	Overall response rate	N (%) 95%CI	30 (58.8) 44.2, 72.4	Single arm trial, exploratory study. Indication sought for NTRK+ solid tumour. CMA Short follow up. Enrolment ongoing. CSR addendum 15-Oct-2023	3.3.4.2
	DoR	Median duration of response	Months 95%CI	NE NE, NE		
EXP-6 N=69 **TKI pretreated NTRK+ solid tumour**	ORR	Overall response rate	N (%) 95%CI	33 (47.8) 35.6, 60.2		3.3.4.2
	DoR	Median duration of response	Months 95%CI	9.76 7.4, 13.0		
Unfavourable Effects Overall safety populations: TRIDENT-1 (adult population, n = 565) and CARE (paediatric population, n = 38)						
Overall adverse events experience TEAE TRAE TEAE grade ≥3 SAE (serious adverse events) TEAE leading to discontinuation TEAE leading to dose modification TEAE leading to death			% (TRIDENT-1 /CARE)	 99.5 / 100 94.7 / 84.2 57.2 / 55.3 40.7 / 36.8 10.8 / 5.3 57.2 / 34.2 6.2 / 7.9	Uncertainties - Single arm trial - Limited median exposure time - Limited sample size, in particular for the paediatric population	3.3.7.2
Most common TEAE by SOC Nervous system disorders Gastrointestinal disorders			% (TRIDENT-1 /CARE)	 90.3/ 57.9 71.9/ 76.3		3.3.7.2
TEAE of special interest (AESI) Dizziness Dysgeusia Paraesthesia Ataxia Hepatic Enzyme Elevation Cognitive Disorders Muscular weakness Peripheral Sensory Neuropathy Sleep Disorders Vision Disorders Mood Disorders Pneumonitis Skeletal Fractures QT prolongation			% (TRIDENT-1 /CARE)	 65.5 / 21.1 56.5 / 26.3 39.1 / 13.2 29.0 / 15.8 26.9/ 26.3 22.3 / 10.5 21.6 / 7.9 20.2 / 5.3 17.3 / 18.4 14.2 / 10.5 6.5 / 15.8 3.2 / 0 3.5 / 18.4 0.9 / 15.8	Grouped terms used, not single PTs.	3.3.7.3
Most common SAE Pneumonia Dyspnoea Pleural effusion			% (TRIDENT-1)	 6.2 3.5 3.0		3.3.7.3

Abbreviations: PT (preferred term), SOC (system organ class), TEAE (treatment-emergent adverse event), TRAE (treatment-related adverse event)
Notes: (TRIDENT-1 data cut-off: 15 Oct 2023). Unfavourable Effects are described from the overall safety populations in TRIDENT-1 and CARE (DCO 15 Oct 2023)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

ROS1 positive advanced NSCLC

An ORR of approximately 77% is expected to translate into a clinical benefit and is in line with response rates observed for approved ROS1-TKIs in the TKI-naïve patients. Supported by a duration of response (mDoR 33.6 months) that is higher than for the approved products, a clinically relevant benefit can be expected. In the setting of an uncontrolled trial, uncertainties regarding magnitude of efficacy and translation into gain in PFS and OS will remain.

Also, in the TKI-pretreated patients, a reasonable clinical benefit can be expected. An ORR of 48% supported by a stable mDoR of 14.75 months is considered clinically meaningful. For this population, treatment options in terms of chemotherapy are available and viewed as standard of care according to clinical treatment guidelines. Pemetrexed-based chemotherapy in 2nd line treatment indicate lower response rates and shorter duration of response than shown for repotrectinib. Further, considering that some patients are not eligible for chemotherapy, the ORR and DoR achieved in the TKI-pretreated patients are deemed clinically relevant.

The efficacy data indicate that ROS1+ patients respond to repotrectinib treatment despite baseline resistance mutations. However, the number of patients with resistance mutations are quite small and it is not possible to estimate ORR per type of baseline resistance mutation. Patients are not expected to be tested for resistance mutations in clinical practice. This is currently not considered problematic taking into consideration the reported ORR in the TKI pretreated patients, including the patients with resistance mutations.

It is established that brain metastases influence the overall survival more than other metastases across tumour types. As presence of brain metastases at baseline or development of brain metastases during the course of the disease is high among ROS1 positive NSCLC patients (20-50%), intracranial activity is essential regardless of treatment line. Among the 53 participants with brain metastasis at baseline, 14 (26%) had received recent (within 60 days prior to study treatment) CNS intervention which may have confounded the results. From a post-hoc analysis, it did not seem that the timing of CNS-intervention influenced the IC-ORR.

The safety database for the ROS1+ NSCLC indication (n = 367) is considered acceptable and consistent with overall safety data (n =565). Adverse events occur commonly (99.5 %) and are often of higher grade (≥3: 58.0 %) or serious (41.7 %), which may affect quality of life. However, toxicities are generally handled with temporary interruptions (54.5 %) or dose reductions (38.4 %), whereas discontinuation is less common (10.6 %). Based on available data presented, the toxicity appears manageable.

NTRK positive advanced solid tumours

In the context of advanced cancer in rare tumour types or rare NTRK mutations in common tumours with limited targeted treatment options, an ORR ranging from 40 to 60% can be considered clinically relevant and in line with the response rates for the conditionally approved products in TKI-naïve setting although no direct comparison is available. Confirmation from DoR is critical in a single arm setting, however, median DoR is still not reached in the TKI-naïve population. In the TKI-pretreated

patients a median DoR of 9.76 months could be considered clinically relevant to patients in 2nd line and beyond who are expected to have exhausted other treatment options, above all for subjects not eligible for chemotherapy or immunotherapy.

The heterogeneity of the cohorts in terms of histology hampers the efficacy evaluation per tumour type due to small subgroups, and the magnitude of effect estimates is still uncertain. Nevertheless, objective responses were seen across 6 different tumour types in the TKI-naïve NTRK-population and across 10 different tumour types in the TKI-pretreated population. The short time to response (TTR) is considered valuable for the patients as it may alleviate symptoms after tumour shrinkage and may support the clinician in decision making related to toxicities.

The safety database supporting the claimed NTRK+ indication in adults is considered rather limited (n = 144), but acceptable given the rare condition, and is further supported by consistency with overall safety data (n = 565). Similar to results for the ROS1 indication, adverse events occur commonly (99.3 %), and are often of higher grade (≥3: 57.6 %) or serious (38.9 %), which may affect quality of life. Toxicities are generally handled with temporary interruptions (52.8 %) or dose reductions (45.1 %), and discontinuation is less common (9.7 %). Based on available data presented, the toxicity appears manageable.

The paediatric efficacy data is limited to 13 patients, including five responders. The safety database for the NTRK+ adolescent patients is strictly limited with only 8 patients, supported by a total of 38 paediatric patients. Data appear overall comparable to those reported in adults, however uncertainties remain on the safety profile in adolescents. Additional efficacy and safety data from a larger number of patients and with a longer follow up will be provided from the CARE study as a specific obligation. The indication in adolescents is primarily supported by extrapolation of efficacy and safety from adults via exposure matching. The PK bridge is informed by observed repotrectinib concentration data from thirteen adolescents and popPK modelling and simulation. The proposed dose of 160 mg QD/BID is acceptable for adolescents across the expected body weight range.

In the setting of treatment failure to TKI-treatment, an unmet medical need is also acknowledged, especially in patients not eligible for chemotherapy or when other treatment options have been exhausted. The data indicate a similar efficacy to repotrectinib in patients with resistance mutations compared to the overall population, however, further confirmation is necessary. In a population with >20% brain metastases at baseline, intracranial efficacy is crucial in the B/R assessment of a product. The number of patients with measurable brain metastases by BICR at baseline was too limited for assessment and inclusion in the SmPC. Although supported by the IC results in the ROS1+ NSCLC population, further data for confirmation is expected through final data from TRIDENT-1 and CARE.

3.7.2. Balance of benefits and risks

ROS1 positive advanced NSCLC

The ORR and DoR are similar to what has been demonstrated for the approved ROS1-inbititors in the TKI-naïve setting and is deemed a clinical benefit to the patients. In the TKI-pretreated setting, the ORR seems higher than what is expected for 2nd line chemotherapy. The responses are more durable for repotrectinib than for chemotherapy although only based on indirect comparison. Uncertainty remains regarding the intracranial (IC) efficacy of repotrectinib and its ability to overcome resistance mutations. Available data indicate a manageable safety profile, but uncertainties remain regarding characterisation of long-term safety and less common adverse events.

The ongoing randomised phase 3 trial, TRIDENT-3, comparing repotrectinib with crizotinib in TKI-naïve ROS1+ NSCLC patients will include investigations of mechanisms of resistance to repotrectinib. Thus,

the data from TRIDENT-3 are of high interest, and the final data is agreed to be provided through a Recommendation (**REC**).

NTRK fusion positive solid tumours

The activity in solid tumours with NTRK fusions, in terms of ORRs ranging from approximately 40% to 60%, is assumed to represent a clinical benefit, regardless of prior TRK-TKI. The responses in the TKI-naïve are in line with therapies available through conditional approval although the response per tumour type is uncertain. Durable responses in TKI-naïve subjects should be confirmed to strengthen the clinical relevance of the ORR. Available safety data suggest manageable toxicities, but the safety database supporting the claimed NTRK+ indication in adults is considered rather limited.

The data on efficacy and safety are non-comprehensive in the paediatric population. The NTRK indication in adolescents is supported by extrapolation of pivotal adult data through PK exposure matching under the assumption of similarity of disease and response to treatment.

Furthermore, uncertainties remain regarding efficacy across different histologies, IC responses, activity in tumours presenting with resistance mutations, detection of less common adverse events and characterisation of long-term safety. The final data from CARE and TRIDENT-1 will be submitted post authorisation as specific obligations (SOB).

3.7.3. Additional considerations on the benefit-risk balance

NTRK fusion positive solid tumours indication:

Conditional marketing authorisation

As comprehensive data on the product are not available for the treatment of patients with tumours that harbour NTRK1/2/3 alterations, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

The product is considered to fulfil the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive (as discussed above).
- It is likely that the applicant will be able to provide comprehensive data.

The main areas of non-comprehensive data are estimates of efficacy across tumour types, long-term safety data, data in paediatric patients, efficacy despite resistance mutations and responses intracranially.

The applicant plans to report efficacy and safety for approximately 230 adults and paediatric patients with NTRK positive solid tumours in total; 200 adults from TRIDENT-1 and 30 paediatric patients from CARE, including the existing patients in the trials. The last patient will be followed for a minimum of 12 months from onset of response. The existing patients from primary analysis will be followed for at least 24 months from onset of response for long-term characterisation of efficacy and safety. Safety results from all treated subjects (N>600) across the repotrectinib program, including ROS1 positive NSCLC subjects.

Completion of both studies, TRIDENT-1 and CARE, is estimated to be February 2028 and November 2029, respectively.

To provide efficacy data across histology, 20 subjects will be enrolled in 4 identified common tumour types in TRIDENT-1, to evaluate whether repotrectinib can provide an ORR of at least 30% across TKI-naïve and pre-treated subjects. A futility interim analysis will be conducted when 9 subjects in two of the tumour types have minimum 12 months follow-up. Results will be provided from participants of at least 15 tumour types, including the 4 most common tumours; NSCLC, non-secretory breast, CRC and sarcomas.

The applicant's plan to provide comprehensive data post-authorisation is acknowledged in terms of additional data on efficacy and safety to increase the sample size both in adults and paediatric patients with NTRK positive solid tumours

A delay to completion of the CARE study by almost 2 years was agreed by the PDCO in 2023, and the study expanded into European study sites. It is acknowledged that due to the rarity of NTRK fusions and the distribution across the globe, it is challenging for participating sites to enrol eligible paediatric patients. In order to address the remaining uncertainties in the paediatric population and confirm the B/R in the proposed indication, the applicant will submit the final CARE data post-authorization (**SOB**).

From a safety perspective, safety results from > 600 subjects are considered acceptable for the adult indication. Regarding the paediatric population, a patient pool of 30 is still considered very limited. Uncertainties regarding detection of adverse events specific to this patient group remain, including assessing whether repotrectinib potentially causes developmental impairment. Additional safety data with longer follow-up and larger number of patients for the CARE study will be provided as part of the Specific obligation.

The applicant has planned to report intracranial results along with the totality of results from TRIDENT-1 (n=230) and CARE (n=30) to allow for an overall benefit/risk assessment in patients with NTRK-positive solid tumours. Approximately 20% of patients are expected to have intracranial lesions, but the population size for IC-ORR will depend on the presence of measurable baseline brain lesions and on-study brain imaging by BICR. The applicant expects the accumulated data to be sufficient to demonstrate intracranial efficacy more robustly in the population corresponding to the applied indication.

IC response data in NTRK+ patients are currently limited to 15 patients (paediatric, adolescents and adults) from two ongoing single arm trials. Although promising and support is provided from the ROS1+ NSCLC population in TRIDENT-1, the results are not considered sufficient to finally conclude. The IC data in the NTRK+ population need to be confirmed through final data from TRIDENT-1 and CARE. Therefore, the applicant has committed to provide the final data from TRIDENT-1 in a separate **SOB**.

The clinical data (TRIDENT-1) indicate similar efficacy in NTRK positive patients with resistance mutations as in the overall population. However, the data is limited, and it is not possible to assess response by mutation type. The applicant will report efficacy by baseline resistance mutation status as part of the specific obligation on reporting results from both studies TRIDENT-1 and CARE to further support the ability of repotrectinib to overcome resistance mutations.

- Unmet medical needs will be addressed.

Repotrectinib is intended for patients with NTRK positive solid tumours in advanced stage consisting of rare tumours or common tumours with rare NTRK gene alterations. Such conditions are generally associated with poor prognosis and limited survival and the main goal of treatment is palliation. The TKI-naïve patients have available targeted treatment options through products approved during the last five years, whereas the TKI-pretreated population is in lack of authorised TKI-products. Despite available therapies, there is still an unmet medical need in patients with advanced solid tumours expressing a NTRK gene fusion.

Intracranial (IC) efficacy of a treatment is of clinical relevance to a large proportion of the patients with brain metastases at baseline or developing them at a later stage of the disease and, thus, part of an unmet medical need. The limited data provided in the NTRK+ population through TRIDENT-1 and CARE, indicate IC activity of repotrectinib in line with the overall responses. The data, supported by IC-data from the ROS1+ population, is promising.

Acquired resistance mutations are observed in patients with prior NTRK-TKI treatment and may result in treatment failure. No NTRK-targeted product is currently approved for use after failure to initial TKI treatment. The applicant claims that the compact and rigid structure of repotrectinib and the deep binding to the ATP binding pocket, decrease the tendency to develop resistance mutations of ROS1, TRK and ALK kinases (compared to larger TKIs). Theoretically, based on size of the molecule, these mechanisms to overcome resistance mutations are acknowledged. The clinical data (TRIDENT-1) indicate similar efficacy in NTRK positive patients with resistance mutations as in the overall TKI pretreated population.

In the same setting, Vitrakvi (larotrectinib) and Rozlytrek (entrectinib) have already received a conditional marketing authorization in the EU and repotrectinib is expected to "address the unmet medical needs to a similar or greater extent than what is understood for the already conditionally authorised products" in line with the guideline on CMA (EMA/CHMP/509951/2006, Rev.1).

Although limited data, responses in brain metastases have been shown also for conditionally approved entrectinib. Despite the limitations of cross-study comparison, due to heterogeneity in dataset composition and the small number of subjects representing each tumour types, the available data support the conclusion that repotrectinib, entrectinib and larotrectinib address the unmet medical need to a similar extent in TKI-naïve patients.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Repotrectinib ability to overcome resistance mutations, durable responses and intracranial activity is promising.

Furthermore, based on the limited available data, toxicities of repotrectinib appear overall comparable to other similar treatments.

To conclude, the benefits to public health of immediate availability is considered to outweigh the risks inherent in the fact that additional data are still required.

Additional expert consultation

The comments from the European Organisation for Research and Treatment of Cancer (EORTC) and the patients' organization Lung cancer Europe (LuCE) with regards to repotrectinib were received.

EORTC presented the perspective of the treating physicians recommending that guidance is provided on which line repotrectinib would be most appropriate and on the criteria for when to terminate and start another treatment. This perspective is fully understandable; the CHMP adopts an opinion on the indication, posology and duration of treatment for which the Benefit/risk balance is positive and cannot provide clinical practice guideline. The comments are acknowledged.

The LuCE focused on the problem of accessibility of new treatments across countries and importance of the patient-centred approach with regards to the new treatments instead of solely focusing on the life-prolongation. The challenges related to the access to new treatments across countries is acknowledged, however it cannot be commented upon as it is subject to discussions at the national

level and the purpose of this application is to evaluate the Benefit/Risk of repotrectinib in the intended indication.

Conclusions

The overall benefit/risk balance of Augtyro is positive, subject to the conditions stated in section 'Recommendations'.

Divergent position is appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Augtyro is not similar to dinutuximab beta, retifanlimab, tebentafusp, lutetium (177Lu), avapritinib, cabozantinib, sorafenib tosylate, irinotecan hydrochloride trihydrate, pemigatinib, ripretinib, ivosidenib, dabrafenib, trametinib, telotristat, niraparib, zolbetuximab, mirvetuximab soravtansine and serplulimab within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Augtyro is favourable in the following indication(s):

Augtyro as monotherapy is indicated for the treatment of adult patients with *ROS1*-positive advanced 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 *NTRK* 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 sections 4.4 and 5.1)

The CHMP therefore recommends the granting of the conditional marketing authorisation <under exceptional circumstances>subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order 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).	Q1 2029
In order 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 (CARE).	Q4 2030

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Repotrectinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0335/2023and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Divergent position

Divergent position to the majority recommendation is appended to this report.

5. Appendices

5.1. Divergent position to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 14 NOVEMBER 2024

DIVERGENT POSITION DATED 14 November 2024

Augtyro EMEA/H/C/6005

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Augtyro for the following indication:

Augtyro as monotherapy is indicated for the treatment of adult patients with ROS1-positive advanced non-small cell lung cancer (NSCLC).

The reason for divergent opinion on the line-agnostic ROS1-positive NSCLC indication, is the following:

This application is based on a subpopulation from an ongoing uncontrolled first-in-human study (TRIDENT-1). It is acknowledged that Augtyro in this dataset showed antitumour activity by inducing responses of some durability in the first-line and TKI-pre-treated setting. However, the dataset cannot be considered comprehensive as it is small, the analysis exploratory and, in addition, time related endpoints are difficult to be interpreted because of a lack of randomised controlled data. Having already approved crizotinib and entrectinib in this population a conditional marketing authorisation in the TKI-pre-treated setting only having the ongoing randomised controlled TRIDENT-3 study (comparing repotrectinib vs crizotinib) in the first-line setting as specific obligation is deemed more appropriate.

CHMP Members expressing a divergent opinion:

Janet Koenig

Jan Müller-Berghaus