EU RISK MANAGEMENT PLAN (RMP)

VITRAKVI®

BAY No. 2757556
(Larotrectinib)

No. 2.1

Date of Report:
09 APR 2024

[redacted]

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

EU Risk Management Plan for Vitrakvi® (Larotrectinib)

RMP version to be assessed as part of this application:

RMP Version number: 2.1

Data lock point for the pivotal clinical trial data in this RMP: 20 JUL 2022

Date of final sign-off: 09 APR 2024

Rationale for submitting an updated RMP:

A sample size adjustment for non-interventional PASS ON-TRK was added. Modules were updated with more recent epidemiological, clinical trial and post-marketing data. In addition, editorial changes for close alignment with the EU EMA Guidance on the RMP presentation in integrated format (EMA/164014/2018 Rev.2.0.1) have been introduced.

Presentation of the safety concerns was updated with clinical trials data from the "NTRK Gene Fusion Treated at Recommended Dose Analysis Set (N=335)", and post-marketing data.

Study 20288 (formerly LOXO-TRK-14001) was completed and removed from the Pharmacovigilance Plan.

Summary of significant changes in this RMP:

- Part I – Updated according to latest SmPC.
- Part II SI – Addition of NTRK gene fusion frequency in different tumour types in adults and children. Update of data on incidence and prevalence.
- Part II SII – Relevance to human usage was updated with more recent pivotal clinical trial data (updated dataset of N=418, data cut-off 20 JUL 2022).
- Part II SIII – Overall Exposure in pivotal clinical trials was updated with more recent data (the Overall Safety Analysis Set includes now 418 cancer patients (paediatric and adult) who were enrolled in studies 20288, 20289 and 20290).
- Part II SIV – Exposure of special populations included in clinical trial development programs was updated with the more recent data (updated dataset of N=418).
- Part II SV – Post-authorisation exposure data was updated.
- Part II SVI – No changes.
- Part II SVII – Presentation of the safety concerns was updated with data from the "NTRK Gene Fusion Treated At Recommended Dose Analysis Set (N=335)", and with post-marketing data.
- Part III – Study 20288 was completed and removed from the Pharmacovigilance plan. A sample size adjustment for non-interventional PASS ON-TRK was added. Milestones for studies listed as additional pharmacovigilance activities were updated.
- Part IV – No significant changes.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

- Part V – Risk minimisation measures were updated with the latest SmPC.
- Part VI – Summary was updated to reflect the changes introduced to the respective modules of this RMP.
- Part VII – Annex 7.1: Literature references were updated. New Annex 7.2: Exposure data for patients who reached more than two years of treatment with Vitrakvi® was added.

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number: 2.1

Approved with procedure: EMEA/H/C/004919/II/0036

Date of approval (opinion date): 11 JUL 2024

QPPV signature:

EU QPPV name Dr. Jutta Pospisil

EU QPPV Deputy name [redacted]

Contact person for this RMP [redacted]

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Electronic QPPV signature is attached at the end of the document.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

Table of content

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

Table of tables

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

List of abbreviations

ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
AIDS	Acquired immunodeficiency syndrome
AIEOP-STSC	Associazione Italiana Ematologia Oncologia-Pediatrica Soft Tissue Sarcoma Committee
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ATC	Anaplastic thyroid cancer
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AYA	Adolescents and young adults
BBB	Blood-brain barrier
BCRP	Breast cancer resistance protein
BID	Two times a day (bis in die)
BRAF	B-raf gene
BSA	Body surface area
BUN	Blood urea nitrogen
C1	Cycle 1
C1D1	Cycle 1, day 1
CA 19-9	Cancer antigen 19-9
CAPOX	Capecitabine, oxaliplatin
CBR	Clinical benefit rate
CDC	Centers for Disease Control
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments

C_{max} (unbound)	Maximum unbound concentration
CMN	Congenital mesoblastic nephroma
CNS	Central nervous system
COG	Children's Oncology Group
CP	Child Pugh
CR	Complete response
CRC	Colorectal cancer
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-drug interactions
DILI	Drug-induced liver injury
DILIN	Drug-induced liver injury network
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DOT	Duration of treatment
DRF	Dose range finding
DSUR	Development Safety Update Report
DTC	Differentiated thyroid cancers
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EE-NF	Efficacy-evaluable NTRK Fusion (Analysis Set)
EFD	Embryo-foetal development
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EoT	End of treatment

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

EPAR	European Public Assessment Report
EpSSG	European-paediatric Soft-tissue Sarcoma Study Group
EQ-5D	EuroQoL Five Dimension Questionnaire
ERN	European Reference Network
ESMO	European Society for Medical Oncology
ESRD	End-stage renal disease
EU	European Union
EU-27	27 member states of the European Union
EURACAN	European Reference Network on Rare Adult Cancers
EUROCARE	European Cancer Registry
Eurostat	Statistical Office of the European Communities
FISH	Fluorescence in situ hybridisation
FOLFIRI	Leucovorin calcium, fluorouracil, irinotecan
FOLFIRINOX	Leucovorin calcium, fluorouracil, irinotecan, oxaliplatin
FOLFOX	Leucovorin calcium, fluorouracil, oxaliplatin
FPFV	First patient first visit
FTC	Follicular thyroid cancer
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
GIT	Gastro-intestinal tract
GLOBOCAN	International Agency for Research on Cancer's Global Cancer Database
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practices
H&N	Head and neck
HER2	Human epidermal growth factor 2
hERG	Human ether-à-go-go related gene
HF	Hepatic function
HI	Hepatic impairment
HIV	Human immunodeficiency virus
HLGT	High-level group term

HLT	High-level term
KIT	Proto-oncogene KIT
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization
ID	Ifosfamide, doxorubicin
IFS	Infantile fibrosarcoma
INN	International non-proprietary name
INR	International normalized ratio
IRC	Independent Review Committee
IVA	Ifosfamide, vincristine, actinomycin D
LLN	Lower limit of normal
LPLV	Last Patient Last Visit
LSM	Least-squares means
MASC	Mammary analogue secretory carcinoma
MATE	Multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase gene
MOA	Mechanism of action
mRNA	Messenger ribonucleic acid
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
MYCN	Myelocytomatosis viral -related oncogene
MYH	DNA glycosylase gene
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCIN	National Cancer Intelligence Network
NGF	Nerve growth factor
NGS	Next-Generation Sequencing
NHS	National Health Service
NOAEL	No-observed-adverse-effect level

NORDCAN	Cancer registry of Nordic countries (Sweden, Finland, Iceland, Norway, Denmark, Faroe Islands, and Greenland)
NSC	Non-small cell
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tropomyosin receptor kinase gene
NTRK	Neurotrophic tropomyosin receptor kinase
OAT	Organic anion transporter
OCT	Organic cation transporter
O-NF	Overall NTRK Fusion (Analysis Set)
ORR	Objective response rate
OS	Overall survival
OS	Overall Safety (Analysis Set)
PD	Progressive disease
PDQ	Physician Data Query
PE	Polyethylene
PedsQL-Core	PedsQL (Paediatric Quality of Life Inventory) -Core Module
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P glycoprotein
PK	Pharmacokinetics
PK	Pharmacokinetic
PND	Postnatal day
PO	Per oral
PORT	Postoperative radiation therapy
PP	Polypropylene
PR	Partial response
preRT	Preoperative radiation therapy
PSUR	Periodic safety update report
PT	Preferred term

PTC	Papillary thyroid cancer
QD	Once daily (*quaque die*)
QLQ-C30	Quality of Life Questionnaire-Core 30
QTc	QT interval corrected for heart rate
RAI	Radioactive iodine
RANO	Response Assessment in Neuro Oncology
RARECARE	Information Network on Rare Cancers
RAS	RAS gene
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, version 1.1
RMP	Risk management plan
RMP	Risk Management Plan
RMS	Rhabdomyosarcoma
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SCT	Stem cell transplant
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results Program
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIOP-MMT	International Society of Paediatric Oncology-Malignant Mesenchymal Tumour Committee
SmPC	Summary of Product Characteristics
SOC	System organ class
SRC	Safety Review Committee
STS	Soft tissue sarcoma
TDI	Time-dependent inhibition
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TPN	Total parenteral nutrition
TRAE	Treatment-related adverse event

TRK	Tropomyosin-related kinase
TTR	Time to response
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USA	United States of America
VA	Vincristine, actinomycin D
VAC	Vincristine, actinomycin D, cyclophosphamide
VEGF	Vascular endothelial growth factor

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

Part I: Product(s) overview

Table Part I.1: Product(s) overview	
Active substance (INN or common name):	Larotrectinib
Pharmaco-therapeutic group (ATC Code):	L01XE53
Name of Marketing Authorisation Holder or Applicant:	Bayer AG
Medicinal products to which this RMP refers:	1
Invented name in the European Economic Area (EEA):	Vitrakvi®
Marketing authorisation procedure:	Centralised
Brief description of the product:	Chemical class Larotrectinib is an adenosine triphosphate (ATP)-competitive and selective tropomyosin receptor kinase (TRK) inhibitor.
	Summary of mode of action Vitrakvi® was rationally designed to avoid activity with off target kinases. The target for larotrectinib is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by *NTRK1*, *NTRK2* and *NTRK3* genes, respectively. In a broad panel of purified enzyme assays, larotrectinib inhibited TRKA, TRKB, and TRKC with IC_{50} values between 5-11 nM. The only other kinase activity occurred at 100-fold higher concentrations. In *in vitro* and *in vivo* tumour models, larotrectinib demonstrated anti-tumour activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression. In-frame gene fusion events resulting from chromosomal rearrangements of the human genes *NTRK1*, *NTRK2*, and *NTRK3* lead to the formation of oncogenic TRK fusion proteins. These resultant novel chimeric oncogenic proteins are aberrantly expressed, driving constitutive kinase activity subsequently activating downstream cell signalling pathways involved in cell proliferation and survival leading to TRK fusion positive cancer.
	Important information about its composition

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan

	Vitrakvi® capsules contain no excipients apart from the gelatine capsule shell, titanium dioxide (E 171), and the printing ink. Vitrakvi® solution drug product consists of 100 mL or 50 mL of a 20 mg/mL Vitrakvi® solution. The formulation components are: 100 mL bottle: Purified water, sucrose, hydroxypropylbetadex 0.69, glycerol (E 422), sorbitol (E 420), sodium citrate (E 331), sodium dihydrogen phosphate dihydrate (E 339), citric acid (E 330), propylene glycol (E 1520), potassium sorbate (E 202), methyl parahydroxybenzoate (E 218), citrus fruit flavour, natural flavour 50 mL bottle: Purified water, hydroxypropylbetadex 0.69, sucralose (E 955), sodium citrate (E 331), sodium benzoate (E 211), strawberry flavour, and citric acid (E 330).
Hyperlink to the Product Information	**Module 1.3.1**
Indication(s) in the EEA:	Current Vitrakvi® as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display 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 • who have no satisfactory treatment options.
	Proposed Not applicable
Dosage in the EEA:	Current Larotrectinib (Vitrakvi®) is available as a capsule (25 mg and 100 mg) and oral solution formulation (20 mg/mL) with equivalent oral bioavailability and may be used interchangeably. The patient should be advised to swallow the capsule whole with a glass of water. Due to the bitter taste, the capsule should not be opened, chewed or crushed. The capsules can be taken with or without food but should not be taken with grapefruit or grapefruit juice. The oral solution should be administered by mouth using an oral syringe of 1 mL or 5 mL volume or enterally by using a nasogastric feeding tube. The oral solution can be taken with or without food but should not be taken with grapefruit or grapefruit juice. **Adults** The recommended dose in adults is 100 mg larotrectinib twice daily, until disease progression or until unacceptable toxicity occurs. **Paediatric population**

	Dosing in paediatric patients is based on body surface area (BSA). The recommended dose in paediatric patients is 100 mg/m^2 larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs.
	Proposed Not applicable
Pharmaceutical form(s) and strengths:	Current (if applicable) **Hard capsule (capsules).** High density polyethylene (HDPE)-bottles with a child resistant polypropylene (PP) screw cap with a polyethylene (PE) heat seal layer containing 56 hard capsules. Vitrakvi® 25 mg hard capsules White opaque hard gelatine capsule, size 2 (dimensions 18 x 6 mm), with blue printing of “BAYER”-cross and “25 mg” on body of capsule. Vitrakvi® 100 mg hard capsules White opaque hard gelatine capsule, size 0 (dimensions 22 x 7 mm), with blue printing of “BAYER”-cross and “100 mg” on body of capsule. **20 mg/mL oral solution**. Each mL of oral solution contains larotrectinib sulfate, equivalent to 20 mg of larotrectinib. 50 mL bottle: Colourless to yellow or orange or red or brownish solution. Amber glass (type III) bottle with 50 mL oral solution with a child-resistant polypropylene (PP) screw cap. 100 mL bottle: Clear yellow to orange oral solution. Amber glass (type III) bottle with 100 mL oral solution with a child resistant polypropylene (PP) screw cap with a polyethylene (PE) seal liner.
	Proposed Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Indication: Treatment of Locally Advanced or Metastatic Solid Tumours with *NTRK* Gene Fusion in Adult and Paediatric Patients

Vitrakvi® as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display 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**
- who have no satisfactory treatment options.

The first report of an *NTRK* gene fusion was described in colorectal cancer in 1986 (1, 2). More recently, 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. In very rare tumours, such as infantile fibrosarcoma (IFS), secretory / juvenile breast cancer and mammary analogue secretory cancer (MASC) of the salivary glands, *NTRK* gene fusions are the defining genetic feature of and pathognomonic for these tumour types. TRK fusion cancer may be among the first truly genomically defined cancers, where tumour site of origin is a minor variable in the pathologic description of these cancers and in the choice of systemic treatment for advanced disease.

Although frequency data of *NTRK* gene fusion have been reported in the past few years, systematic estimates on incidence and prevalence of *NTRK* gene fusion are limited. In the following sections, an overview on incidences (section SI.1.1) and prevalences (section SI.1.2) of locally advanced / metastatic disease stages concerning specific tumour types of interest will be given. The latter sections will address the demographic aspects (section SI.1.3), risk factors (section SI.1.4), main existing treatment options (section SI.1.5), natural history of disease (section SI.1.6), and important comorbidities (section SI.1.7) of patients with *NTRK* gene fusion. Further stratification by the frequency of *NTRK* gene fusions in different tumour types in adults and children are summarised in Appendix C Table SI.6 and Appendix C Table SI.7, respectively (Appendix C: *NTRK* gene fusion frequency in different tumour types in adults and children). The data show that TRK fusion cancer is a rare condition.

SI.1.1 Incidence

SI.1.1.1 Results

More studies have been conducted and reported on the frequencies of *NTRK* gene fusion status in the past few years, however incidence data of NTRK fusion cancer (and stage-based incidence) are still limited. A systematic review and meta-analysis of *NTRK* gene fusion frequencies in solid tumours were performed recently (3). This analysis included studies from

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SI - Epidemiology of the indication(s) and target population(s)

North America, Europe, Asia, Brazil, Australia and multi-continental. The estimated global overall *NTRK* gene fusion incidence was reported as 0.52 per 100,000 persons.

The incidence of each cancer type, unselected by TRK fusion status, was calculated and an estimate of *NTRK* gene fusion frequency applied, as illustrated in Table SI.2. The methodology of individual tumour type incidence calculations is provided in Appendix A: Methodology of Incidence Calculations.

Table SI.2: Annual incidence of selected TRK fusion cancer

Disease	Disease Ontology	Incidence Estimate	*NTRK* gene Fusions Observed	Sample Count	*NTRK* Frequency[a]	References
Sarcoma	Infantile fibrosarcoma	90	N/A[b]	N/A[b]	90.56%	Forsythe 2020 (3)
	Sarcoma	17,038	N/A[b]	5,080	0.69%	O'Haire 2023 (4)
	Gastrointestinal stromal tumour	10,900	N/A[b]	1,009	0.59%	O'Haire 2023 (4)
NSC Lung	Lung large cell neuroendocrine	11,249	N/A	919	0.44%	Westphalen 2021 (5)
	Lung adenocarcinoma	123,738	N/A	36,897	0.26%	Westphalen 2021 (5)
Salivary	MASC	229	N/A[b]	N/A[b]	79.68%	Forsythe 2020 (3)
Thyroid	Papillary thyroid cancer	49,526	N/A[b]	1,552	2.04%	O'Haire 2023 (4)
	Papillary thyroid cancer (post-radiation exposure)	24,268	9	62	14.50%	Leeman-Neill 2014 (6)
Primary CNS	Astrocytoma	7,108	N/A	721	0.28%	Westphalen 2021 (5)
	Brain low-grade glioma	8,797	N/A[b]	534	0.94%	O'Haire 2023 (4)
	Non-brainstem high-grade glioma	35,190	6	58	10.30%	Wu 2014 (7)
	Glioblastoma	19,143	N/A	6,434	0.37%	Westphalen 2021 (5)
	Diffuse intrinsic pontine glioma	244	2	54	3.70%	Wu 2014 (7)
	Paediatric neuroblastoma	387	No data[c]	No data	No data	No data
Biliary	Intrahepatic cholangiocarcinoma	9,015	1	555	0.18%	Xu 2023 (8)
	Pancreatic cancer	95,812	N/A	12,195	0.17%	Westphalen 2021 (5)
Colorectal	Colorectal cancer	344,712	N/A[b]	29,578	0.22%	O'Haire 2023 (4)
Other	Spitz neoplasms nevi	53	N/A[b]	128	12.5%	O'Haire 2023 (4)
	Secretory breast carcinoma	538	N/A[b]	N/A[b]	92.87%	Forsythe 2020 (3)
	Head and neck squamous cell carcinoma	69,833	N/A	3,987	0.15%	Westphalen 2021 (5)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Table SI.2: Annual incidence of selected TRK fusion cancer

Disease	Disease Ontology	Incidence Estimate	*NTRK* gene Fusions Observed	Sample Count	*NTRK* Frequency[a]	References
	Congenital mesoblastic nephroma	60	N/A[b]	N/A[b]	21.52%	Forsythe 2020 (3)
	Breast invasive carcinoma	358,885	N/A[b]	N/A[b]	0.10%	Forsythe 2020 (3)
	Skin cutaneous melanoma	107,395	N/A	N/A	0.20%	Gouda 2023 (9)

[a] Some frequencies were at the sample level, not patient-level.
[b] Meta-analytic summary estimate.
[c] No data available for *NTRK* frequency in pancreatic cancer or paediatric neuroblastoma.
CNS = Central nervous system; MASC = Mammary analogue secretory carcinoma of the salivary glands; N/A = Not applicable; NSC = Non-small cell; *NTRK* = Neurotrophic tyrosine kinase receptor gene (referring to family).

SI.1.2 Prevalence

SI.1.2.1 Results

Similarly for incidence, there is limited epidemiologic data reported on the prevalence (and stage-based prevalence) of TRK fusion cancer. As data are still being accumulated for this novel tumour agnostic approach, the overall prevalence of tumour types will be addressed instead. Due to the rarity of most cancer entities in this document, the 5-year prevalence was selected in order to be most inclusive of the population of interest. Thus, the 5-year prevalence of each cancer (unselected by fusion status) was calculated and an estimate of *NTRK* gene fusion frequency is provided. The methodology of individual tumour type 5-year prevalence calculations is provided in Appendix B: Methodology of Prevalence Calculations. Further stratification by the frequency of *NTRK* gene fusions in different tumour types in adults and children are summarized in Appendix C Table SI.6 and Appendix C Table SI.7, respectively (Appendix C: *NTRK* gene fusion frequency in different tumour types in adults and children). The data show that TRK fusion cancer is a rare condition.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Table SI.3: 5-Year Prevalence of selected TRK fusion cancer

Disease	Disease Ontology	Prevalence Estimate	*NTRK* Gene Fusions Observed	Sample Count	*NTRK* Frequency[a]	References
Sarcoma	Infantile fibrosarcoma	173	N/A[b]	N/A[b]	90.56%	Forsythe 2020 (3)
	Sarcoma	62,724	N/A[b]	5,080	0.69%	O'Haire 2023 (4)
	Gastrointestinal stromal tumour	44,531	N/A[b]	1,009	0.59%	O'Haire 2023 (4)
NSC Lung	Lung large cell neuroendocrine	13,948	N/A	919	0.44%	Westphalen 2021 (5)
	Lung adenocarcinoma	153,427	N/A	36,897	0.26%	Westphalen 2021 (5)
Salivary	MASC	879	N/A[b]	N/A[b]	79.68%	Forsythe 2020 (3)
Thyroid	Papillary thyroid cancer	188,638	N/A[b]	1,552	2.04%	O'Haire 2023 (4)
	Papillary thyroid cancer (post-radiation exposure)	92,433	9	62	14.50%	Leeman-Neill 2014 (6)
Primary CNS	Astrocytoma	21,123	N/A	721	0.28%	Westphalen 2021 (5)
	Brain low-grade glioma	26,143	N/A[b]	534	0.94%	O'Haire 2023 (4)
	Non-brainstem high-grade glioma	104,571	6	58	10.30%	Wu 2014 (7)
	Glioblastoma	56,887	N/A	6,434	0.37%	Westphalen 2021 (5)
	Diffuse intrinsic pontine glioma	803	2	54	3.70%	Wu 2014 (7)
	Paediatric neuroblastoma	6,550	No data[c]	No data	No data	No data
Biliary	Intrahepatic cholangiocarcinoma	8,136	1	555	0.18%	Xu 2023 (8)
	Pancreatic cancer	69,139	N/A	12,195	0.17%	Westphalen 2021 (5)
Colorectal	Colorectal cancer	1,036,675	N/A[b]	29,578	0.22%	O'Haire 2023 (4)
Other	Spitz neoplasms nevi	177	N/A[b]	128	12.5%	O'Haire 2023 (4)
	Secretory breast carcinoma	2,207	N/A[b]	N/A[b]	92.87%	Forsythe 2020 (3)
	Head and neck squamous cell carcinoma	333,926	N/A	3,987	0.15%	Westphalen 2021 (5)
	Congenital mesoblastic nephroma	320	N/A[b]	N/A[b]	21.52%	Forsythe 2020 (3)
	Breast invasive carcinoma	1,471,666	N/A[b]	N/A[b]	0.10%	Forsythe 2020 (3)
	Skin cutaneous melanoma	373,334	N/A	N/A	0.20%	Gouda 2023 (9)

[a] Some frequencies were at the sample level, not patient-level.
[b] Meta-analytic summary estimate.
[c] No data available for *NTRK* frequency in pancreatic cancer or paediatric neuroblastoma.
CNS = Central nervous system; MASC = Mammary analogue secretory carcinoma of the salivary glands; N/A = Not applicable; NSC = Non-small cell; *NTRK* = Neurotrophic tyrosine kinase receptor gene (referring to family).

SI.1.3 Demographics of the Population in the Authorized Indication

Currently, there are limited epidemiologic data reported for the demographics of TRK fusion cancer. Available reports are generally limited by small sample size, imperfectly sensitive and specific assay methods, and potential enrichment biases. A recent retrospective study of 33,429 cancer patients based on the Flatiron Health-Foundation Medicine Clinico-Genomic Database was conducted (10). This study included patients whose tumours had been profiled by comprehensive genomic profiling between JAN 2011 and JUL 2018. The results of this study suggest that in patients with tumours harbouring *NTRK* gene fusions, co-occurrence of other actionable biomarkers is generally uncommon, supporting the hypothesis that *NTRK* gene fusions are the primary oncogenic drivers in tumours that harbour them. Although not statistically significant, patients with *NTRK* gene fusions may have an increased risk of death compared with the NTRK wild-type cohort (hazard ratio [HR]: 1.44; 95% confidence interval [CI]: 0.61, 3.37).

An overall description of the cancers best represented in the Vitrakvi® clinical trial experience is provided.

SI.1.3.1 Sarcoma

Infantile fibrosarcoma (IFS)

Paediatric fibrosarcomas can present any time between the newborn period and adolescence (11); however the majority are diagnosed at less than 1 year of age, and are thus referred to as IFS (12). The majority of true IFS are present at birth or before age of 3 months, classified as congenital fibrosarcoma, while the remaining cases become evident by 2 years of age (13-15). Both genders are affected; however, there is a slight male predilection, particularly for diagnoses less than 1 year of age (12, 13). Thus far, there is no evidence to support a differential race / ethnicity distribution for IFS (16).

Soft tissue sarcoma

The mean age at diagnosis for soft tissue sarcoma is 58. Soft tissue sarcomas are more common in newborns and children up to age 5, with declines in incidence in young adulthood. Incidence increase more rapidly again after age 50 (17). In the US, a Surveillance, Epidemiology, and End Results Program (SEER) analysis of data from 1973-2008 found highest incidence among Blacks (5.1 / 100,000), followed by Whites (4.5 / 100,000) and American Indian / Pacific Islander (2.8 / 100,000) (17).

Soft tissue sarcomas comprise 10% of cancers diagnosed before age 25. Rhabdomyosarcoma (RMS) accounts for about 60% of soft tissue sarcoma in cases under 10 years old, but incidence of RMS declines after age 10 (18-21). Alveolar RMS has roughly equal frequency across age groups, sex and ethnicities. Embryonal RMS is more common under age 5, in boys and in Caucasians (22-25). RMS is the most common sub-type of soft tissue sarcoma. Overall, soft tissue sarcoma is more common in males, other than leiomyosarcoma, alveolar soft part sarcoma, and blood vessel sarcoma in adults (18). Soft tissue sarcomas are more common in

Africans due to increased rates of human immunodeficiency virus (HIV) infection and resulting Kaposi's sarcomas (26). RMS incidence is lowest in Asian populations (27-29).

An analysis of 2,031 advanced cancers in patients younger than 21 assayed for *NTRK* gene fusions resulted in 9 cases (0.44%) with *NTRK* gene fusion. Of these, 5 cases were female, 4 had *NTRK3* gene fusions and 5 had *NTRK1* gene fusions. Four of these cases were children younger than 2 with IFS and 2 had *ETV6-NTRK3* fusion breakpoints (30). A second study found *NTRK1* gene fusions in spindle cell sarcoma not otherwise specified with myo / haemangiopericytic growth in an 11 month old male, a 2 year old female, a 51 year old female, and an 80 year old male (31). Among four uterine sarcomas with *NTRK1* gene fusions, patients were aged 46, 27, 47 and 42 (32).

SI.1.3.2 Non-Small Cell Lung Cancer

Lung cancer is the most prevalent cancer worldwide, excluding non-melanoma skin cancers. The median age at diagnosis is approximately 70 years, but NSCLC may present at a younger age (<40 years). NSCLC comprises the majority of lung cancers and is composed of two histological subtypes: adenocarcinoma and squamous cell carcinoma. In Europe in recent decades, the proportion of adenocarcinoma has been increasing and the proportion of squamous cell carcinoma has been decreasing in men, though both subtypes have been increasing in women (33).

SI.1.3.3 Salivary

Salivary gland cancer

Salivary gland cancer is more frequently diagnosed among males than females (1.7:1) and incidence rates increase with age. In the US, rates are higher for Whites than for other race and ethnic groups. Globally, age-adjusted incidence rates among males are highest in the indigenous population of the Australian Northern Territory, in the Canadian Northwest Territories, and among Filipinos in Hawaii. The lowest rates for males are reported in the Eastern Cape province in South Africa, Prince Edward Island in Canada and in Kingston, Jamaica. The highest age-adjusted incidence rates among females are reported among Filipinas in Hawaii, American Indians in Montana, and in Manizales, Colombia, with the lowest rates observed in China, Algeria, and South Africa (34). A RARECARE (Information Network on Rare Cancers) study reported that among 10,514 epithelial salivary gland cancer cases diagnosed in Europe from 1995-2002, cases were more frequently diagnosed among males than females (14.74 per million vs. 11.47 per million) and among persons aged 65 years and older (43.1 per million) compared to those aged 0-24 (0.94 per million) and those aged 25-64 (11.23 per million). Incidence rates were highest in Northern Europe (12.2 per million) compared to Central (11.3 per million), Eastern (11.0 per million), or Southern (11.4 per million) Europe, or the UK and Ireland (10.4 per million) (35).

Mammary analogue secretory carcinoma (MASC) is a rare salivary gland tumour which was first described by Skalova et al in 2010 (36). This entity shares similar histologic and genetic features of another rare malignancy, the secretory carcinoma of breast.

MASC is typically identified by the presence of *ETV6-NTRK3* gene fusion (37, 38). MASC affects both men and women with most studies showing male predominance (38). The ages reported among MASC case series ranges from 14-78 (39).

SI.1.3.4 Thyroid

Thyroid carcinoma

Thyroid cancer occurs more frequently among females than males (approximately three times) and in people aged 25-65 years (40-42). Global incidence among women varies widely, with the highest rates observed in certain countries in South and North America, Italy, Japan, Korea, and the Pacific Islands (41, 43). Incidence is nearly two-fold higher among high-income countries compared to lower-income countries (44). A study of thyroid cancer in England reported higher rates of thyroid cancer incidence among all ethnic groups except Indians, including Pakistanis, Bangladeshis, Black Africans, Black Caribbean, and Chinese, compared to Whites (45). Thyroid cancer incidence has increased in recent decades across the globe, almost entirely due to an increase in differentiated thyroid cancers (DTCs) and papillary thyroid cancers (PTCs) in particular resulting from improved diagnostic accuracy (42). Incidence rates for follicular (FTC), anaplastic (ATC) and medullary (MTC) thyroid cancers have remained relatively stable over the past 30 years.

A series of paediatric papillary thyroid carcinomas identified 7 patients with an *NTRK* gene fusion. Two patients were male, five were female, and the age ranged from 6-18 (median 14) (46). Another study found no gender difference in *NTRK* gene fusion frequency (47).

SI.1.3.5 Primary Central Nervous System

Paediatric neuroblastoma

Neuroblastoma is the most common paediatric extra-cranial solid tumour. The median age at diagnosis is 19 months and 40% of cases are diagnosed under one year of age (48, 49). Neuroblastomas are slightly more frequently diagnosed among males, and have been shown in the US to be more frequent among Whites than Asian / Pacific Islanders, Blacks, and Hispanics (49). Clinical outcomes in patients with neuroblastoma appear to correlate with TRK expression. High TRKA expression in neuroblastoma is a positive prognostic feature and correlates inversely with lower myelocytomatosis viral -related oncogene (MYCN) amplification (50). Preclinically, low-grade neuroblastomas over-expressing TRKA show enhanced survival and terminal differentiation with NGF exposure, the natural ligand for TRKA (50). Conversely, aggressive neuroblastomas overexpressing TRKB exhibit increased drug resistance and angiogenesis, with decreased survival in patients (50).

SI.1.3.6 Biliary

Biliary tract carcinoma (Cholangiocarcinoma)

Biliary tract cancer is slightly more frequent among males than females. Cholangiocarcinoma incidence and mortality rates have been increasing in most Western countries with the exception of Denmark, Norway, and the Czech Republic (51). The incidence of biliary tract cancer is substantially higher (up to 40 times) in China and Thailand than in UK (52). In the

US, rates of gallbladder cancer were higher among all minority ethnic groups, including American Indians / Alaska Natives, Hispanics, Asian / Pacific Islanders, and Blacks, than whites. Rates were higher among females than males for all groups. Rates of extrahepatic cholangiocarcinomas were higher among all minority groups other than Blacks when compared to whites, although the rates were lower among females than males (53). Biliary tract cancers occur more often with increasing age, and a UK study identified higher rates of cholangiocarcinoma among lower socioeconomic status groups compared to affluent groups (54).

Pancreatic cancer

The incidence of pancreatic cancer is approximately 36% higher in males than in females (55). Because patients seldomly exhibit symptoms until an advanced stage of the disease, pancreatic cancer remains one of the most lethal malignant neoplasms that caused 432,242 new deaths in 2018 (GLOBOCAN 2018 estimates) (56). Some geographic variation is present with higher incidence in higher income countries, although this may be due in part to differences in diagnostic techniques and surveillance in low-resource areas. In the US, incidence rates are highest among African-Americans. The median age at diagnosis is 71 years in men and 75 years in women (57). Men are typically diagnosed at a younger age than women and have higher mortality rates (55). Deaths from pancreatic cancer have been increasing in Europe, from 75,439 in 2009 to 82,300 in 2014 (57).

SI.1.3.7 Colorectal

Colorectal cancer

The lifetime risk for colorectal cancer in the US is 4.5% for men and 4.2% for women (58). Colorectal cancer incidence is rare at ages younger than 40. The median age of diagnosis for men is 63 for rectal cancer and 69 for colon cancer. The median age of diagnosis for women is 65 for rectal cancer and 73 for colon cancer (59). Worldwide, the age-standardised incidence rate of colorectal cancer is about 69% higher in men than women (60). The male to female ratio increases with age. Males are also more likely to have cancer in the left colon, and women are more likely to develop right colon cancer (59). African American men and women have the highest incidence and mortality due to colorectal cancer in the US (59).

SI.1.3.8 Other

Secretory breast cancer

Secretory breast carcinoma is a rare, invasive type of breast cancer which accounts for <0.1% of all cases of invasive breast cancer (61). Secretory breast cancer occurs in both males and females and is typically diagnosed during the third decade (median age at diagnosis: 25 years) (62). Most secretory breast cancers are triple-negative hormonal subtype (62, 63). An investigation of the US National Cancer Database from 1998-2011 identified 246 cases of secretory breast cancer. Compared to infiltrating ductal carcinoma (n=1,564,068), secretory breast cancer patients were younger (mean age 56.4 vs. 60.4), more frequently African-American (24.1 vs. 14.8%), and less likely to be hormone receptor-positive (ER: 31 vs. 76%; PR: 43 vs. 65%) (64). A SEER study (1983-2007) identified a median age of 53 years (range

11-86) at diagnosis (61). A series of secretory breast carcinomas tested for *ETV6-NTRK3* gene fusion, identified fusions in 11 / 12 cases. All of the *NTRK* gene fusion cases were female, ranging in age from 6-76 years (65).

Congenital mesoblastic nephroma (CMN)

Most cases of CMN (90%) are diagnosed within the first year of life (median age of diagnosis: 1-2 months) (66, 67). A predominance of males (2:1) was observed among 50 CMN patients enrolled in nephroblastoma trials in Germany, Austria, and Switzerland (68). Right-sided neoplasms were more frequent than left-sided neoplasms (68). A cohort of 51 children also reported, that CMN was more frequently diagnosed among males than females (69).

Melanoma

Melanoma is more common among men, and those who have light skin (70). The median age at diagnosis is 64 in the US, and less than 20% of cases are diagnosed before age 45 (70). In Europe, the incidence is lowest in Mediterranean countries (3-5 / 100,000 per year) and highest in Nordic countries (12-25 / 100,000 per year). The mortality to incidence ratio is higher in patients in Eastern European countries than those in Western Europe (71). In Northern Europe, melanoma is more frequent among those with higher socioeconomic status (72).

SI.1.4 Risk Factors for the Disease

There are no known validated risk factors for the development of a TRK fusion cancer. However, *NTRK* gene fusions result from chromosomal rearrangements following a double strand break in DNA. And risk factors for this structural genomic change include exposure to ionising irradiation, subatomic particles, ions, and electromagnetic waves (e.g. γ-rays and X-rays) (73). However, there are no data connecting these risk factors to specific cancers harbouring *NTRK* gene fusions. Thus, in the following sections, well-characterised primary risk factors are discussed for each cancer type, without specific consideration given to *NTRK* gene fusion status.

SI.1.4.1 Sarcoma

Infantile fibrosarcoma

Currently, there are no identified causal risk factors for IFS, however the majority of the cases exhibit a specific genetic aberration of t(12;15)(q13;q25), which results in the *ETV6-NTRK3* gene fusion (15, 16). Table SI.4 highlights some of the major literature in Europe and worldwide that have studied the frequency of *ETV6-NTRK3* gene fusions in IFS.

Table SI.4: Frequency of *ETV6-NTRK3* gene fusion in infantile fibrosarcoma

Study	Country of Study	Publication Year	Total Patients Sampled (N)	*ETV6-NTRK3* Observed (N)	Frequency of *ETV6-NTRK3* (%)
EpSSG (74)	Europe	2016	39	34	87.2%
AIEOP-STSC & SIOP-MMT (75)	Europe	2010	13	9	69.2%

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Table SI.4: Frequency of *ETV6-NTRK3* gene fusion in infantile fibrosarcoma

Study	Country of Study	Publication Year	Total Patients Sampled (N)	*ETV6-NTRK3* Observed (N)	Frequency of *ETV6-NTRK3* (%)
Bourgeois *et al.* (76)	Canada	2000	11	10	90.9%
Rubin *et al.* (77)	USA	1998	5	3	60.0%
Sheng *et al.* (78)	Japan	2001	10	7	70.0%

EpSSG = European-paediatric Soft-tissue Sarcoma Study Group; AIEOP-STSC = Associazione Italiana Ematologia Oncologia-Pediatrica Soft Tissue Sarcoma Committee; SIOP-MMT = International Society of Paediatric Oncology-Malignant Mesenchymal Tumour Committee.

Although the risk factors for IFS are unknown, Ortega-Garcia et al. identified a suspected cluster of 4 IFS cases that were exposed to a likely human carcinogen candidate dibenz[*a,h*]anthracene (79). Additionally, another 15 environmental substances, of undetermined human carcinogenicity to date, were also found to be potentially associated with fibrosarcoma (79).

Further, several other risk factors have been discussed in their association with soft tissue sarcomas in children, though not necessarily associated with IFS, including congenital anomalies, genetic conditions (Li-Fraumeni syndrome, neurofibromatosis type 1), low socioeconomic status, ionising radiation *in utero*, and parental use of marijuana and cocaine during pregnancy (79).

Soft tissue sarcoma

There are few established risk factors for soft tissue sarcomas beyond the strong association between HIV and Kaposi's sarcoma. Diagnostic X-rays during the first trimester of pregnancy are associated with RMS (80, 81). Radiation exposure is known to cause sarcoma (82, 83).

SI.1.4.2 Non-Small Cell Lung Cancer

Smoking is a well-established risk factor and the main cause for lung cancer (84). Non-small cell lung cancer accounts for 80-90% of lung cancer (84, 85). The squamous cell attributable fraction for ever smoking is 97% (93-98%) for women and 97% (94-98%) for men. The adenocarcinoma attributable fraction for ever smoking is 74% (69-77%) for women and 82% (78-86%) for men (86). The relationship between second-hand smoke and lung cancer subtype is not well understood (87). There are several other known risk factors including exposure to asbestos, arsenic, radon, and non-tobacco-related polycyclic aromatic hydrocarbons, and interesting hypotheses about indoor air pollution suspected to contribute to the relatively high burden of non-smoking related lung cancer in women (84).

SI.1.4.3 Salivary

Salivary gland cancer

Exposure to radiation, including X-radiation and gamma-radiation is an established risk factor for salivary gland cancer, but no other clear risk factors have been established (34, 88).

Although alcohol and tobacco smoking are established risk factors for cancers of the oral cavity, there is no clear association with salivary gland cancer (34).

SI.1.4.4 Thyroid

Thyroid cancer

A history of radiation exposure, particularly in infancy or childhood, is a risk factor for thyroid cancer. Increased incidence of thyroid tumours was observed in children in Ukraine and Belarus born or conceived around the time of the Chernobyl accident (42). Other risk factors include history of goiter or benign thyroid nodules, certain non-thyroid autoimmune conditions, history of cancer, *RET* gene mutation, a family history of thyroid disease or multiple endocrine neoplasia syndrome, iodine imbalance, female gender, and Asian race (40, 41, 44). A modest inverse association has been reported with cruciferous vegetable consumption and risk of thyroid cancer (43). Overweight / obesity and taller adult height have been associated with a modestly increased risk of thyroid cancer (41, 44).

SI.1.4.5 Primary Central Nervous System

Paediatric neuroblastoma

Certain germline mutations have been associated with neuroblastoma, including the anaplastic lymphoma kinase (*ALK)* and *PHOX2B* mutations and germline deletion at the 1p36 or 11q14-23 locus. Approximately 1-2% of neuroblastoma patients have a family history of the disease (40). A recent meta-analysis of case-control studies identified an increased risk of neuroblastoma with maternal smoking during pregnancy (89). Other studies have reported an increased risk of neuroblastoma with alcohol use during pregnancy and maternal intake of diuretics, while a decreased risk was reported with maternal vitamin intake during pregnancy and for children with history of allergies (90).

The BDNF / TRKB loop may up-regulate growth and promote survival of unfavourable neuroblastoma through autocrine or paracrine pathways (91). A splice variant of TRKA, TRKAIII, lacking exons 6, 7, and 9 has been shown to act as a ligand-independent constitutively active receptor tyrosine kinase, analogous to many oncogenes (92). While TRKAI and II splice variants have been shown to possibly suppress neuroblastoma (92, 93), TRKAIII has been shown to create an extremely aggressive tumour phenotype, increasing tumour vascularity and altering the angiogenic phenotype (93). High TRKAIII expression has also been hypothesised to be involved in metastatic bone disease of neuroblastoma (94).

SI.1.4.6 Biliary

Biliary tract carcinoma (Cholangiocarcinoma)

Personal history of gallstones is a risk factor for biliary tract cancer (95). Infection with liver fluke is associated with increased risk of biliary tract cancer and is thought to contribute to the high incidence of biliary tract cancer in Thailand and China. Biliary tract cancer in the West has been associated with chronic biliary inflammation, hepatic parenchyma, and primary sclerosing cholangitis (52). Biliary duct cancer may occur more frequently in patients with a history of primary sclerosing cholangitis, chronic ulcerative colitis, choledochal cysts, or

infections with the liver fluke *Clonorchis sinensis* (96). Congenital malformations and obesity are associated with increased risk of gallbladder cancer, specifically (51).

Pancreatic cancer

Approximately 5-10% of pancreatic cancer is due to inherited germline mutations (57). Hereditary syndromes caused by germline mutations in *BRCA1 / BRCA2*, *p16 / CDKN2A, PRSS1, PRSS2, SPINK1, CTRC, STK11 / LKB1, CFTR, APC, TP53, MSH2*, or *MLH1* genes have been associated with increased risk of pancreatic cancer (55). A family history of pancreatic cancer (at least two first-degree relatives with the disease) is associated with an almost ten-fold risk of disease. Smoking is the strongest established risk factor for pancreas cancer (97). There is a lack of consistency in results from studies of diet and risk of pancreatic cancer, although high intake of alcohol, butter, saturated fats, red meat, and processed foods and low intake of fruits and folate have been associated with increased risk (57, 97). Obesity and taller height have been associated with an increased risk of the disease. A history of gallstones, pancreatitis, diabetes, non-O blood type, and primary sclerosing cholangitis may increase the risk of pancreatic cancer (97). Chronic pancreatitis accounts for approximately 5% of pancreatic cancers. Infection with *Helicobacter pylori*, hepatitis B, and HIV have been reported to have an association with pancreatic cancer although the studies did not always adequately adjust for appropriate confounders (57).

SI.1.4.7 Colorectal

Colorectal cancer

Obesity, smoking, and heavy alcohol consumption are all established risk factors for colorectal cancer (98, 99), as is diabetes mellitus (100, 101). Exposure to ionising radiation (X-ray and γ-ray) is also causally associated with increased risk (82). Sedentary lifestyle is an independent risk factor for colorectal cancer due to cellular changes in skeletal muscle, while physical activity is a well-accepted protective factor (100-102). The Western diet, characterised by high consumption of refined grains, red / processed meats, and high-fat dairy products, is consistently linked with increased colorectal cancer risk. Increased folate and vitamin D intake and long-term regular use of non-steroidal anti-inflammatory drugs have been reported to lower the risk (100, 101). Finally, inflammatory bowel disease, which includes ulcerative colitis and Crohn's disease is associated with increased risk of colorectal cancer (103).

Less than 10% of colorectal cancer cases are associated with inherited gene mutations (100). The two most common familial syndromes that increase risk of colorectal cancer are familial adenomatous polyposis and hereditary non-polyposis colorectal cancer syndrome (100, 101). A personal history of inflammatory bowel disease (i.e., ulcerative colitis and Crohn's disease) is associated with colorectal cancer due to dysplasia induced by chronic inflammation (100, 101). Mutations in the *MYH* gene, a family history of colorectal cancer, and a personal history of adenomas are all associated with increased risk of colorectal cancer (100, 101).

SI.1.4.8 Other

Secretory breast cancer

Secretory breast cancer has not been associated with hormonal changes, family history, endocrinopathy, or genetic abnormalities, but has been described as related to gynecomastia or juvenile papillomatosis (62).

Congenital mesoblastic nephroma

Hydropsy, polyhydramnios, and premature birth are associated with CMN (104).

Melanoma

Ultraviolet exposure is the predominant environmental risk factor for melanoma (71, 105). Artificial ultraviolet light from tanning beds is also an established risk factor (106). Greater adult height has been associated with increased risk of melanoma consistently in the literature (107-110). It is also associated with higher nevus counts (111). While there is no evidence of an association between infection and melanoma risk, there are many studies finding an association between immunosuppression and increased melanoma risk. This includes patients receiving organ transplants, HIV / acquired immunodeficiency syndrome (AIDS) cases, inflammatory bowel disease, non-Hodgkin lymphoma and those with rheumatoid arthritis (112-117). Parkinson's disease has also been associated with increased risk of melanoma (118, 119). A small percentage of melanoma cases (<7%) may be attributable to familial risk (120).

SI.1.5 Main Existing Treatment Options

As the novel tumour agnostic treatment approach is currently in development, there is no standard of care specific for *NTRK* gene fusion cancer patients. Thus, patients are treated with the main existing treatment options available for advanced / metastatic stage, regardless of fusion status, as highlighted below.

SI.1.5.1 Sarcoma

Infantile fibrosarcoma

Presently, there is no standard of care for patients with sarcoma harbouring *NTRK* gene fusion, hence IFS patients with *NTRK* gene fusion adhere to IFS-specific treatment. Because of the rarity of IFS and the young age of patients however, there are no strictly defined standardized treatment guidelines for IFS. In general, surgery is the mainstay of treatment, and is part of a multimodal treatment strategy involving chemotherapy but rarely radiotherapy (74).

US National Cancer Institute (NCI) Physician Data Query (PDQ) cancer information summary for infantile fibrosarcoma lists the following treatment options (121):

1) Surgery followed by observation; 2) Surgery followed by chemotherapy; 3) Chemotherapy followed by surgery; 4) Targeted therapy.

Complete resection is curative in most patients with infantile fibrosarcoma. However, the large size of the lesion frequently makes resection without major functional consequences impossible (for instance, tumours of the extremities often require amputation for complete

excision). The European paediatric group has reported that observation may also be an option in patients with group II disease after surgery. Twelve patients with group II disease received no further therapy and two patients relapsed. One patient obtained a complete remission after chemotherapy. Postoperative chemotherapy was administered to patients with higher group disease and those who progressed. In a subsequent study, only one of seven patients with group II disease progressed during observation; that patient achieved complete remission with chemotherapy.

Preoperative chemotherapy has made a more conservative surgical approach possible; agents active in this setting include vincristine, dactinomycin, cyclophosphamide, and ifosfamide.

Three studies of patients with infantile fibrosarcoma suggest that an alkylator-free regimen is effective and should be used as the first treatment choice in patients with macroscopic disease. Two cases with variant LMNA / *NTRK1* fusions responded to crizotinib.

A patient aged 2 months with infantile fibrosarcoma was initially treated with chemotherapy. At disease progression, a response was seen with pazopanib. No robust data are currently available to support either crizotinib or pazopanib therapies as the standard of care treatment of IFS.

In the European experience, the following therapies are described: For failed resection or unresectable tumours, the non-anthracycline and non-alkylating agent vincristine and actinomycin D (VA) regimen is continued in a responsive tumour, until tumour resectability is possible (74). If tumour shrinkage is not sufficient to perform subsequent conservative resection, ifosfamide (ifosfamide, vincristine, dactinomycin [IVA] regimen) or cyclophosphamide (vincristine, actinomycin D, cyclophosphamide [VAC regimen]) may be added (74, 75). In cases of no response to the VA regimen or evidence of tumour progression, the ifosfamide-doxorubicin (ID) regimen may be used instead (74, 75). Mutilating surgery and external radiotherapy is strongly discouraged but may be performed at the lack of all other options (74).

Soft tissue sarcoma

In the US, National Comprehensive Cancer Network (NCCN) guidelines put strong emphasis on the adherence to the evidence-based recommendations, due to the rarity and complexity of soft tissue sarcomas (122). NCI PDQ Cancer information summary for adult soft tissue sarcoma states (123): “In most cases, a combined modality approach of preoperative radiation therapy (preRT) or postoperative radiation therapy (PORT) is used, rather than the radical surgical procedures, such as amputation, that were used in the past. It may even be possible to use surgery without PORT in selected cases. The role of chemotherapy is not as well defined as is the role of radiation therapy. Because of the evolving nature of the treatment options for this disease, patients should be considered for clinical trials when available”.

The European Society for Medical Oncology (ESMO) state that standard of care treatment for adults with advanced soft tissue sarcoma is surgery when disease is resectable. Standard of care is surgery in metachronous resectable lung metastases without extrapulmonary disease, but chemotherapy is standard in cases of synchronous metastases. Metastases outside of the lungs are also treated with chemotherapy. Anthracyclines are the standard chemotherapy,

though different histological subtypes may be treated with other chemotherapies. Taxanes may be used to treat angiosarcoma, doxorubicin + dacarbazine for leiomyosarcoma, and imatinib for dermatofibrosarcoma protuberans patients. Second-line therapy after anthracyclines may include therapy with ifosfamide, trabectedin, eribulin, dacarbazine, gemcitabine + docetaxel, regorafenib, or pazopanib. Radiation therapy may be used as palliative treatment (124).

Targeted therapies may be used in certain histological subtypes. Crizotinib may be used in inflammatory myofibroblastic tumours with anaplastic lymphoma kinase translocations, sunitinib and cediranib in alveolar soft part sarcoma, sirolimus activity in epithelioid haemangioendothelioma, sunitinib in solitary fibrous tumours, where the molecular target is as yet unclear, and mammalian target of rapamycin inhibitors in malignant perivascular epithelioid cell tumours, which are often associated with the loss of tuberous sclerosis complex 1 / 2 (124). There is no standard of care for soft tissue sarcoma patients with *NTRK* gene fusion.

SI.1.5.2 Non-Small Cell Lung Cancer

As is the case for soft tissue sarcomas, the US NCCN guidelines acknowledge the lack of currently available effective treatment options and suggest that newly diagnosed patients should be considered as candidates for emerging therapies (125). NCI PDQ Cancer information summary for NSCLC states (126):

“In NSCLC, results of standard treatment are poor except for the most localised cancers. All newly diagnosed patients with NSCLC are potential candidates for studies evaluating new forms of treatment.

Surgery is potentially the most curative therapeutic option for this disease. Postoperative chemotherapy may provide an additional benefit to patients with resected NSCLC. Radiation therapy combined with chemotherapy can produce a cure in a small number of patients and can provide palliation in most patients. Prophylactic cranial irradiation may reduce the incidence of brain metastases, but there is no evidence of a survival benefit and the effect of prophylactic cranial irradiation on quality of life is not known. In patients with advanced-stage disease, chemotherapy or epidermal growth factor receptor (EGFR) kinase inhibitors offer modest improvements in median survival, although overall survival is poor.

Chemotherapy has produced short-term improvement in disease-related symptoms in patients with advanced NSCLC. Several clinical trials have attempted to assess the impact of chemotherapy on tumour-related symptoms and quality of life. In total, these studies suggest that tumour-related symptoms may be controlled by chemotherapy without adversely affecting overall quality of life; however, the impact of chemotherapy on quality of life requires more study. In general, medically fit elderly patients with good performance status obtain the same benefits from treatment as younger patients.

The identification of gene mutations in lung cancer has led to the development of molecularly targeted therapy to improve the survival of subsets of patients with metastatic disease. In particular, genetic abnormalities in EGFR, MAPK, and PI3K signalling pathways in subsets of NSCLC may define mechanisms of drug sensitivity and primary or acquired resistance to

kinase inhibitors. EGFR mutations strongly predict the improved response rate and progression-free survival of inhibitors of EGFR. Fusions of ALK with EML4 and other genes form translocation products that occur in ranges from 3% to 7% in unselected NSCLC and are responsive to pharmacological inhibition of ALK by agents such as crizotinib. The MET oncogene encodes hepatocyte growth factor receptor. Amplification of this gene has been associated with secondary resistance to EGFR tyrosine kinase inhibitors".

ESMO guidelines for metastatic NSCLC state that subtyping of NSCLC as well as testing for epidermal growth factor receptor (*EGFR*) mutations, *ROS1* and *ALK* rearrangement is necessary for effective treatment decision-making. Chemotherapy is recommended for all metastatic Stage IV NSCLC patients with *EGFR*- and *ALK*-negative disease using four cycles of platinum-based doublets followed by less toxic maintenance monotherapy. Patients with non-squamous tumours are treated with pemetrexed-based combination chemotherapy, while those with squamous tumours are treated with platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes), and necitumumab + gemcitabine / cisplatin has not been adopted as a standard in Europe for advanced SCC and its use should be carefully evaluated. Maintenance therapy (pemetrexed switch in non-squamous tumours and erlotinib switch in *EGFR*-positive disease) is recommended only in patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 (84).

Second-line treatment of *EGFR*- and *ALK*-negative disease includes chemotherapy with pemetrexed (non-squamous tumours only) or docetaxel. Nivolumab is recommended in both squamous and non-squamous NSCLC. Other second-line treatments include nintedanib + docetaxel (in adenocarcinoma patients), ramucriumab + docetaxel, or pembrolizumab. In tumours unfit for chemotherapy, erlotinib may be used in *EGFR*-wild-type tumours and afatinib may be used in squamous cell tumours (33, 84).

EGFR-positive tumours are treated with an *EGFR* tyrosine kinase inhibitor (TKI) (erlotinib, gefitinib, afatinib, or dacomitinib) as standard of care. Patients who progress after *EGFR* TKI therapy and who have the *EGFR* T790M mutation are treated with osimertinib. Patients without this mutation are treated with platinum-based doublet chemotherapy. Patients whose tumours have the *ALK* rearrangement are treated with first-line ALK TKI including crizotinib, ceritinib, alectinib or brigatinib (not EMA-approved) as first-line therapy and a new generation ALK TKI, if not received previously, as second-line therapy (33, 84).

Radiotherapy may be used for symptom control for patients with bone and brain metastases or for chest wall pain. Stereotactic radiosurgery or resection is recommended for patients with a single brain metastasis. Patients in recursive partitioning analysis class I-II with multiple brain metastases are treated with stereotactic radiosurgery, but those in class III should only receive best supportive care. Zoledronic acid or denosumab is used to reduce skeletal-related events in patients with bone metastases (33, 84). There is no standard of care for NSCLC patients with *NTRK* gene fusion.

SI.1.5.3 Salivary

Salivary gland cancer

US NCI PDQ Cancer information summary for salivary gland tumours lists the following treatment options (88): "The minimum therapy for low-grade malignancies of the superficial portion of the parotid gland is a superficial parotidectomy. For all other lesions, a total parotidectomy is often indicated. The facial nerve or its branches should be resected if involved by tumour; repair can be done simultaneously. Growing evidence suggests that postoperative radiation therapy augments surgical resection, particularly for the high-grade neoplasms, when margins are close or involved, when tumours are large, or when histologic evidence of lymph node metastases is present. Clinical trials, which have been completed in the United States and England, indicate that fast neutron-beam radiation therapy improves disease-free survival and overall survival in patients with unresectable tumours or for patients with recurrent neoplasms. Facilities with fast neutron-beam radiation therapy are of limited availability in the United States. Accelerated hyperfractionated photon-beam radiation therapy has also resulted in high rates of long-term local regional controls. The use of chemotherapy for malignant salivary gland tumours remains under evaluation".

No ESMO guidelines are available for treatment of salivary gland cancers. Standard treatment for Stage IV salivary gland cancer includes fast neutron-beam radiation therapy or accelerated hyperfractionated photon-beam schedules. Standard therapy in Stage IV disease is not curative (88).

There is no standard of care for salivary gland cancer patients with *NTRK* gene fusion. One case has been reported where the pan-TRK inhibitor entrectinib was used to treat MASC. A clinically durable response was achieved, but the patient later developed resistance to the drug (127). A summary of MASC case series reported that most patients were treated with surgery; less frequent treatments included post-operative radiotherapy, post-operative radiotherapy + chemotherapy, and neck dissection (39).

SI.1.5.4 Thyroid

Thyroid cancer

In the US, standard treatment options for advanced thyroid cancer differ depending on the tumour subtype and include the following recommendations (128, 129):

- Iodine-sensitive metastatic papillary and follicular tumours: Radioactive iodine; Thyroid-suppression therapy.
- Iodine-resistant metastatic papillary and follicular tumours: Thyroid-suppression therapy; Targeted therapy (sorafenib and Lenvatinib); Surgery; External Beam Radiation Therapy (EBRT).
- Recurrent papillary and follicular thyroid cancer: Surgery with or without postoperative radioactive iodine (RAI) therapy; Targeted therapy; EBRT; Chemotherapy.

- Locally advanced and metastatic medullary thyroid cancer: Targeted therapy (cabozantinib and vandetanib); Palliative chemotherapy.
- Anaplastic thyroid cancer: Surgery; EBRT; Chemotherapy.

ESMO guidelines state that when the diagnosis of thyroid cancer is made before surgery, initial treatment consists of total or near-total thyroidectomy. Post-operative radioactive iodine therapy is indicated in high-risk patients but not in low-risk patients. Thyroid hormone therapy is initiated post-operatively to replace thyroid hormone (130). Distant metastases are most likely to be cured if they have radioactive iodine uptake, are small size, and if they are located in the lungs. Chemotherapy is not indicated in the distant metastatic population (42, 130). Lenvatinib and sorafenib should be considered the first-line systemic therapy for RAI-refractory differentiated thyroid carcinoma and cabozantnib and vandetanib should be considered the first-line systemic therapy for patients with progressive, metastatic medullary thyroid carcinoma. Although they are not considered standard of care, targeted therapy with TKIs such as sorafenib, cabozantinib, sunitinib, pazopanib, axitinib, vandetanib and motesanib diphosphate have shown promising results in clinical trials in terms of partial response and stable disease rates (130). There is no standard of care for thyroid cancer patients with *NTRK* gene fusion.

SI.1.5.5 Primary Central Nervous System

Paediatric neuroblastoma

The treatment of neuroblastoma has evolved over the past 60 years. Generally, treatment is based on whether the tumour is low, intermediate, or high-risk. US NCI PDQ Cancer information summary for neuroblastoma treatment lists the following treatment options (131):

- "*For patients with low-risk tumours, the approach is either observation or resection. Five-year overall survival (OS) was 97% in a large Children's Oncology Group (COG) study. The ongoing COG study is looking at the reduction of therapy in a limited subset of patients with low-risk tumours.*".
- "*For patients with intermediate-risk tumours, chemotherapy is often given before definitive resection, with the amount and duration based on clinical and tumour biological risk factors and response to therapy. In recent studies, select patients have been observed without undergoing chemotherapy or attempted resection. The 3-year OS rate for intermediate-risk patients was about 96% in a large COG study. The current focus of ongoing studies is to decrease the intensity of chemotherapy in a limited subset of intermediate-risk children to further diminish side effects*".
- "*For high-risk patients, treatment has intensified to include chemotherapy, surgery, radiation therapy, myeloablative therapy and stem cell transplantation, isotretinoin, and immunotherapy, resulting in survival rates of about 50%. Statistically significant improvement in survival was observed in a randomised phase III COG study (ANBL0532 [NCT00567567]) with tandem cycles of myeloablative therapy with SCT compared with a single cycle of myeloablative therapy and SCT among patients, all of whom received immunotherapy".*

No ESMO guidelines exist for paediatric neuroblastoma. Resection is used to treat low- and intermediate-risk patients, either immediately or after tumour reduction with chemotherapy. Chemotherapy with cyclophosphamide + vincristine or etoposide + carboplatin is given to patients with unresectable disease. Radiotherapy for unresectable disease has not conclusively shown to improve survival (132). There is no standard of care for paediatric neuroblastoma patients with *NTRK* gene fusion mutations.

SI.1.5.6 Biliary

Biliary tract carcinoma

Most cases of intrahepatic, extrahepatic, and perihilar bile duct cancer are unresectable and cannot be completely removed by the surgeon. In the US, for patients with unresectable bile duct cancer, management is directed at palliation which includes both palliative therapy and systemic chemotherapy (133, 134). US NCCN guidelines state that participation in prospective clinical trials is the preferred option for treatment of patients with this type of tumour (134).

According to ESMO guidelines, advanced or metastatic biliary tract cancers, systemic chemotherapy with cisplatin / gemcitabine is the standard of care. Gemcitabine monotherapy may be used in ECOG PS 2 patients. There is no established second-line chemotherapy option. The role of radiation therapy is unclear, although radioembolisation may be considered in patients with inoperable intrahepatic cholangiocarcinoma after first-line therapy. Currently, there is no evidence supporting the use of targeted therapies outside of the clinical trial setting (51). There is no standard of care for biliary tract cancer patients with *NTRK* gene fusion.

Pancreatic cancer

The survival rate of patients with any stage of pancreatic exocrine cancer is poor. In the US, NCCN guidelines strongly recommend participation in clinical trials over standard or accepted therapy (135). US NCI PDQ Cancer information summary for pancreatic cancer treatment lists palliative surgery, chemoradiation therapy, and chemotherapy as appropriate treatment options in Stage III disease. For Stage IV and the recurrent pancreatic cancer, palliative therapy and chemotherapy are suggested (136).

Patients with metastatic pancreatic cancer require pain management and therapy for malnutrition and biliary and / or duodenal obstruction. Treatment depends on ECOG PS. Patients with ECOG PS 3 or 4 with significant comorbidities and a short life expectancy only require symptomatic treatment. Some patients with ECOG PS 2 due to heavy tumour load are treated with gemcitabine and nab-paclitaxel. Patients with ECOG PS 2 and high bilirubin levels should be treated with gemcitabine monotherapy. Patients with ECOG PS 0 or 1 with low bilirubin levels may be treated with either FOLFIRINOX therapy or a gemcitabine-nab-paclitaxel combination therapy (57).

Although a few targetable mutations have been identified in pancreatic cancer (*KRAS, TP53, CDKN2A, SMAD4, BRCA2*), no therapy is currently indicated for this disease (57). There is no standard of care for pancreatic cancer patients with *NTRK* gene fusion.

SI.1.5.7 Colorectal

Colorectal cancer

In the US, a distinction is made in the treatment approaches for advanced tumours of the colon and the rectum (137-139). The management of rectal cancer varies somewhat from that of colon cancer because of the increased risk of local recurrence and a poorer overall prognosis. Differences include surgical technique, the use of radiation therapy, and the method of chemotherapy administration. In addition to determining the intent of rectal cancer surgery (i.e., curative or palliative), it is important to consider therapeutic issues related to the maintenance or restoration of normal anal sphincter, genitourinary function, and sexual function. The approach to the management of rectal cancer is multimodal and involves a multidisciplinary team of cancer specialists with expertise in gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology (137, 140). US NCI PDQ Cancer information summary for colon and rectal tumours treatment list the following treatment options:

- Stage III colon cancer: Surgery; Adjuvant chemotherapy (139, 141).
- Stages II and III rectal cancer: Standard treatment options: Surgery; Preoperative chemoradiation therapy; Postoperative chemoradiation therapy; Chemotherapy Regimens: Preoperative oxaliplatin with chemoradiation therapy; Postoperative oxaliplatin-containing regimens; Primary chemoradiation therapy followed by intensive surveillance for complete clinical responders (137, 140).
- Stage IV and recurrent colon cancer: Surgery; Chemotherapy and targeted therapy (139, 141).
- Stage IV and recurrent rectal cancer: Surgery with or without chemotherapy or radiation therapy; First-line chemotherapy and targeted therapy; Palliative therapy (137, 140).
- Treatment of liver metastasis in colon cancer: Surgery; Neoadjuvant chemotherapy for unresectable liver metastases; Local ablation; Adjuvant or neoadjuvant chemotherapy for resectable liver metastases; Intra-arterial chemotherapy after liver resection (139, 141).
- Treatment of liver metastasis in rectal cancer: Surgery; Neoadjuvant chemotherapy; Local ablation; Adjuvant chemotherapy (137, 140).

ESMO guidelines for metastatic colorectal cancer state that determining patients' "fitness" for treatment according to medical condition not due to malignant disease is typically the first step in understanding the treatment goals for patients with metastatic colorectal cancer. "Unfit" patients are offered palliative care. "Fit" patients with resectable metastases are referred to surgery for removal of the metastatic tumour and perioperative chemotherapy. "Fit" patients without the option of surgery are given systematic treatment to shrink the tumours allowing their resection or to reduce tumour burden due to impending clinical threat such as organ dysfunction or severe symptoms. For those "fit" patients where tumour shrinkage or tumour burden are not necessary, the goal is disease control through systemic

therapies and targeted therapies. Assessment of *RAS* mutation status is mandatory at the time of diagnosis, as *RAS* status is a negative predictive biomarker for anti-EGFR antibody therapy. *BRAF* and microsatellite instability testing are also recommended (142).

First-line therapies include a cytotoxic doublet such as fluoropyrimidine plus oxaliplatin or irinotecan (leucovorin calcium, fluorouracil, oxaliplatin [FOLFOX] or leucovorin calcium, fluorouracil, irinotecan [FOLFIRI]), capecitabine combined with oxaliplatin (CAPOX), or in very selected patients the cytotoxic triplet FOLFOXIRI or fluoropyrimidine monotherapy in selected patients with asymptomatic primarily unresectable metastases that are likely to be eligible for multiple lines of treatment and who are not candidates for a combination chemotherapy. Anti-vascular endothelial growth factor (VEGF; bevacizumab) or anti-EGFR (cetuximab and panitumumab) monoclonal antibodies are also used with these combination chemotherapy regimens in the first-line settings for indicated patients. For second-line therapy, the chemotherapy backbone should be changed and an anti-VEGF therapy should be considered for those patients who are bevacizumab naive. Patients treated with bevacizumab in the first-line may also be treated with bevacizumab in the second-line or with aflibercept or ramucirumab (in combination with FOLFIRI) when treated in first-line with oxaliplatin. EGFR antibodies may be used in second-line therapy for patients with *RAS* wild-type disease. Anti-EGFR treatments (cetuximab and panitumumab) should be considered as third-line therapy for indicated patients not previously treated with EGFR antibodies. Further, third-line therapy recommendations consist of regorafenib in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies and trifluridine / tipiracil for patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies (142). There is no standard of care for metastatic colorectal cancer patients with *NTRK* gene fusion.

SI.1.5.8 Other

Secretory breast cancer

There is no current consensus on treatment guidelines for secretory breast cancer (63, 143, 144). According to US NCI PDQ Cancer information summary for unusual cancers of childhood (145, 146): “Breast cancer is the most frequently diagnosed cancer among adolescents and young adults (AYA) women aged 15 to 39 years, accounting for about 14% of all AYA cancer diagnoses. Breast cancer in this age group has a more aggressive course and worse outcome than in older women. Expression of hormone receptors for oestrogen, progesterone, and human epidermal growth factor 2 (HER2) on breast cancer in the AYA group is also different from that in older women and correlates with a worse prognosis. Treatment of the AYA group is similar to that of older women. However, unique aspects of management must include attention to genetic implications (i.e., familial breast cancer syndromes) and fertility”.

ESMO guidelines state that no systemic chemotherapy should be used in low-risk endocrine nonresponsive secretory breast cancer (147, 148). Surgical excision is the primary treatment, with local excision recommended for children and adolescents but simple mastectomy recommended for adults due to an increased rate of recurrence. Patients with node-positive

disease may receive adjuvant chemotherapy (144). The SEER analysis of secretory breast cancer patients reported that 47% underwent lumpectomy and 53% underwent mastectomy, with 42.2% receiving radiation (61). There is no standard of care for secretory breast cancer patients with *NTRK* gene fusion.

Congenital mesoblastic nephroma (CMN)

According to US NCI PDQ Cancer information summary for Wilms tumour and other childhood kidney tumours (66, 149) the standard treatment for Stage III Cellular subtype includes nephrectomy and adjuvant chemotherapy, primarily actinomycin / vincristine and occasionally doxorubicin. Infants younger than 2 months with fully resected Stage III disease may not need chemotherapy (66, 67, 149). Other chemotherapy combinations used successfully in the treatment of CMN include vincristine, cyclophosphamide and doxorubicin; and isophosphamide, carboplatin, and etoposide (104). No ESMO guidelines exist for CMN. There is no standard of care for CMN patients with *NTRK* gene fusion.

Melanoma

For patients with unresectable Stage III, Stage IV, and recurrent melanoma, the following standard of care options are available in the US: Intralesional therapy, immunotherapy, signal-transduction inhibitors, chemotherapy, as well as palliative local therapy (150, 151).

In general, patients with metastatic disease should have the primary tumour or, preferably, the metastasis screened for a mutation in *BRAF* V600. Anti-PD1 antibodies such as pembrolizumab, nivolumab, or an anti-CTLA4 antibody such as ipilimumab should be used for all patients. Those with the *BRAF* mutation may be treated with a *BRAF* or *MEK* inhibitor combination. Cytotoxic therapies such as temozolomide or dacarbazine have shown modest activity (71, 152). There is no standard of care for melanoma patients with *NTRK* gene fusion.

SI.1.6 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

The natural history of the *NTRK* gene fusion population is not available due to limited epidemiologic data. Thus, the natural history of the unselected population is presented for each cancer.

SI.1.6.1 Sarcoma

Infantile fibrosarcoma

IFS is a soft tissue tumour, classified in the heterogeneous group of non-RMS malignant mesenchymal tumours (13, 14). Fibrosarcoma originates predominantly in the connective fibrous tissue of the extremities (arms or legs) before spreading to other surrounding soft tissues including fat, muscles, tendons, nerves, joint tissues, blood vessels, and other fibrous tissue (14-16). Table SI.5 shows the predilection for limbs and trunk for IFS tumour primary sites.

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Table SI.5: Distribution of primary tumour site of infantile fibrosarcoma (16), modified

Primary Site	Frequency (%)
Extremity	45%
Trunk	30%
Head and Neck	15%
Genitourinary	5%
Other	5%

IFS is characterised by a cellular proliferation reproducing fibroblasts of intermediate malignancy (74, 75). IFS typically presents as a sizeable tumour (>5cm) with initial rapid local aggressive growth (16, 74), and is more likely to be diagnosed at the local / regional stages as compared to metastatic (50% local, 40% regional, 10% metastatic) (16).

Further, tumour recurrence rate within a year of initial resection is moderate and ranges anywhere from 17-43% (75). The tumour recurrence commonly presents as local relapse and will rarely relapse to metastatic spread (74). Some patients require amputation due to the extensive involvement of the extremities. Overall, IFS has a very good prognosis and favourable survival with 5- and 10-year overall survival rates between 80-100% (16, 74, 75).

Soft tissue sarcoma

Sarcomas are tumours of putative mesenchymal origin and comprise more than fifty distinct histological subtypes. Soft tissue sarcomas may arise in the muscles, joints, fat, nerves, deep skin tissues, or blood vessels (17).

Using the survival analysis in the European Cancer Registry (EUROCARE)-5 database, the age-weighted relative survival for soft tissue cancer at 5 years was 60.33% in Europe from 2000-2007 (153). A Danish study of 1,246 soft tissue sarcoma patients from 1979-2008 reported 5-year overall survival of 67.2% and a 10-year overall survival of 64%. Patients with low-grade disease did not have significantly increased mortality when compared with the general population. Mortality was greater for patients within the first five years after diagnosis than 5-10 years after diagnosis, compared to the general population (154). A French study of 1,024 metastatic soft tissue sarcoma patients from 1980-2006 reported a median overall survival of 21.3 months. Diagnostic age ≥55 years is an independent prognostic factor for decreased survival. Patients with RMS had the highest risk of mortality compared to other subtypes (155). Important prognostic factors in soft tissue sarcoma include age, duration of symptoms, tumour size, anatomical and compartmental location, radiotherapy, histologic grade, comorbidities before or at diagnosis, as well as the pre-treatment with albumin and haemoglobin levels and neutrophil to lymphocyte ratios (155, 156). Approximately 40-50% of soft tissue sarcoma patients will develop metastatic disease (155).

SI.1.6.2 Non-Small Cell Lung Cancer

NSCLC comprises the majority of lung cancers and is composed of two histological subtypes: adenocarcinoma and squamous cell carcinoma (33). Lung cancer is still increasing both in

prevalence and mortality worldwide (157). In developed countries, the mortality has begun to decline in men, reflecting a decrease in smoking, and is reaching a plateau for women in most European countries and in the United States (157). Lung cancer deaths in women are expected to increase (+7%) in the EU in 2012 (157).

A report from the National Lung Cancer Audit in England reported a median survival of 189 days among 120,745 NSCLC patients diagnosed 2004-2010. Male patients had a significantly decreased survival compared with females. Survival decreased with increasing age, stage, ECOG PS, and Charlson comorbidity index (158). An analysis of Stage IIIB / IV NSCLC patients reported a median survival among untreated patients of 59 days (interquartile range 25-145). Untreated females had a median survival of 65 days, while males had a median survival of 55 days. Survival also decreased by ECOG PS (159). Recurrence rates in resected stage I NSCLC are between 22% and 38% (160-164). Median time to recurrence in resected adenocarcinoma patients was 18 months, with 29.8% 5-year post-recurrence survival (165).

SI.1.6.3 Salivary

Salivary gland cancer

Salivary gland cancer may arise in either the major or minor salivary glands, including the parotid, submandibular and sublingual glands as well as their associated ducts. Salivary gland cancers arise in the parotid gland in 81% of cases, and most are adenocarcinomas, although other histologies include squamous cell carcinoma and other epidermoid carcinomas (34).

The 5-year relative survival rate for major salivary gland cancers is 72.5% and varies by stage, with 93.0% for localized disease, 68.1% for regional disease, and 35.6% for distant disease (34). Using the survival analysis in the EUROCARE-5 database, the age-weighted relative survival for salivary gland cancer at 5 years was 58.91% in Europe from 2000-2007 (153). A study of salivary gland cancer in the Netherlands reported a relative 5-year survival rate of 69% (166). Distant metastases at 10 years post-diagnosis occur in 30-40% of salivary gland cancer cases (167). Prognosis depends on tumour stage, histology, grade, facial nerve paralysis, extra-salivary gland tumour extension, and cervical node involvement (88, 167). An analysis of the US SEER database from 1988-2010 demonstrated 5-year disease-specific survival rate of about 85% among all races; however, a multivariate model demonstrated significantly worse survival among Blacks than Whites (168). Survival rates were higher among females than males regardless of race (34).

A summary of case series that reported disease-related outcomes among 72 MASC patients reported that 14 experienced locoregional recurrence, 2 had distant metastases, and 4 died from the disease (39).

SI.1.6.4 Thyroid

Thyroid cancer

Nearly all thyroid cancers arise in the follicular epithelium. The most common histological subtype is papillary thyroid cancer, followed by medullary thyroid cancer and anaplastic thyroid cancer. Medullary thyroid cancers arise from the calcitonin-producing C-cells (41).

A recent analysis from EUROCARE-5 demonstrated the 5-year relative survival of thyroid cancer patients as 88% in women and 81% in men. Survival was improved among patients with papillary thyroid cancer (5-year relative survival: 98% in women and 94% in men) compared with anaplastic thyroid cancer (5-year relative survival: 14% in women and 12% in men) (169). The most important adverse prognostic factor for thyroid cancer patients is age. Other adverse prognostic factors include follicular histology, primary tumour larger than 4 cm, extrathyroid extension, radioactive iodine-refractory differentiated thyroid carcinoma (170), and distant metastases. Favourable prognostic factors include female gender and multifocality, and regional lymph node involvement (128).

SI.1.6.5 Primary Central Nervous System

Paediatric neuroblastoma

Paediatric neuroblastomas are embryonal tumours arising from neural crest cells that normally mature into the sympathetic nervous system. It is found in the adrenal glands in 40% of localised cases (48).

A global cohort of 8,800 paediatric neuroblastoma patients observed an overall 5-year overall survival rate of 70.0% and a 5-year event-free survival rate of 63.0%. Patients with adrenal tumours had significantly worse event-free survival than all other primary sites, and stage, age, histologic category, grade of differentiation were all prognostic factors (171). A nationwide Finnish study reported the age-adjusted 5-year cumulative survival of neuroblastoma patients diagnosed between ages 0-14 from 2001-2010 of 68.2% (95% Confidence interval [CI]: 50.3 – 80.8%) (172). The 5-year survival rate for neuroblastoma in the US in 2010 was 95% for children younger than 1 year and 68% for children aged 1-14 years (40). Low- and intermediate-risk neuroblastomas have a 5-year survival of 95%, while high-risk neuroblastoma is 50% (48).

SI.1.6.6 Biliary

Biliary tract carcinoma (Cholangiocarcinoma)

Biliary tract cancer is subclassified into intrahepatic cholangiocarcinoma, arising from the biliary tree within the liver, or extrahepatic cholangiocarcinoma, arising from outside the liver parenchyma. Extrahepatic cholangiocarcinoma is further classified into perihilar cholangiocarcinoma, or Klatskin tumour, and distal cholangiocarcinoma. Intrahepatic cholangiocarcinoma comprises approximately 10-20% of tumours, while 30-40% are extrahepatic cholangiocarcinoma and about 50% are perihilar cholangiocarcinoma (51).

The majority of cholangiocarcinoma patients present at an advanced stage with a five-year overall survival rate of approximately 30% (173). The 5-year rate of relative survival for biliary tract cancers in Europe as reported by EUROCARE-5 was 17% (174). Overall survival at 5 years ranges from 21-63% for intrahepatic cholangiocarcinoma (52) and is estimated at only 5% for gallbladder cancer (175). The presence of involved lymph nodes and perineural invasion are associated with unfavourable prognosis, as are a personal history of primary sclerosing cholangitis, an elevated cancer antigen 19-9 (CA 19-9) level, a periductal

infiltrating tumour growth pattern, and a presence of hepatic venous invasion (176). Locoregional recurrence may occur in up to 60% of cases even after curative resection (52).

Pancreatic cancer

Cancer of the pancreas may arise in the cells lining the ducts or in the islet cells. Ductal adenocarcinoma comprises nearly all (80-95%) pancreatic cancers. Cancers arising in the islet cells are neuroendocrine in origin (55, 57). Pancreatic cancer is metastatic at diagnosis in 50% of cases, and localized in only 9% of cases at diagnosis (97).

Approximately 60-70% of pancreatic cancer arises in the head of the pancreas, 20-25% in the body and tail, and 10-20% are diffuse tumours that involve the pancreas. Tumours in the body and tail of the pancreas are more likely to be diagnosed at advanced stages than those in the head due to obstruction of the common bile duct and / or pancreatic duct resulting in clinical symptoms. Tumours may grow into the duodenum, resulting in upper gastroduodenal obstruction (57).

The overall survival rate for all pancreatic cancer Is around 5% at 5 years (57). Using the survival analysis in the EUROCARE-5 database, the age-weighted relative survival for pancreatic cancer at 5 years was 6.9% in Europe from 2000-2007 (153). Tumours with regional spread at diagnosis have a 5-year survival of 11% and those with distant metastases at diagnosis have a 5-year survival of only 2% (97). A systematic review of the burden of pancreatic cancer in Europe reported a median survival after diagnosis of 2.8 – 5.7 months in patients with metastatic disease (177).

SI.1.6.7 Colorectal

Colorectal cancer

Colorectal cancer can arise in the left colon, right colon, or rectum. There is biological and clinical evidence supporting the hypothesis that right- and left-sided colon cancers follow distinct carcinogenesis pathways as they have unique gene expression profiles and embryonic origins (178). Left-sided colon cancers are diagnosed more frequently than right-sided tumours (179).

The median overall survival for patients with metastatic colorectal cancer is approximately 30 months (142). The EUROCARE-4 study reported 5-year relative survival rates for colorectal cancer which varied across region: survival was lowest in Eastern Europe (37.0%) and highest in Central Europe (61.1%) from 2000-2002. Relative survival was slightly higher among females than males in all regions (180). A study of 164,996 colorectal cancer patients from 11 German cancer registries observed a relative 5-year survival of 65.0% in 2006, with survival slightly higher among women than men and decreasing by age group. Patients with advanced disease had a 5-year relative survival of 15.7%, substantially lower than patients with localized disease (90.6%) and those with regional disease (67.6%) (181). Most disease recurrence happens within the first 5 years, and the most common site of metastasis is the liver (182). Patients with left-sided colon cancer have been shown to have improved prognosis over those with right-sided colon cancers (179). Other prognostic factors include performance status, elevated levels of lactate dehydrogenase, white blood cells, serum

albumin, liver transaminases, haemoglobin, platelets, tumour markers like carcinoembryonic antigen and CA 19-9, and pathological tumour grade (183).

SI.1.6.8 Other

Secretory breast cancer

As it is the most frequent breast cancer in children and adolescents, secretory breast cancer was first reported as "juvenile breast carcinoma". Secretory breast cancer may arise anywhere within the breast (63).

Secretory breast cancer patients generally have a favourable prognosis compared to usual ductal carcinoma (62). The SEER analysis of secretory breast cancer patients reported a 5-year overall survival rate of 87.2% and a 10-year overall survival rate of 76.5%. The cancer-specific survival was 94.4% at 5 years and 91.4% at 10 years (61).

Congenital mesoblastic nephroma (CMN)

CMN is a mesenchymal renal tumour that is distinct from Wilms' tumour (184). The two histological subtypes are cellular and classic, with the cellular subtype accounting for 42-63% of cases (104).

When diagnosed within the first 7 months of life, the five-year overall survival rate for CMN is 96% and the five-year event-free survival rate is 94% (67). The cellular variant is associated with worse survival (85%) compared to the classic variant (104). In the cohort of 50 patients enrolled in nephroblastoma trials in Germany, Austria, and Switzerland, 3 / 50 patients experienced recurrence (68).

Melanoma

Melanoma arises in melanocytes and involve activation of oncogenes *NRAS*, *BRAF*, and *KIT* or inactivation of tumour suppression genes *CDKN2A*, *PTEN*, and *TP53* (185).

The estimated median survival of patients with metastatic melanoma is 6-10 months, with <5% of patients surviving five years (186). The EUROCARE-5 study reported that the 5-year relative survival of patients with melanoma was 83% (95% CI: 83 – 84%), with higher values for those in Northern and Central Europe and lowest values in Eastern Europe (74%). Relative survival was higher in females than males and decreased with age. Relative survival also varied by morphology and skin sub-site (187). Higher mortality to incidence ratios have been observed in Central and Eastern Europe (0.35) compared to Western Europe (0.13) (188). Survival has been associated with tumour thickness, mitotic rate, ulceration, site on skin. *BRAF* mutations are also associated with poorer survival (189).

SI.1.7 Important Comorbidities

The comorbidities of the TRK fusion cancer population were not available as the epidemiologic data are limited. Thus, the comorbidities of the unselected population are presented for each cancer.

SI.1.7.1 Sarcoma

Infantile fibrosarcoma

Because of its rarity and young age presentation, little is reported on the comorbidities of IFS, but do include bleeding diathesis, congenital abnormalities, and genetic aberrations. Though the association is not well established to date, Salman et al. report 21 IFS cases in addition to their 2 cases of bleeding diathesis due to consumptive coagulopathy (190). Anaemia, thrombocytopenia, and even hydrops fetalis were found in IFS patients (190). The mortality rate of IFS in those reported cases were attributable to bleeding complications and / or hydrops fetalis (190).

Additionally, Orbach et al. reported 2 cases of congenital abnormalities of ductus arteriosus persistens and occipital haemangioma in the European-paediatric Soft-tissue Sarcoma Study Group (EpSSG) database (74). No differential survival was reported for cases with congenital abnormalities as compared to those without (74).

Further, the polysomies of chromosomes 8, 11, 17, and / or 20 have been reported in many IFS cases (191). Trisomy of chromosome 11 has been suggested to be the primary cytogenetic change, but may not necessarily be the initiating molecular event in the evolution of IFS tumours (191). Indeed, these polysomies are hypothesized to be secondary oncogenic events responsible for histological progression as opposed to tumour initiation (192). As such, there is little evidence to suggest differential mortality / morbidity between IFS cases with polysomies as compared to those without (192).

Soft tissue sarcoma

A Danish analysis of 1,246 soft tissue sarcoma patients reported that 75% of patients had a Charlson comorbidity score of 0, 9% had a score of 1, 9% had a score of 2, and 7% had a score ≥3. The most common comorbidity was “Any tumour” (excluding soft tissue sarcoma) occurring in 9.9% of patients, followed by chronic pulmonary disease in 3.9% of patients and myocardial infarction and cerebrovascular disease both occurring in 3.6% of patients (193).

SI.1.7.2 Non-Small Cell Lung Cancer

For locally advanced NSCLC, the individual patient risk profile can be heterogeneous (194). Long-term smokers still represent the majority of lung cancer patients who typically harbour significant smoking-induced comorbidities such as reduced pulmonary function due to chronic obstructive pulmonary disease, significant cardiac problems related to coronary heart disease and vascular problems due to smoking-induced arteriosclerosis including peripheral and cerebral extension (194).

A nationwide study in Sweden evaluated comorbidities among 19,587 NSCLC patients diagnosed between 2002 and 2011. More than half of patients (55.7%) had a Charlson comorbidity score of 0, 32.4% had a score of 1-2, and 11.9% had a score ≥3. The most prevalent comorbidity was cancer in 13.2% of patients, followed by chronic pulmonary disease in 12.6% of patients, and cerebrovascular disease in 9.0% of patients. Patients with metastatic disease at diagnosis had lower Charlson comorbidity scores than patients with non-metastatic disease at diagnosis (195).

SI.1.7.3 Salivary

Salivary gland cancer

The Dutch Head and Neck Oncology Group identified 666 patients with salivary gland cancer and evaluated comorbidity scores according to the Adult Comorbidity Evaluation-27 index. Sixty-four percent of the cohort had grade 0 comorbidity, 19% had grade 1 comorbidity, 12% had grade 2 comorbidity, and 5% had grade 3 comorbidity. The most common comorbidities were not discussed in the paper (196).

SI.1.7.4 Thyroid

Thyroid cancer

A population-based study of 417 thyroid cancer patients diagnosed between 1993 and 2002 in Eindhoven, the Netherlands, reported that 32% of patients had comorbidities at thyroid cancer diagnosis. The most frequent comorbidity was hypertension in 18% of patients, followed by "other cancers" in 7% of patients, cardiovascular diseases in 6% of patients, and diabetes mellitus in 6% of patients. The prevalence of hypertension among thyroid cancer patients was twice as high as the general population in all age groups examined (197). A retrospective analysis of Polish thyroid cancer patients reported significant associations between thyroid cancer diagnosis and occurrence of hypertension, coronary artery disease, and gastric ulcers (198).

SI.1.7.5 Primary Central Nervous System

Paediatric neuroblastoma

At clinical presentation, neuroblastoma patients may have proptosis and periorbital ecchymosis, abdominal distention, bone pain, pancytopenia, fever, hypertension, anaemia, paralysis, watery diarrhoea, Horner syndrome, and subcutaneous skin nodules (40). Survivors of neuroblastoma may experience chronic pulmonary symptoms and focal nodular hyperplasia later in life (199, 200).

SI.1.7.6 Biliary

Biliary tract carcinoma (Cholangiocarcinoma)

A Greek study of cholangiocarcinoma patients reported that diabetes mellitus and coronary disease were common comorbidities (201). A study of extrahepatic cholangiocarcinoma patients in Spain reported that the median Charlson comorbidity score of the patients was 1 (range 0-4). Forty-six percent of patients had a score of 0, 27% had a score of 1, and 28% had a score ≥2. The most common comorbidities included hypertension (44%), diabetes mellitus (17.6%), chronic obstructive pulmonary disease (16%), coronary heart disease (11.7%), cerebrovascular disease (8.8%), and a history of previous malignancy (5.8%) (157).

Pancreatic cancer

A study of multi-morbidity patterns in European pancreatic ductal adenocarcinoma patients identified patterns of gastric morbidity (heartburn, acid regurgitation, *Helicobacter pylori*

infection, and ulcers) and metabolic syndrome (obesity, type 2 diabetes, hypercholesterolemia, and hypertension (202).

SI.1.7.7 Colorectal

Colorectal cancer

A retrospective study evaluated 751 patients who were diagnosed with metastatic colorectal cancer (CRC) between 2000 and 2013 at 75 years of age or older from 10 oncology centres in Italy (203). This study showed that 34.5%, 14.5%, and 49.7% of patients presented with cardiovascular disease, diabetes, and hypertension, respectively, at the time of diagnosis (203).

A Danish nationwide cohort study of 56,189 colorectal cancer patients diagnosed from 1995-2010 reported that 62% of patients had a Charlson comorbidity score of 0, 17% had a score of 1, 17% had a score of 2, and 3.7% had a score ≥3. The most common comorbidity was another invasive solid tumour (8.6% of patients), followed by cerebrovascular disease in 8.4% of patients, and chronic pulmonary disease in 6.7% of patients (204).

A retrospective cohort study using US claims database evaluated 12,648 patients with a diagnosis of metastatic CRC between 2005 and 2008 (205). The study showed that cardiovascular diseases were the most commonly reported comorbidities (55.7%), followed by digestive system disorders (29%), a history of bleeding (28.3%) and diabetes mellitus (19.1%) (205). Among the patients with comorbid cardiovascular disease (CVD), hypertension was the most common condition (40.8%) followed by heart disease (28%), including cardiac dysrhythmia (14.2%), coronary artery disease (13.5%), congestive heart failure (7.2%), ischemic heart disease (6.2%), arterial thromboembolism (6.2%), and venous thromboembolism (4.6%) (205).

SI.1.7.8 Other

Secretory breast cancer

No published scientific literature was identified that described comorbidities in the secretory breast cancer population. In a Danish study of 47,904 general breast cancer patients diagnosed between 1994 and 2008, 80.2% of patients had a Charlson comorbidity score of 0, 11% had a score of 1, 6.1% had a score of 2, and 2.3% of patients had a score ≥3. Chronic pulmonary disease was the most prevalent comorbidity diagnosed in 4.3% of patients, followed by “any tumour” (excluding breast cancer) in 3.9% of patients and cerebrovascular disease in 3.7% of patients (206).

Congenital mesoblastic nephroma

In the cohort of 50 CMN patients from a nephroblastoma trial in Germany, Austria, and Switzerland, 13 patients were symptomatic and presented with abdominal protrusion, hypertension, and abdominal pain with or without emesis; less frequent symptoms included hypercalcemia and haematuria (68). 71% of gestations with CMN also have polyhydramnios (104).

Melanoma

A Danish analysis of 23,746 melanoma patients diagnosed between 1987 and 2009 and matched to 233,021 members of the general population reported that 81% of melanoma patients had a Charlson comorbidity score of 0, 9.9% had a score of 1, 5.8% had a score of 2, 1.8% had a score of 3, and 1.4% had a score ≥4. "Any cancer" (excluding melanoma and non-melanoma skin cancer) was the most prevalence comorbidity in 3.9% of patients. Cerebrovascular disease was diagnosed in 3.4% of patients and chronic pulmonary disease was found in 2.4% of patients (207).

SI.2 Appendices

SI.2.1 Appendix A: Methodology of Incidence Calculations

SI.2.1.1 Methods Overview

The International Agency for Research on Cancer's Global Cancer Database (105) (Cancer Today), was searched for incidence of each cancer in the 27 member states of the European Union (EU-27). Cancer Today only publishes the incidence of large cancer groupings (e.g., lung cancer, thyroid cancer). To estimate the incidence of a more specific cancer, published literature was used to estimate the proportion of the large cancer grouping comprised by the cancer subtype to apply to the Cancer Today estimate. The latest available incidence data in Cancer Today is for the year 2020. In order to estimate the incidence in the 2023 population, an incidence rate was calculated using the EU-27 population on 01 JAN 2021 (representing the total population at the end of 2020) using the population tables of the Statistical Office of the European Communities' (Eurostat) database (208). The incidence rate was then applied to the population on 01 JAN 2023. Although this method assumes that there has been little to no change in cancer incidence between 2020 and 2023, this was the latest incidence data available for the EU.

The incidence of some specific cancers was identified in several national registries within the EU. The NORDCAN cancer registry of Nordic countries (Sweden, Finland, Iceland, Norway, Denmark, Faroe Islands, and Greenland) (209) and the Netherlands Cancer Registry (210) provided incidence estimates specific to soft tissue sarcoma, gastrointestinal stromal tumours (GIST), salivary gland cancer, intrahepatic cholangiocarcinoma, and head and neck cancers. The latest available incidence data in NORDCAN and the Netherlands registry was for 2020. Thus, an incidence rate was calculated using the population estimate from 01 JAN 2021 in Eurostat, and the rate was applied to the EU-27 population on 01 JAN 2023. In some cases, the published literature was again searched to provide an estimate of the proportion of these cancers comprised by a histological subtype.

IFS was not available in either the Cancer Today database or the national registries. A search of the published literature was conducted to calculate the incidence of IFS in the EU-27. Further detail on each incidence estimate is provided in section SI.2.1.2.

SI.2.1.2 Description of Incidence Calculations

SI.2.1.2.1 Sarcomas

Infantile fibrosarcoma

The incidence of IFS was not available in the Cancer Today database. IFS is a very rare neoplasm, accounting for 10% of all paediatric soft tissue sarcomas, and 5-10% of all sarcomas in infants younger than the age of one (12-15). Despite its rarity, IFS is the most common soft tissue sarcoma in children less than 1 year of age (16). With an incidence range of 0.1-0.2 cases per million in Europe (211), there were 16 cases total in the United Kingdom (UK) from 2010-2013 (212) for example. The incidence rate range (0.1-0.2 / 1,000,000) was applied to the EU-27 population on 01 JAN 2023 from the Eurostat population database (208) (451,385,792) to calculate the incidence range of IFS in the EU-27 ((0.1 / 1,000,000) * 451,385,792 = 45, lower range estimate) - ((0.2 / 1,000,000) * 451,385,792 = 90, upper range estimate).

Sarcoma

The incidence of sarcoma was not available in the Cancer Today database. The incidence of soft tissue sarcoma was identified from the NORDCAN registry (209) and from the Netherlands Cancer Registry (210). The number of incident cases was identified from each registry and the populations of the respective countries for that year were identified from either the NORDCAN registry or the Eurostat population database (208). The total number of incident cases in both registries (968 from NORDCAN + 732 from the Netherlands) was divided by the total population from both regions (27,563,059 from Nordic countries and 17,475,415 from the Netherlands) to calculate an incidence rate. The incidence rate was applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the total number of incident cases of soft tissue sarcoma in the EU-27 (((968+732) / (27,563,059+17,475,415)) * 451,385,792 = 17,038).

Gastrointestinal stromal tumour (GIST)

The incidence of GIST was not available in the Cancer Today database. The incidence of GIST was only available in the Netherlands Cancer Registry (210). There were 422 incident GIST in the Netherlands in 2020. The number of incident cases was divided by the Netherlands population on 01 JAN 2021 from Eurostat (17,475,415) (208). The incidence rate was then applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the total number of incident cases of GIST in the EU-27 ((422 / 17,475,415) * 451,385,792 = 10,900).

SI.2.1.2.2 Non-Small Cell Lung Cancer (NSCLC)

Large cell neuroendocrine lung cancer

The incidence of all lung cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (318,327) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((318,327 / 447,073,916) * 451,385,792 =

321,397). Large cell neuroendocrine tumours comprise 2.1-3.5% of all lung cancers (213, 214). The total incidence of lung cancer was multiplied by 3.5% to calculate the incidence of large cell neuroendocrine lung cancer (321,397 * 0.035 = 11,249).

Lung adenocarcinoma

The incidence of all lung cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (318,327) (105). Non-small cell adenocarcinoma comprises 38.5% of all lung cancer cases (215). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((318,327 / 447,073,916) * 451,385,792 = 321,397). The total incidence of lung cancer was multiplied by 38.5% to calculate the incidence of non-small cell adenocarcinoma (321,397 * 0.385 = 123,738).

SI.2.1.2.3 Salivary

Mammary analogue secretory carcinoma of the salivary glands

The incidence of MASC, or all salivary gland cancer, was not available in the Cancer Today database. The incidence of salivary gland cancer was identified from the NORDCAN cancer registry (209) and from the Netherlands Cancer Registry (210). The total number of incident cases in both registries (313 from NORDCAN + 195 from the Netherlands) was divided by the total population from both regions (27,563,059 from Nordic countries and 17,475,415 from the Netherlands) from the Eurostat population database (208) to calculate a incidence rate. The incidence rate was applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the total number of incident cases of soft tissue sarcoma in the EU-27 in 2023 (((313+195) / (27,563,059+17,475,415)) * 451,385,792 = 5,091). MASC comprises 4-4.5% of all salivary gland cancers (38). The total incidence of salivary gland cancer was multiplied by 4.5% to calculate the incidence of MASC (5,091 * 0.045 = 229).

SI.2.1.2.4 Thyroid

Papillary thyroid cancer

The incidence of all thyroid cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (57,709) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((57,709 / 447,073,916) * 451,385,792 = 58,266). Papillary thyroid cancer comprises 80-85% of all thyroid cancers (216). The total incidence of thyroid cancer was multiplied by 85% to calculate the incidence of papillary thyroid tumours (58,266 * 0.85 = 49,526).

The estimate of papillary thyroid cancer post-radiation exposure was calculated by applying the proportion of thyroid cancer cases that are treated with radiation therapy in the frontline setting (49%), from SEER*STAT, to the 2020 incidence of papillary thyroid cancer (49,526 * 0.49 = 24,268) (217).

SI.2.1.2.5 Primary Central Nervous System (CNS)

Astrocytoma

The incidence of all brain and CNS cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (43,567) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((43,567 / 447,073,916) * 451,385,792 = 43,987). Gliomas comprise 80% of all malignant brain / CNS tumours, and astrocytomas comprise 20.2% of all gliomas (218). The total incidence of brain / CNS cancers was multiplied by 80% and then 20.2% to calculate the incidence of astrocytomas (43,987 * 0.8 * 0.202 = 7,108).

Brain low-grade glioma

The incidence of all brain and CNS cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (43,567) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((43,567 / 447,073,916) * 451,385,792 = 43,987). Low-grade gliomas account for 10-20% of all primary brain tumours (219). The total incidence of brain / CNS cancers was multiplied by 20% to calculate the incidence of low-grade gliomas (43,987 * 0.2 = 8,797), although this estimate was not specific to the brain.

Non-brainstem high-grade glioma

The incidence of all brain and CNS cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (43,567) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((43,567 / 447,073,916) * 451,385,792 = 43,987). High-grade gliomas comprise 80% of all CNS tumours (220). The total incidence of brain / CNS cancers was multiplied by 80% to calculate the incidence of high-grade gliomas (43,987 * 0.8 = 35,190), although this estimate was not specific to the non-brainstem.

Glioblastoma

The incidence of all brain and CNS cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (43,567) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((43,567 / 447,073,916) * 451,385,792 = 43,987). Gliomas comprise 80% of all malignant brain / CNS tumours, and glioblastomas comprise 54.4% of all gliomas (218). The total incidence of brain / CNS cancers was multiplied by 80% and then 54.4% to calculate the incidence of glioblastoma (43,987 * 0.8 * 0.544 = 19,143).

Diffuse intrinsic pontine glioma

The incidence of all brain and CNS cancer diagnosed among ages 0-14 years was taken from the Cancer Today 2020 incidence data for the EU-27 (1,608) (105). This incidence was divided by the EU-27 population aged 0-14 years on 01 JAN 2021 from Eurostat (67,266,044)

to calculate an incidence rate which was applied to the EU-27 population aged 0-14 years on 01 JAN 2023 (67,673,329) ((1,608 / 67,266,044) * 67,673,329 = 1,618). Diffuse intrinsic pontine glioma comprises 10-15% of all paediatric brain tumours. The total incidence of brain / CNS cancers among those aged 0-14 was multiplied by 15% to calculate the incidence of diffuse intrinsic pontine gliomas (1,618 * 0.15 = 244), although this estimate was not specific to the brain.

Paediatric neuroblastoma

The incidence of paediatric neuroblastoma was not available in Cancer Today or the national registries. RARECARENet (221), a centralised network of rare cancers in Europe, provided the incidence rate of neuroblastoma among those aged 0-14 (0.572 per 100,000). This rate was applied to the EU-27 population aged 0-14 on 01 JAN 2023 identified in Eurostat (67,673,329) to calculate a total incidence estimate for paediatric neuroblastoma ((0.572 / 100,000) * 67,673,329 = 387).

SI.2.1.2.6 Biliary

Intrahepatic cholangiocarcinoma

The incidence of intrahepatic cholangiocarcinoma was not available in the Cancer Today database. The incidence of intrahepatic cholangiocarcinoma was only available in the Netherlands Cancer Registry (210). There were 349 cases of incident intrahepatic cholangiocarcinoma in the Netherlands in 2020. The number of incident cases was divided by the Netherlands population on 01 JAN 2021 from Eurostat (17,475,415) (208). The incidence rate was then applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the total number of incident cases of intrahepatic cholangiocarcinoma in the EU-27 ((349 / 17,475,415) * 451,385,792 = 9,015).

Pancreatic cancer

The incidence of pancreatic cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (94,897) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((94,897 / 447,073,916) * 451,385,792 = 95,812).

SI.2.1.2.7 Colorectal

Colorectal cancer

The incidence of colorectal cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (341,419) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((341,419 / 447,073,916) * 451,385,792 = 344,712).

SI.2.1.2.8 Other

Spitz neoplasms / nevi

The incidence of all melanomas diagnosed among ages 0-14 years was taken from the Cancer Today 2020 incidence data for the EU-27 (131)(105). This incidence was divided by the EU-27 population aged 0-14 years on 01 JAN 2021 from Eurostat (67,266,044) to calculate an incidence rate which was applied to the EU-27 population aged 0-14 years on 01 JAN 2023 (67,673,329) ((131 / 67,266,044) * 67,673,329 = 132). Spitz neoplasms comprise 13-40% of all paediatric melanomas (222-224). The total incidence of paediatric melanomas was multiplied by 40% to calculate the incidence of Spitz neoplasms (132 * 0.4 = 53).

Secretory breast carcinoma

The incidence of breast cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (355,457) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((355,457 / 447,073,916) * 451,385,792 = 358,885). Secretory breast carcinoma comprises <0.15% of all breast cancers (62, 63, 144). The total incidence of breast cancer was multiplied by 0.15% to calculate the incidence of secretory breast carcinoma (358,885 * 0.0015 = 538).

Head and neck squamous cell carcinoma

The incidence of head and neck cancer was not available in the GLOBOCAN database. The incidence of head and neck cancer was identified from the NORDCAN cancer registry (209) and from the Netherlands Cancer Registry (210). The total number of incident cases in both registries (4,662 from NORDCAN + 3,080 from the Netherlands) was divided by the total population from both regions (27,563,059 from Nordic countries and 17,475,415 from the Netherlands) from the Eurostat population database (208) to calculate an incidence rate which was applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the total number of incident cases of head and neck cancer in the EU-27 (((4,662+3,080) / (27,563,059 + 17,475,415)) * 451,385,792 = 77,592). Squamous cell carcinomas represent 90% of all head and neck cancers (225, 226). The total incidence of head and neck cancers was multiplied by 90% to calculate the incidence of head and neck squamous cell carcinomas (77,592 * 0.9 = 69,883).

Congenital mesoblastic nephroma (CMN)

The incidence of all kidney cancers diagnosed among ages 0-14 years was taken from the Cancer Today 2020 incidence data for the EU-27 (601) (105). This incidence was divided by the EU-27 population aged 0-14 years on 01 JAN 2021 from Eurostat (67,266,044) to calculate an incidence rate which was applied to the EU-27 population aged 0-14 years on 01 JAN 2023 (67,673,329) ((601 / 67,266,044) * 67,673,329 = 605). CMNs comprise 3-10% of all paediatric renal tumours (104, 227). The total incidence of paediatric kidney cancer was multiplied by 10% to calculate the total number of incident cases of congenital mesoblastic nephroma (605 * 0.1 = 60).

Breast invasive carcinoma

The incidence of breast cancer was taken from the Cancer Today 2020 incidence data for the EU-27 (355,457) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((355,457 / 447,073,916) * 451,385,792 = 358,885).

Skin cutaneous melanoma

The incidence of melanoma was taken from the Cancer Today 2020 incidence data for the EU-27 (106,369) (105). This incidence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate an incidence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((106,369 / 447,073,916) * 451,385,792 = 107,395).

SI.2.2 Appendix B: Methodology of Prevalence Calculations

SI.2.2.1 Methods Overview

Cancer Today (105) was searched for prevalence of each cancer in the 27 member states of the EU (EU-27). Cancer Today only publishes the prevalence of large cancer groupings (e.g. lung cancer, thyroid cancer). To estimate the prevalence of a more specific cancer, published literature was used to identify the proportion of the large cancer grouping comprised by the cancer subtype to apply to the Cancer Today estimate. The Cancer Today database provides prevalence at 1, 3, and 5 years after diagnosis from 2020. These three time-periods are intended to represent different stages of therapy for cancer, with 1-year prevalence representing initial treatment, 3-year prevalence representing clinical follow-up, and 5-year prevalence representing cure. For this analysis, 5-year prevalence was selected in order to be most inclusive of the populations of interest and also to include the rare cancer entities. The latest available prevalence in Cancer Today is 2020. In order to estimate the prevalence in the EU-27 population in 2023, a prevalence rate was calculated using the EU-27 population on 01 JAN 2021 (representing the total population at the end of 2020) using the population tables of the Eurostat database (208). The prevalence rate was then applied to the estimate of the EU-27 population size on 01 JAN 2023. Although this method assumes that there has been little to no change in 5-year cancer prevalence between 2023 and 2023, this was the latest prevalence data available for the EU.

The prevalence of some specific cancers was identified in several national registries within the EU. The NORDCAN (209), the Netherlands Cancer Registry (210), a report of the complete prevalence of cancer in Italy (228), and the National Health Service (NHS) England (229) provided prevalence estimates specific to soft tissue sarcoma, GISTs, salivary gland cancer, paediatric melanomas, paediatric kidney tumours, intrahepatic cholangiocarcinoma, and head and neck cancers. The 5-year prevalence was selected as this was the most complete prevalence available in Cancer Today. The latest available prevalence in NORDCAN, NHS England, and the Netherlands registry was 2020, and in the Italian registry the latest available prevalence year was 2010. Thus, a prevalence rate was calculated using the population estimate from the respective year in Eurostat, and the rate was applied to the EU-27

population on 01 JAN 2023. In some cases, the published literature was again searched to provide an estimate of the proportion of these cancers comprised by a histological subtype.

IFS was not available in either the Cancer Today database or the national registries. The prevalence rate was identified from the United States (US) SEER*Stat database (230) and used to calculate the prevalence of IFS in the EU-27 in 2023. Further detail on each prevalence estimate is provided in section SI.2.2.2.

SI.2.2.2 Description of Prevalence Calculations

SI.2.2.2.1 Sarcomas

Infantile fibrosarcoma

The prevalence rate for IFS was only available in the US SEER*Stat database (231). The age-adjusted 5-year limited-duration prevalence for IFS in 2020 was 0.000038%, and the prevalence rate was applied to the 2023 EU-27 population from the Eurostat population database (208) (0.00000038 * 451,385,792 = 173).

Sarcoma

The prevalence of sarcoma was not available in the Cancer Today database. The prevalence of soft tissue sarcoma was identified from NORDCAN (209), the Netherlands Cancer Registry (210), a report of the complete prevalence of cancer in Italy (228), and the National Health Service (England) (229). The latest available data in each database was 2020 in NORDCAN, the Netherlands, 2020 and England, and 2010 in Italy. The 5-year prevalence was selected as this was the most complete prevalence available in Cancer Today. The 5-year prevalence was identified from each registry and the populations of Nordic Countries, the Netherlands, and Italy on 01 JAN of the following year (2021 for NORDCAN and the Netherlands, and 2011 in Italy), representing the population at the end of the year, were identified from the Eurostat population database (208). Population data from England were not available in Eurostat but were available from the NHS Statistics Office for mid-year (as opposed to the beginning of the year). Thus, the mid-year population estimate from 2020 was used for the English cancer prevalence rates. The sum of the 5-year prevalence in the registries (6,541 from Italy + 3,352 from NORDCAN + 10,182 from England + 2,291 from the Netherlands) was divided by the total population from all regions (59,364,690 from Italy, 27,563,059 from Nordic countries, 56,550,138 from England, and 17,475,415 from the Netherlands) to calculate a prevalence rate which was applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the 5-year prevalence of soft tissue sarcoma in the EU-27 (((6,541 + 3,352 + 10,182 + 2,291) / (59,364,690 + 27,563,059 + 56,550,138 + 17,475,415)) * 451,385,792 = 62,724).

Gastrointestinal stromal tumour (GIST)

The prevalence of GIST was not available in the Cancer Today database. The prevalence of GIST was only available in the Netherlands Cancer Registry (210). The 5-year prevalence of GIST in the Netherlands in 2020 was 1,724. The prevalence was divided by the Netherlands population on 01 JAN 2021 from Eurostat (17,475,415) (208). The prevalence rate was then applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the 5-year prevalence of GIST in the EU-27 ((1,724 / 17,475,415) * 451,385,792 = 44,531).

SI.2.2.2.2 Non-Small Cell Lung Cancer

Large cell neuroendocrine lung cancer

The 5-year prevalence of all lung cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (394,704) (105). This prevalence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((394,704 / 447,073,916) * 451,385,792 = 398,511). Large cell neuroendocrine tumours comprise 2.1-3.5% of all lung cancers (213, 214). The prevalence of lung cancer was multiplied by 3.5% to calculate the 5-year prevalence of large cell neuroendocrine lung cancer (394,704 * 0.035 = 13,948).

Lung adenocarcinoma

The 5-year prevalence of all lung cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (394,704) (105). This prevalence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((394,704 / 447,073,916) * 451,385,792 = 398,511). Non-small cell adenocarcinoma comprises 38.5% of all lung cancer cases (215). The prevalence of lung cancer was multiplied by 38.5% to calculate the 5-year prevalence of non-small cell adenocarcinoma (398,511 * 0.385 = 153,427).

SI.2.2.2.3 Salivary

Mammary analogue secretory carcinoma of the salivary glands

The prevalence of MASC, or all salivary gland cancer, was not available in the Cancer Today database. The 5-year prevalence of salivary gland cancer was identified from NORDCAN (209), the Netherlands Cancer Registry (210), and a report of the complete prevalence of cancer in Italy (228). The sum of the 5-year prevalence in the registries (2,562 from Italy + 1,271 from NORDCAN + 686 from the Netherlands) was divided by the total population from all regions (59,364,690 from Italy, 27,563,059 from Nordic countries, and 17,475,415 from the Netherlands) to calculate a prevalence rate. The prevalence rate was applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the 5-year prevalence of salivary gland cancer in the EU-27 (((2,562 + 1,271 + 686) / (59,364,690 + 27,563,059 + 17,475,415)) * 451,385,792 = 19,538). MASC comprises 4-4.5% of all salivary gland cancers (38). The 5-year prevalence of salivary gland cancer was multiplied by 4.5% to calculate the 5-year prevalence of MASC (19,538 * 0.045 = 879).

SI.2.2.2.4 Thyroid

Papillary thyroid cancer

The 5-year prevalence of thyroid cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (219,807) (105). This prevalence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((219,807 / 447,073,916) * 451,385,792 = 221,927). Papillary thyroid cancer comprises 80-85% of all thyroid cancers (216). The 5-

year prevalence of thyroid cancer was multiplied by 85% to calculate the 5-year prevalence of papillary thyroid tumours (221,927 * 0.85 = 188,638).

The estimate of papillary thyroid cancer post-radiation exposure was calculated by applying the proportion of thyroid cancer cases that are treated with radiation therapy in the frontline setting (49%), from SEER*STAT, to the 5-year prevalence of papillary thyroid cancer (188,638 * 0.49 = 92,433) (217).

SI.2.2.2.5 Primary Central Nervous System (CNS)

Astrocytoma

The 5-year prevalence of all brain and CNS cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (129,465) (105). This prevalence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((219,807 / 447,073,916) * 451,385,792 = 130,714). Gliomas comprise 80% of all malignant brain / CNS tumours, and astrocytomas comprise 20.2% of all gliomas (218). The 5-year prevalence of brain / CNS cancers was multiplied by 80% and then 20.2% to calculate the 5-year prevalence of astrocytoma (130,714 * 0.8 * 0.202 = 21,123).

Brain low-grade glioma

The 5-year prevalence of all brain and CNS cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (129,465) (105). This prevalence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((219,807 / 447,073,916) * 451,385,792 = 130,714). Low-grade gliomas account for 10-20% of all primary brain tumours (219). The 5-year prevalence of brain / CNS cancers was multiplied by 20% to calculate the 5-year prevalence of low-grade gliomas (130,714 * 0.2 = 26,143, although this estimate was not specific to the brain.

Non-brainstem high-grade glioma

The 5-year prevalence of all brain and CNS cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (129,465) (105). This prevalence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((219,807 / 447,073,916) * 451,385,792 = 130,714). High-grade gliomas comprise 80% of all CNS tumours (220). The 5-year prevalence of brain / CNS cancers was multiplied by 80% to calculate the 5-year prevalence of high-grade gliomas (130,714 * 0.8 = 104,571), although this estimate was not specific to the non-brainstem.

Glioblastoma

The 5-year prevalence of all brain and CNS cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (129,465) (105). This prevalence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((219,807 / 447,073,916)

* 451,385,792 = 130,714). Gliomas comprise 80% of all malignant brain / CNS tumours, and glioblastomas comprise 54.4% of all gliomas (218). The 5-year prevalence of brain / CNS cancers was multiplied by 80% and then 54.4% to calculate the 5-year prevalence of glioblastomas (130,714 * 0.8 * 0.544 = 56,887).

Diffuse intrinsic pontine glioma

The 5-year prevalence of paediatric brain / CNS cancers (brain / CNS cancers among those aged 0-14) was identified from the Cancer Today 2020 prevalence data for the EU-27 (5,321) (232). This prevalence was divided by the EU-27 population aged 0-14 years on 01 JAN 2021 from Eurostat (67,266,044) to calculate a prevalence rate which was applied to the EU-27 population aged 0-14 years on 01 JAN 2023 (67,673,329) ((5,321 / 67,266,044) * 67,673,329 = 5,353). Diffuse intrinsic pontine glioma comprises 10-15% of all paediatric brain tumours. The 5-year prevalence of brain / CNS cancers among those aged 0-14 was multiplied by 15% to calculate the 5-year prevalence of diffuse intrinsic pontine gliomas (5,353 * 0.15 = 803), although this estimate was not specific to the brain.

Paediatric neuroblastoma

The prevalence of paediatric neuroblastoma was not available in Cancer Today or the national registries. RARECARENet (221) provided the complete prevalence rate of neuroblastoma in Europe, but the rate was not stratified by age group. However, neuroblastomas are most frequent in children and adolescents. The complete prevalence rate of neuroblastoma was 1.451 / 100,000, which was applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the prevalence of neuroblastoma in the EU ((1.451 / 100,000) * 451,385,792 = 6,550), although the prevalence was not specific to the paediatric population.

SI.2.2.2.6 Biliary

Intrahepatic cholangiocarcinoma

The 5-year prevalence of intrahepatic cholangiocarcinoma was not available in the Cancer Today database. The prevalence of intrahepatic cholangiocarcinoma was only available in the Netherlands Cancer Registry (210). The 5-year prevalence of intrahepatic cholangiocarcinoma in the Netherlands in 2020 was 315. The prevalence was divided by the Netherlands population on 01 JAN 2021 from Eurostat (17,457,415) (208). The prevalence rate was then applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the 5-year prevalence of intrahepatic cholangiocarcinoma in the EU-27 ((315 / 17,457,415) * 451,385,792 = 8,136).

Pancreatic cancer

The 5-year prevalence of pancreatic cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (68,479) (105). This prevalence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((68,479 / 447,073,916) * 451,385,792 = 69,139).

SI.2.2.2.7 Colorectal

Colorectal cancer

The 5-year prevalence of colorectal cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (1,026,772) (105). This prevalence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((1,026,772 / 447,073,916) * 451,385,792 = 1,036,675).

SI.2.2.2.8 Other

Spitz neoplasms / nevi

The 5-year prevalence of paediatric melanomas (melanomas among those aged 0-14) was identified from the Cancer Today 2020 prevalence data for the EU-27 (441) (232). This prevalence was divided by the EU-27 population aged 0-14 years on 01 JAN 2021 from Eurostat (67,266,044) to calculate a prevalence rate which was applied to the EU-27 population aged 0-14 years on 01 JAN 2023 (67,673,329) ((441 / 67,266,044) * 67,673,329 = 444). Spitz neoplasms comprise 13-40% of all paediatric melanoma (222-224). The 5-year prevalence of paediatric melanoma was multiplied by 40% to calculate the 5-year prevalence of Spitz neoplasms (444 * 0.4 = 177).

Secretory breast carcinoma

The 5-year prevalence of breast cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (1,457,608) (105). This prevalence was divided by the EU-27 population on 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((1,457,608 / 447,073,916) * 451,385,792 = 1,471,666). Secretory breast carcinoma comprises <0.15% of all breast cancers (62, 63, 144). The 5-year prevalence of breast cancer was multiplied by 0.15% to calculate the 5-year prevalence of secretory breast carcinoma (1,471,666 * 0.0015 = 2,207).

Head and neck squamous cell carcinoma

The 5-year prevalence of head and neck cancer was not available in the GLOBOCAN database. The 5-year prevalence of head and neck cancer was identified from NORDCAN (209), the Netherlands Cancer Registry (210) a report of the complete prevalence of cancer in Italy (228), and the Macmillan-NCIN Cancer Prevalence Project (UK) (233). The sum of the 5-year prevalence in the registries (36,933 from Italy + 15,667 from NORDCAN + 41,880 from the UK + 16,456 from the Netherlands) was divided by the total population from all regions (59,364,690 from Italy, 26,592,090 from Nordic countries, 63,022,532 from UK, and 17,081,507 from the Netherlands) to calculate a prevalence rate. The prevalence rate was applied to the total population of the EU-27 on 01 JAN 2023 (511,522,671) to calculate the 5-year prevalence of head and neck cancer in the EU-27 (((36,933 + 15,667 + 41,880 + 16,456) / (59,364,690 + 26,592,090 + 63,022,532 + 17,081,507)) * 511,522,671 = 341,720). Squamous cell carcinomas comprise 90% of all head and neck cancers (225, 226). The 5-year prevalence of head and neck cancers was multiplied by 90% to calculate the 5-year prevalence of head and neck squamous cell carcinomas (341,720 * 0.9 = 307,548).

The 5-year prevalence of head and neck cancer was not available in the Cancer Today database. The 5-year prevalence of head and neck cancer was identified from NORDCAN (209), the Netherlands Cancer Registry (210) a report of the complete prevalence of cancer in Italy (228), and the National Health Service (England) (229). The sum of the 5-year prevalence in the registries (36,933 from Italy + 34,196 from England + 10,798 from the Netherlands + 16,177 from the Nordic countries) was divided by the total population from all regions (59,364,690 from Italy, 56,550,138 from England, 17,475,415 from the Netherlands, and 27,563,059 from the Nordic countries) to calculate a prevalence rate. The prevalence rate was applied to the total population of the EU-27 on 01 JAN 2023 (451,385,792) to calculate the 5-year prevalence of head and neck cancer in the EU-27 (((36,933 + 34,196 + 10,798 + 16,177) / (59,364,690 + 56,550138 + 17,475,415 + 27,563,059)) * 451,385,792 = 371,029). Squamous cell carcinomas comprise 90% of all head and neck cancers (225, 226). The 5-year prevalence of head and neck cancers was multiplied by 90% to calculate the 5-year prevalence of head and neck squamous cell carcinomas (371,029 * 0.9 = 333,926).

Congenital mesoblastic nephroma (CMN)

The 5-year prevalence of paediatric kidney cancer (kidney cancer among those aged 0-14) was identified from the Cancer Today 2020 prevalence data for the EU-27 (3,185) (232). This prevalence was divided by the EU-27 population aged 0-14 years on 01 JAN 2021 from Eurostat (67,266,044) to calculate a prevalence rate which was applied to the EU-27 population aged 0-14 years on 01 JAN 2023 (67,673,329) ((3,185 / 67,266,044) * 67,673,329 = 3,204). CMNs comprise 3-10% of all paediatric renal tumours (104, 227). The 5-year prevalence of paediatric kidney cancer was multiplied by 10% to calculate the 5-year prevalence of CMN (3,204 * 0.1 = 320).

Breast invasive carcinoma

The 5-year prevalence of breast cancer was taken from the Cancer Today 2020 prevalence data for the EU-27 (1,457,608) (105). This prevalence was divided by the EU-27 population on 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((1,457,608 / 447,073,916) * 451,385,792 = 1,471,666).

Skin cutaneous melanoma

The 5-year prevalence of melanoma was taken from the Cancer Today 2020 prevalence data for the EU-27 (369,768) (105). This prevalence was divided by the EU-27 population on 01 JAN 2021 from Eurostat (447,073,916) to calculate a prevalence rate which was applied to the EU-27 population on 01 JAN 2023 (451,385,792) ((369,768 / 447,073,916) * 451,385,792 = 373,334).

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EU Risk Management Plan
Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.2.3 Appendix C: *NTRK* gene fusion frequency in different tumour types in adults and children

SI.2.3.1 *NTRK* gene fusion frequency in adult tumour types

Appendix C Table SI.6: NTRK gene fusion frequency in adult tumour types

Disease	Disease Ontology	Frequency						Year	Ref
		Number of Fusions Observed				Sample Count	Freq		
		NTRK1	*NTRK2*	*NTRK3*	NTRK All				
Sarcoma	Sarcoma	1	0	0	1	103	1.0%	2014	(234)
		2	0	0	2	263	0.8%	2018	(235)
		9	0	4	13	1,915	0.68%	2020	(236)
		N/A	N/A	N/A	N/A	5,080	0.69%	2023	(4)
		N/A	N/A	N/A	N/A	2,173	1.70%	2021	(5)
		N/A	N/A	N/A	34	N/A	0.8%	2023	(9)
		N/A	N/A	N/A	17	571	2.98%	2023	(8)
	Gastrointestinal stromal tumours	0	0	1	1	31	3.2%	2016	(237)
		0	0	1	1	186	0.5%	2016	(238)
		N/A	N/A	N/A	N/A	1,009	0.59%	2023	(4)
		N/A	N/A	N/A	N/A	604	0.83%	2021	(5)
Non-small cell lung	Lung large cell neuroendocrine cancer	1	0	0	1	60	1.7%	2014	(239)
		N/A	N/A	N/A	N/A	69	1.45%	2023	(4)
		N/A	N/A	N/A	N/A	919	0.44%	2021	(5)
		0	0	0	0	467	0.0%	2021	(240)
	Lung adenocarcinoma	0	1	0	1	513	0.2%	2014	(234)
		1	1	2	4	4,073	0.1%	2019	(241)
		6	1	2	9	3,993	0.23%	2020	(236)
		N/A	N/A	N/A	N/A	8,982	0.09%	2023	(4)
		7	N/A	N/A	7	8,167	0.09%	2021	(242)
		N/A	N/A	N/A	N/A	36,897	0.26%	2021	(5)
	Squamous cell carcinoma	0	0	0	0	502	0.0%	2018	(235)
		N/A	N/A	N/A	N/A	9,235	0.17%	2021	(5)
Salivary	Mammary analogue secretory carcinoma of the salivary glands	0	0	15	15	15	100.0%	2013	(37)
		N/A	N/A	6	6	6	100.0%	2017	(243)

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EU Risk Management Plan
Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Appendix C Table SI.6: NTRK gene fusion frequency in adult tumour types

Disease	Disease Ontology	Frequency						Year	Ref
		Number of Fusions Observed				Sample Count	Freq		
		NTRK1	*NTRK2*	*NTRK3*	NTRK All				
Thyroid	Papillary thyroid cancer	N/A	N/A	7	7	14	50.0%	2018	(244)
		N/A	N/A	N/A	N/A	48	83.33%	2023	(4)
		N/A	N/A	N/A	N/A	N/A	79.68%	2020	(3)
		N/A	N/A	N/A	N/A	12	66.67%	2021	(5)
	Acinic cell carcinoma	N/A	N/A	3	3	72	4.17%	2016	(245)
		N/A	N/A	N/A	N/A	N/A	11.11%	2020	(3)
		N/A	N/A	N/A	N/A	183	2.73%	2021	(5)
		9	N/A	N/A	9	76	11.8%	1998	(246)
		4	N/A	N/A	4	33	12.1%	2006	(247)
		0	0	3	3	151	2.0%	2014	(6)
		4	N/A	6	10	484	1.9%	2014	(248)
		N/A	N/A	N/A	57	846	6.7%	2021	(249)
		N/A	N/A	N/A	N/A	1,552	2.04%	2023	(4)
		N/A	N/A	N/A	N/A	1,038	1.83%	2021	(5)
	Papillary thyroid cancer (post-radiation exposure)	0	0	9	9	62	14.5%	2014	(6)
		N/A	N/A	N/A	N/A	59	5.08%	2023	(4)
		N/A	N/A	N/A	4	73	5.5%	2023	(250)
Primary CNS	Glioblastoma	2	0	0	2	162	1.2%	2014	(251)
		3	9	2	14	982	1.4%	2019	(241)
		N/A	N/A	N/A	N/A	1,095	1.02%	2023	(4)
		N/A	N/A	N/A	N/A	6,434	0.37%	2021	(5)
	Astrocytoma	0	3	0	3	96	3.1%	2013	(252)
		N/A	N/A	N/A	N/A	316	2.22%	2023	(4)
		N/A	N/A	N/A	N/A	721	0.28%	2021	(5)
	Brain low-grade glioma	0	2	0	2	461	0.4%	2014	(234)
		N/A	N/A	N/A	N/A	534	0.94%	2023	(4)
	Non-brainstem high-grade glioma	3	2	1	6	58	10.3%	2014	(253)

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EU Risk Management Plan
Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Appendix C Table SI.6: NTRK gene fusion frequency in adult tumour types

Disease	Disease Ontology	Frequency						Year	Ref
		Number of Fusions Observed				Sample Count	Freq		
		NTRK1	*NTRK2*	*NTRK3*	NTRK All				
Biliary	Intrahepatic cholangiocarcinoma	1	0	0	1	28	3.6%	2014	(254)
		1	N/A	0	1	242	0.4%	2017	(255)
		0	N/A	0	0	195	0%	2018	(256)
		0	0	0	0	36	0%	2018	(235)
		N/A	N/A	N/A	1	555	0.18%	2023	(8)
	Hepatocellular carcinoma	0	0	0	0	374	0.0%	2018	(235)
		N/A	N/A	N/A	2	1,133	0.18%	2023	(8)
GI	Esophageal carcinoma	0	0	0	0	185	0.0%	2018	(235)
	Gastric adenocarcinoma	0	0	0	0	414	0.0%	2018	(235)
		0	0	0	0	477	0.0%	2022	(257)
	Colorectal cancer	0	0	2	2	286	0.7%	2014	(234)
		2	0	0	2	1,272	0.2%	2019	(241)
		N/A	N/A	N/A	N/A	29,578	0.22%	2023	(4)
		1	0	0	1	917	0.1%	2022	(258)
		3	0	0	3	1,200	0.25%	2018	(259)
		N/A	N/A	N/A	N/A	N/A	0.2%	2023	(9)
		N/A	N/A	N/A	7	1,225	0.6%	2023	(8)
	Appendiceal adenocarcinoma	0	N/A	0	0	19	1.3%	2017	(255)
		1	N/A	N/A	1	208	0.48%	2020	(236)
		N/A	N/A	N/A	N/A	1,217	0.0%	2021	(5)
	Goblet cell carcinoid of the appendix	0	N/A	0	0	8	0.0%	2017	(255)
	Mucinous adenocarcinoma of the appendix	1	N/A	0	1	48	2.1%	2017	(255)
	Signet ring cell type of the appendix	0	N/A	0	0	5	0.0%	2017	(255)
Kidney	Renal clear cell carcinoma	0	0	0	0	541	0.0%	2018	(235)
		N/A	N/A	N/A	N/A	1,585	0.06%	2021	(5)
	Renal papillary cell carcinoma	0	0	0	0	291	0.0%	2018	(235)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Appendix C Table SI.6: NTRK gene fusion frequency in adult tumour types

Disease	Disease Ontology	Frequency						Year	Ref
		Number of Fusions Observed				Sample Count	Freq		
		NTRK1	*NTRK2*	*NTRK3*	NTRK All				
	Renal chromophobe tumour	0	0	0	0	66	0.0%	2018	(235)
Gynecological	Cervical carcinoma	1	0	0	1	68	1.5%	2019	(241)
		N/A	N/A	N/A	N/A	N/A	0.33%	2023	(4)
		N/A	N/A	N/A	N/A	N/A	0.36%	2020	(3)
	Uterine / endometrial carcinoma	0	0	0	0	242	0.0%	2018	(235)
		N/A	N/A	N/A	N/A	1,080	0.19%	2023	(4)
	Ovarian carcinoma	0	0	0	0	428	0.0%	2018	(235)
		N/A	N/A	N/A	N/A	11,590	0.18%	2023	(4)
Other	Pheochromocytoma / paraganglioma	0	0	0	0	184	0.0%	2018	(235)
	Lacrimal gland carcinoma	N/A	N/A	1	1	350	0.3%	2018	(260)
	Thymoma	0	0	0	0	120	0.0%	2018	(235)
	Mesothelioma	0	0	0	0	87	0.0%	2018	(235)
	Pancreatic adenocarcinoma	0	0	1	1	179	0.6%	2018	(235)
		N/A	N/A	N/A	3	3,426	0.09%	2018	(261)
		N/A	N/A	N/A	N/A	1,492	0.34%	2023	(4)
		N/A	N/A	N/A	N/A	N/A	0.31%	2020	(3)
		N/A	N/A	N/A	N/A	12,195	0.17%	2021	(5)
	Bladder carcinoma	0	0	0	0	414	0.0%	2018	(235)
		N/A	N/A	N/A	N/A	284	0.0%	2021	(5)
		N/A	N/A	N/A	0	96	0%	2023	(8)
	Adrenocortical carcinoma adult	0	0	0	0	79	0.0%	2018	(235)
		N/A	N/A	N/A	N/A	566	0.53%	2021	(5)
	Prostate adenocarcinoma	0	0	0	0	502	0.0%	2018	(235)
		N/A	N/A	N/A	N/A	141	0.71%	2021	(5)
	Testicular tumour	0	0	0	0	156	0.0%	2018	(235)
	Secretory breast carcinoma	0	0	11	11	12	91.7%	2002	(262)
		N/A	N/A	N/A	N/A	44	88.64%	2023	(4)

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EU Risk Management Plan
Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Appendix C Table SI.6: NTRK gene fusion frequency in adult tumour types

Disease	Disease Ontology	Frequency						Year	Ref
		Number of Fusions Observed				Sample Count	Freq		
		NTRK1	*NTRK2*	*NTRK3*	NTRK All				
		N/A	N/A	N/A	N/A	N/A	92.87%	2020	(3)
	Acute myeloid leukemia	0	0	1	1	N/A	N/A	2011	(263)
	Breast invasive carcinoma	0	0	1	1	1,072	0.1%	2014	(234)
		0	1	1	2	1,119	0.2%	2018	(235)
		0	0	1	1	769	0.1%	2019	(241)
		N/A	N/A	N/A	1	323	0.3%	2023	(8)
		N/A	N/A	N/A	N/A	4,854	0.08%	2023	(4)
		N/A	N/A	N/A	N/A	N/A	0.10%	2020	(3)
		10	0	6	16	12,214	0.13%	2018	(264)
		N/A	N/A	N/A	42	N/A	0.3%	2023	(9)
	Skin cutaneous melanoma	0	0	1	1	374	0.3%	2014	(234)
		0	0	1	1	476	0.2%	2018	(235)
		N/A	N/A	N/A	N/A	395	0.76%	2023	(4)
		N/A	N/A	N/A	N/A	N/A	0.31%	2020	(3)
		N/A	N/A	N/A	N/A	N/A	0.2%	2023	(9)
	Head and neck squamous cell carcinoma	0	1	1	2	411	0.5%	2014	(234)
		0	1	1	2	522	0.4%	2018	(235)
		N/A	N/A	N/A	N/A	3,987	0.15%	2021	(5)

N/A in place of 0 indicates that no testing was performed for specific NTRKx
Abbreviations: CNS = central nervous system; Freq = frequency; GI = gastrointestinal, N/A = not applicable; NTRK = neurotrophic tyrosine kinase receptor gene (referring to family); Ref = reference.

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EU Risk Management Plan
Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.2.3.2 NRK gene fusion frequency in paediatric tumour types

Appendix C Table SI.7: *NTRK* gene fusion frequency in paediatric tumour types

Disease	Disease Ontology	Frequency						Year	Ref
		Number of Fusions Observed				Sample Count	Freq		
		NTRK1	*NTRK2*	*NTRK3*	NTRK All				
Sarcoma	Ewing sarcoma	0	0	0	0	123	0%	2018	(235)
		N/A	N/A	1	1	475	0.2%	2017	(265)
		N/A	N/A	1	1	101	1%	2014	(266)
		N/A	N/A	N/A	N/A	177	0%	2021	(5)
	Infantile fibrosarcoma	N/A	N/A	25	25	26	96.2%	2018	(267)
		1	0	4	5	45	11.1%	2018	(268)
		N/A	N/A	10	10	43	23.3%	2017	(265)
		N/A	N/A	34	34	39	87.2%	2016	(74)
		N/A	N/A	10	10	11	90.9%	2000	(76)
		N/A	N/A	3	3	5	60.0%	1998	(77)
		N/A	N/A	N/A	N/A	N/A	90.56%	2020	(3)
		3	0	33	36	44	81.8%	2021	(269)
	Osteosarcoma	0	0	0	0	53	0%	2018	(235)
		N/A	N/A	N/A	N/A	279	0.72%	2021	(5)
	Rhabdomyosarcoma	0	0	0	0	58	0%	2018	(235)
		N/A	N/A	N/A	N/A	113	0.88%	2021	(5)
		1	0	0	1	37	2.7%	2019	(270)
	Inflammatory myofibroblastic tumour	0	N/A	N/A	0	62	0%	2015	(271)
		N/A	N/A	N/A	0	5	0%	2015	(272)
		N/A	N/A	1	1	36	2.8%	2016	(273)
		N/A	N/A	2	2	30	6.7%	2017	(274)
		N/A	N/A	N/A	N/A	36	2.78%	2021	(5)
		0	0	1	1	24	4.2%	2020	(275)
Thyroid	Paediatric DTC/PTC	N/A	N/A	4	4	26	15.4%	2018	(276)
		1	N/A	2	3	46	6.5%	2017	(277)
		1	N/A	6	7	27	25.9%	2016	(46)
		1	N/A	3	4	18	22.2%	2016	(278)
		N/A	N/A	N/A	N/A	N/A	25.93%	2020	(3)
		N/A	N/A	N/A	N/A	N/A	22.22%	2020	(3)
		N/A	N/A	N/A	N/A	40	22.5%	2021	(5)
Kidney	Congenital mesoblastic nephroma	N/A	N/A	17	17	79	21.5%	2018	(279)
		N/A	N/A	5[a]	5	16[a]	31.2%	2018	(267)
		N/A	N/A	15	15	20	75%	2017	(265)
		N/A	N/A	13	13	19	68.4%	2016	(280)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Appendix C Table SI.7: *NTRK* gene fusion frequency in paediatric tumour types

Disease	Disease Ontology	Frequency						Year	Ref
		Number of Fusions Observed				Sample Count	Freq		
		NTRK1	*NTRK2*	*NTRK3*	NTRK All				
		N/A	N/A	1	1	10	10.0%	2009	(281)
		N/A	N/A	3	3	13	23.1%	2006	(282)
		N/A	N/A	11	11	12	91.7%	2000	(283)
		N/A	N/A	10	10	15	66.7%	1998	(284)
		N/A	N/A	3	3	6	50.0%	1998	(77)
		N/A	N/A	N/A	N/A	N/A	21.52%	2020	(3)
	Wilms Tumour	0	0	0	0	91	0.0%	2018	(235)
		N/A	N/A	N/A	N/A	130	0%	2021	(5)
Primary CNS	Paediatric high grade glioma	4	2	1	7	132	5.3%	2018	(235)
		3	3	2	8	118	6.8%	2014	(253)
	Paediatric low grade glioma	0	2	1	3	120	2.5%	2018	(235)
		N/A	0	N/A	0	48	0.0%	2018	(285)
		N/A	1	N/A	1	91	1.1%	2016	(286)
		N/A	N/A	N/A	N/A	N/A	1.61%	2020	(3)
	Paediatric pilocytic astrocytoma	0	3	0	3	96	3.1%	2013	(252)
	Paediatric ependymoma	0	0	0	0	92	0.0%	2018	(235)
	Paediatric choroid plexus carcinoma	0	0	0	0	29	0.0%	2018	(235)
	Paediatric neuroblastoma	0	0	0	0	382	0.0%	2018	(235)
	Paediatric medulloblastoma	0	0	0	0	714	0.0%	2018	(235)
	Diffuse intrinsic pontine glioma	0	1	1	2	54	3.7%	2014	(253)
Other	Retinoblastoma	0	0	0	0	39	0.0%	2018	(235)
	Spitz neoplasms nevi	8	0	0	8	75	10.7%	2014	(287)
		N/A	N/A	N/A	N/A	128	12.5%	2023	(4)
	Paediatric adrenocortical carcinoma	0	0	0	0	40	0.0%	2018	(235)
		N/A	N/A	N/A	N/A	22	0.0%	2021	(5)

[a] Numbers of fusions confirmed by targeted RNA-based next-generation sequencing

N/A in place of 0 indicates that no testing was performed for specific NTRKx

Abbreviations: CNS = central nervous system; DTC = differentiated thyroid cancer; Freq = frequency; N/A = not applicable; NTRK = neurotrophic tyrosine kinase receptor gene (referring to family); PTC = papillary thyroid cancer; Ref = reference.

Part II: Module SII - Non-clinical part of the safety specification

SII.1 Key Safety Findings from Non-Clinical Studies and Relevance to Human Usage

The toxicology program included 25 toxicity studies, including Good Laboratory Practice (GLP) and non-GLP repeat-dose studies and GLP embryo-foetal development (EFD) studies with different species. In the Sprague-Dawley (SD) rat, a single-dose toxicity study was followed by 5 repeat-dose studies that were 7, 28 (two studies – one non- GLP and one GLP), 42, and 91 days in treatment duration. In the cynomolgus monkey, 5 repeat-dose studies were 7, 14 (two studies - both non-GLP), 28, and 91 days in treatment duration. The toxicology program also included the following studies: Dose range finding (DRF) EFD studies in SD rats and New Zealand rabbits followed by GLP EFD studies in SD rats and New Zealand rabbits; DRF studies in juvenile SD rats from postnatal day (PND) 7 to PND 28 (two studies) with a subsequent GLP repeat dose oral toxicity study in juvenile male and female SD rats from PND 7 through PND 70; an *in vitro* Ames and an *in vitro* mouse lymphoma assays and an *in vivo* mouse micronucleus assay and an *in vitro* phototoxicity study in BALB/c 3T3 mouse fibroblasts. Toxicokinetic investigations were performed in all toxicity studies to determine the extent and duration of exposure of Vitrakvi®.

The GLP toxicity evaluations were conducted in rats and monkeys given Vitrakvi® two times a day (BID) and once daily (QD), respectively. Vitrakvi® doses were per oral (PO) for 28 and 91 days, followed each by a 28-day recovery period in both species. The doses used in the GLP 28-day study in rat and monkey were 0, 10, 30, and 100 mg/kg/dose BID and 0, 10, 30, and 100 mg/kg/day (QD), respectively.

13-week (i.e. 91 days) repeat-dose studies were conducted in rats and monkeys. The doses used in this study were 0, 7.5, 25/17.5, and 75/50/37.5 mg/kg/dose (BID) for male rats and 0, 7.5/5, 25/10, and 75/50/20 mg/kg/dose (BID) for female rats and 0, 10, 30, and 100 mg/kg/day (QD) in monkey. Clinical signs of gastrointestinal toxicity without histopathological correlate were dose limiting in monkeys. The following additional main findings were observed: increased body weight in both species which is regarded as related to the pharmacological activity as TRK inhibitor; a mainly adaptive response in the liver, increased liver transaminases; histopathological changes in lymphoid tissues without relevant changes in differential white blood cell counts in both species; pancreatic changes in the rats; minor, reversible changes on red blood cell parameters without histopathological correlate in the bone marrow in both species; and increased heart weights in the rats without histopathological correlate. Margin of exposures of 1.2- to 2-times in rats to STD_{10} (13-week study) and >10-times in monkeys (high dose, 13-week study) to the No-observed-adverse-effect level (NOAEL) were achieved.

The majority of the toxicity findings were rat-specific, and the rat was deemed the more sensitive species. The discussion of non-clinical data presented in the table below focuses mainly on the rat, as there were no additional noteworthy findings in the monkey, unless specifically mentioned.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Neurobehavioural and Neuromuscular There were no relevant Vitrakvi®-related effects on behaviour (e.g. Irwin test, Functional Observational Battery, Motor Activity) in both single dose safety pharmacology studies and repeat dose toxicity studies in rat and monkey. The compound distributes into tissues with volumes of distribution ranging from 1 to 2 L/kg; however, it does not distribute significantly into the brain. Brain/plasma ratio of Vitrakvi® was determined in mouse (3-23%) and rat (1-2%); these values suggest low-to-negligible penetration of the blood brain barrier in rodents. A brain microdialysis study of larotrectinib in the rat (50 mg/kg oral single dose) showed that the unbound (free) brain concentration was approximately 5% of the unbound plasma concentration. The NOAEL for neurobehavioural toxicity in the juvenile rat study was considered to be 7.5/22.5 mg/kg/dose BID (approximately 24 times the human area under the plasma concentration-time curve [AUC] at the recommended clinical dose).	There is potential for on-target central effects in humans (neurologic reactions) due to the mechanism of action (MOA) of Vitrakvi® (neurotrophins signalling). In the postnatal period, tropomyosin-related kinase (TRK) receptors are expressed in the brain and nervous system and are thought to regulate mood, memory, cognition, and proprioception. The concentration of larotrectinib in a single sample of cerebrospinal fluid collected from the Ommaya reservoir of a pediatric patient in Study 20290 was approximately 28% of the unbound plasma concentration collected at the same time (1 hour after oral administration of larotrectinib. In the overall clinical safety database (n=418), regardless of attribution, CNS related reactions (≥5% of patients) were mostly of Grade 1 and 2 including the most commonly reported: Dizziness (22%), gait disturbance, and paraesthesia (6% each). There was a total of 4 (<1%) cases each of Grade 3 events of dizziness, 6 (1%) cases each of Grade 3 events of gait disturbance, and 3 (<1%) cases of Grade 3 paraesthesia. Relatedness rate (percentage of cases reported as drug-related) was 64% (dizziness), 36% (gait disturbance), and 54% (paraesthesia). Severe neurologic reactions are considered as an **important potential risk**.
Liver In repeat-dose GLP studies, the primary target organ for both toxicity species was the liver. A change seen in both species was a dose-related	Transaminase elevation and hepatic abnormalities in preclinical species may be

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
increase in liver weights. Fully reversible, dose-dependent increased liver weights were recorded in all treated groups which correlated microscopically with hepatocellular hypertrophy and likely resulted from hepatic drug-metabolizing enzyme induction. Additional findings in the liver were increases in serum transaminases, alanine aminotransferase (ALT) (rat, monkey) and aspartate aminotransferase (AST) (monkey), in the GLP 28-day repeat dose studies (from <2-fold in rat and 4-fold in monkey) that were reversible. Single cell necrosis was a minor histologic change in the liver. It was difficult to attribute elevated transaminases solely to single cell necrosis. Liver effects in both species were fully reversible.	indicative of potential hepatotoxic effects in human patients. Administration of a single oral dose of 100 mg Vitrakvi® to male and female subjects with normal hepatic function (n=11) or with mild (n=8), moderate (n=8), or severe (n=8) hepatic impairment was considered to be safe and well tolerated in clinical study LOXO-TRK-16013. Elevations of liver enzymes AST or ALT were reported as TEAEs in ongoing clinical trials (30% ALT and 29% AST reported frequency; n=418). Most of the cases reported were classified as Grade 1 and 2 severity; however, three cases (ALT elevated) and two cases (AST elevated) were classified as Grade 4. Thirty-two (32%) ALT cases and 30% AST cases were considered related to treatment. Current clinical data indicate an overall mild effect of Vitrakvi® on liver, primarily within first 3 treatment cycles with transient increases in transaminases which resolved under continued Vitrakvi® treatment in the majority of cases without any dose reduction. Severe drug-induced liver injury is considered an **important potential risk**.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Kidney Elevated blood urea nitrogen (BUN) (male monkey, rat) and creatinine (rat) were observed without any microscopic changes in the kidneys of either species. At 50 mg/kg/dose BID in rats, increased BUN and decreased potassium were recorded without microscopic findings (7-days repeat dose range finding study). In the non-GLP 28-days repeat-dose rats study, kidney weights were increased without correlated histologic findings in the kidney. In the GLP 28-day repeat-dose rats study, dose-related increases in BUN and creatinine at ≥10 mg/kg/dose BID were noted but with no microscopic findings in the kidney. In the GLP 28-day repeat dose monkeys study, reversible changes included increased BUN at all doses in males.	As no severe and/or permanent renal adverse effects were noted in non-clinical species at all doses tested, renal toxicity in human patients is not anticipated based on the results of non-clinical studies. Clinical data from the pharmacokinetic study LOXO-TRK-17014 with a single oral dose of 100 mg Vitrakvi® administered under fasted conditions to 8 subjects with end-stage renal disease and to 8 healthy matched subjects has shown a 1.46-fold increase in Vitrakvi® exposure in patients with end-stage renal disease. As there were no adverse events reported in that study, the treatment appeared to be safe and well tolerated. No dose adjustment to the initial dose is required for patients with renal impairment.
Hematopoietic effects In both species (monkey and rat), reductions in multiple hematologic parameters were evident, with no corresponding microscopic changes in the bone marrow. A consistent finding was a mild decrease in red cell mass parameters. Regenerative responses observed in the rat included extramedullary haematopoiesis in the spleen, along with increases in spleen weight and circulating reticulocytes. Prolonged prothrombin time (rat, monkey), increased fibrinogen (rat), and shortened activated partial thromboplastin time (rat) were observed, but with no blood coagulation disorders clinically apparent. The exact aetiology of these changes was not determined.	Neutropenia: In the overall clinical safety database (n=418), neutropenia was reported as TEAE in 64 (15%) of the patients, with Grade 3 occurring in 26 cases, and seven reported cases of Grade 4, where 37 (14%) cases were drug-related. There were two cases of febrile neutropenia (one Grade 3 and one Grade 4), reported as serious, unrelated. Relatedness rate (percentage of cases reported as drug-related) was 58%. A disproportion of neutropenia incidence was noted between the paediatric population (30%) and the adults (8%). Serious infections secondary to neutropenia is considered as an

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
	important potential risk due to medical significance. In the overall clinical safety database (n=418), a total of 60 SAEs from SOC "Infections and infestations" were reported, and none were assessed as related to study medication (except for one case [<1%] of Grade 3 pneumonia. None of the cases of serious infections were co-reported in combination with neutropenia with the exception of a single patient (febrile neutropenia and sepsis). Anaemia, leukopenia (leukocyte count decreased) and thrombocytopenia (platelet count decreased) events have been reported as TEAEs in 28%, 13%, and 7%, respectively, of the overall 418 patients. The majority of these events were reported as unrelated and of Grade 1 and Grade 2 severity. Grade 4 events were reported in 2 (<1%, leukocyte count decreased) and 1 (<1%, platelet count decreased) cases (all unrelated). No Grade 5 events were reported. Anaemia and leukopenia are listed as very common ADRs in the SmPC.
Cardiovascular effects Cardiac safety was evaluated in an *in vitro* assay for human ether-à-go-go related gene (hERG) activity, and in conscious telemetry-instrumented rats and monkeys. Vitrakvi® had a 50% inhibitory concentration (IC_{50}) value of 147 µM in the hERG assay, which is approximately 216-fold higher than the maximum unbound concentration ($C_{max(unbound)}$ = 0.68 µM) at the human dose regimen of 100 mg BID. No adverse cardiovascular effects were noted *in vivo* in rats and monkeys dosed up to 300 mg/kg and 100 mg/kg, respectively. Heart Heart weights were increased in the rat, but with no associated histologic findings. The exact cause of increased heart weight in rats was not established.	No adverse cardiovascular effects of human relevance are expected based on non-clinical studies. In the overall clinical safety database (n=418), hypertension was reported in 37 (9%) of patients, mainly of Grade 1 and 2 severity and as unrelated in the majority of events. Also, one event each of myocardial ischaemia/infarction,

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Blood pressure Systolic blood pressure was increased after a single Vitrakvi® dose of 300 mg/kg. This slight, non-adverse increase was not considered a causative factor in heart weight changes. Heart weight increase paralleled body weight gain, especially in females at ≥60 mg/kg/day in the GLP 28-day study. In rats, it is known that body weight increase can affect heart weights (288), and thus, the significant body weight increase in rats treated with Vitrakvi® could have contributed to the heart weight changes.	arrhythmias or (congestive) heart failure have been reported. Grade 2 myocardial ischaemia/infarction and Grade 1 congestive heart failure have been reported in a [redacted] male patient with NTRK fusion cancer. The TEAEs were reported as PT "myocardial ischemia" (verbatim: demand ischemia) and as PT "Cardiac failure congestive" (verbatim: mild congestive heart failure). Both TEAEs were classified as not serious and not related. Thus, no action with study drug or otherwise was taken. Grade 1 arrhythmia has been reported in a [redacted] female patient with NTRK fusion cancer. The TEAE was reported as PT "arrhythmia" (verbatim: arrhythmia) and classified as not serious and not related. Thus, no action with study drug or otherwise was taken.
Pancreas Pancreatic changes included reduction in zymogen granules, acinar cell atrophy, and inflammation. Alterations in the pancreas were treatment-related although the MOA responsible for these effects was not determined.	Not a safety concern relevant for human use. In the overall clinical safety database (n=418), one Grade 3 pancreatitis event has been reported (not related to study drug).
Spleen Increased spleen weights in male rats correlated with extramedullary haematopoiesis as a response to decreased red cell mass parameters.	Not a safety concern relevant for human use.
Thyroid Increased thyroid weights in females correlated with hypertrophy of thyroid follicular epithelia and this effect was potentially related to hepatic enzyme induction (289).	Not a safety concern relevant for human use. In the overall clinical safety database (n=418), no events related to thyroid (function) have been reported.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Mammary gland Mammary gland hyperplasia was noted in females in the GLP 28-day repeat-dose study. Alterations in the mammary gland were treatment-related although the MOA responsible for these effects was not determined.	Not a safety concern relevant for human use.
Genotoxicity Vitrakvi® was not genotoxic in any of the assays conducted. At maximum feasible concentrations, Vitrakvi® tested negative in 2 bacterial mutagenesis (Ames) assays with or without metabolic activation and 2 *in vitro* mammalian mutagenesis assays (L5178Y/TK$^{+/-}$ mouse lymphoma), with or without metabolic activation. *In vivo*, Vitrakvi® was negative in the mouse micronucleus test.	Not a safety concern relevant to human use.
Carcinogenicity No carcinogenicity studies have been performed to date with Vitrakvi®.	Not applicable, as according to the International Conference on Harmonization (ICH)-S9 (Step 4) Guidance, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.
Reproductive and Developmental Toxicology <u>Females</u> In the GLP 28-day repeat-dose study in rats, uterus weights were decreased due to reversible uterine atrophy (approximately 8-37 times the human AUC at the recommended clinical dose); fewer corpora lutea and a higher incidence of anestrus were observed at ≥60 mg/kg/day and fully reversible. There were no Vitrakvi®-related findings in the female reproductive organs in the monkey. <u>Males</u> In the 91-day repeat-dose oral toxicity studies in rats, there were no Vitrakvi®-related effects on sperm count, density, motility, or morphology at all doses tested. No effects in male reproductive organs in any of the repeat-dose studies conducted in rats and monkeys. <u>Juvenile animals</u> The slight reduction in reproductive performance parameters at high doses are regarded as not relevant since they were in the range of historical control data and no effects on any of the other parameters addressed concomitantly in that study were seen. <u>Embryo-foetal development</u> EFD studies were conducted in pregnant rats and rabbits. Vitrakvi® caused maternal toxicity in rats at 120 mg/kg/dose BID (deaths, and clinical signs of rales, gasping, laboured respiration, ataxia, piloerections, head tilt and pale and/or cool body) and rabbits at 75 mg/kg/dose BID (deaths, ataxia, prostration, body weight loss, decrease food consumption, impaired use of hind limbs, prostrate body, decreased defecation, and tremors upon	Based on the mechanism of action, fetal harm cannot be excluded when administering Vitrakvi® to a pregnant woman. The use of highly effective contraceptive methods is advised in both males and females of reproductive potential. Use in pregnancy and lactation is considered as **missing information**. Larotrectinib selectively and potently inhibits TRK A/B/C, kinases which play a role in neurotrophic signalling in the brain, including in neuronal cell proliferation and differentiation in embryogenesis and postnatal development. As a result, impairment of neurodevelopment in paediatric patients is categorised as an **important potential risk**. Growth and neurodevelopmental impairments in paediatric

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
handling). Based on these findings, 40 mg/kg/dose BID and 30 mg/kg/dose BID were the NOAELs for maternal toxicity in rat and rabbit, respectively. The NOAELs for EFD toxicity in rats and rabbits were 120 mg/kg/dose BID and 75 mg/kg/dose BID, and were the highest doses tested in rat and rabbit, respectively. Malformations seen in these studies were either observed in a single animal (anasarca, lobular dysgenesis of lungs; EFD study in rats) or lacked any dose-relationship (omphalocele; EFD study in rabbits), thus they were not considered treatment-related. Effects might be expected due to the mode of action of larotrectinib. <u>Juvenile development</u> In juvenile male rats (on postnatal day 61) Vitrakvi® lowered hindlimb grip strength and footsplay, which were likely secondary to decreased body weights. There were no test article-related effects on other FOB parameter, on auditory startle response or on learning and memory (Biel maze). No microscopic abnormalities in neuronal tissues were found. Findings in juvenile rats are considered non-adverse.	patients have not been observed to date. However, there is currently a lack of comprehensive long-term exposure data in this population, with the anticipated survival rate due to the severity of the indication further limiting long-term use data collection. In paediatric patients with brain tumours, the presence of larotrectinib was demonstrated at high concentration in the cerebrospinal fluid (CSF), presuming that larotrectinib has activity on the brain side of the BBB (blood-brain barrier). In clinical trials, larotrectinib demonstrated overall response rates of 22% (95% CI [11, 38]) in patients with primary CNS malignancies. The risk will be monitored with the Non-Interventional PASS (ON-TRK), in post-marketing experience, and in ongoing clinical trials. Paediatric development assessment is included in ongoing clinical trial 20290 (formerly LOXO-TRK-15003; SCOUT) utilising the standard procedures recommended for preventive paediatric health care (i.e., American Academy of Paediatrics, Recommendations for Preventive Paediatric Health Care, 2017 and Children's Oncology Group Guidelines, 2013) supported with neurologic exam and development questionnaire. Neurocognitive development will be captured by the ASQ3 (ages and stages questionnaire) until 66 months and by assessment of development milestones by standard of care

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
	thereafter. Data will be assessed at screening for newly enrolled participants and every 6 months thereafter until 5 years of follow up.
Phototoxicity Vitrakvi® did not demonstrate a phototoxic potential in mouse 3T3 fibroblasts *in vitro*.	Not a safety concern relevant for human use.
Weight gain For the Vitrakvi® toxicology program, significantly increased body weight gain mainly in rats was linked to an increase in food consumption. Elevated cholesterol and changes in brown adipose tissue correlated with these changes.	The putative role of the TRK receptor family in regulating food intake and ultimately in changes to body weight is not fully understood. On-target CNS effects are potentially mediated via the inhibition of the NTRKB, a receptor thought to regulate body weight (290). Based on the Company internal ADR analysis, weight increase was reported as related adverse event in 68% of cases (46 related cases/68 total cases). The medical significance, potential on-target CNS effect and high frequency in paediatric group provides a justification to include weight increase as an ADR. A potential class effect can also not be excluded, an observation supported by clinical trial data for entrectinib, with weight gain reported with a similar frequency as for Vitrakvi® (16% versus 10% for entrectinib) (291, 292) (refer to Table SVII.2 in Part II Module SVII for more details).
Skin lesions In the rat, skin lesions, which were characterised as chronic inflammation of the epidermis and dermis, were dose limiting with at least partial recovery after cessation of treatment. Thus, the exact aetiology for changes in the skin was not established in these studies.	Not a safety concern relevant for human use. In the overall clinical safety database (n=418), events of rash, dry skin, and rash maculo-papular have been reported as TEAEs in 10%, 9% and 7% of patients, respectively, mainly of Grade 1 and Grade 2 severity and in the majority of events as

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
	unrelated.
Hypersalivation Hypersalivation in the rat correlated with acinar cell hypertrophy of the salivary gland. Hypersalivation in Vitrakvi®-treated rats may be related to inhibition of salivary gland receptors. However, the exact cause of hypersalivation was not determined.	Not a safety concern relevant for human use.
Serum chemistry changes Serum albumin decreased in both species. In the rat, albumin reduction occurred even though the animals consumed large amounts of food, culminating in significant body weight gain. Generalized oedema was not associated with low serum albumin. The exact aetiology for decreases in serum albumin was not determined.	In the overall clinical safety database (n=418), hypoalbuminaemia events have been reported as TEAEs in 11% of patients, mainly of Grade 1 and Grade 2 severity. Relatedness rate (percentage of cases reported as drug-related from total number of cases) for hypoalbuminaemia was 51%. There was one reported case (<1%) of Grade 1 generalized oedema (not related to study drug).
Respiratory effects There were no Vitrakvi®-related respiratory function effects in safety pharmacology and general toxicology studies.	Not a safety concern relevant for human use. In the overall clinical safety database (n=418), events of pneumonia (two cases were considered related to study drug) and upper respiratory tract infections have been reported as TEAEs in 8% and 17% of patients, respectively, mainly of Grade 1, Grade 2 and Grade 3 severity and in context of underlying (progressive) malignancies.
Gastrointestinal effects Vitrakvi® accelerated the intestinal transit and significantly increased gastric secretion and acidity in rats. Some clinical signs of Gastro-intestinal tract (GIT) toxicity were observed in monkey but no irritating potential was seen.	Gastrointestinal system reactions have been the most common type of treatment emergent adverse events reported. However, gastrointestinal effects are a very common non-specific reaction in patients with advanced stages of cancer. In the overall clinical safety database (n=418), nausea, vomiting, constipation, and

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
	dysgeusia were reported in 25%, 28%, 27%, and 5% respectively, and are reflected as ADRs in SmPC.
Drug-Drug Interactions Effect of Vitrakvi® on Other Drugs *In vitro*, Vitrakvi® showed no significant competitive inhibition of cytochrome P450 (CYP) enzymes: CYP1A2 (IC_{50} >300 μM), CYP2B6 (IC_{50} >300 μM), CYP2C8 (IC_{50} 180 μM), CYP2C9 (IC_{50} >300 μM), CYP2C19 (IC_{50} >300 μM), CYP2D6 (IC_{50} >300 μM), and CYP3A4 (IC_{50} 190 μM, midazolam substrate; IC_{50} >300 μM testosterone substrate). Vitrakvi® also showed no significant time-dependent inhibition (TDI) of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, but weak TDI of CYP3A4. Its value of k_{inact}/K_I was 0.003 and 0.001 min^{-1} μM^{-1} with midazolam and testosterone substrates, respectively. These data suggest the potential for Vitrakvi® to inhibit the clearance of CYP3A4 substrates. In human hepatocytes cultured with Vitrakvi® at concentrations up to 123 μM, CYP1A2 was not induced (messenger ribonucleic acid [mRNA] and activity increases were <2% of the positive control), CYP2B6 mRNA and activity were increased to 50% and 20% of the positive control, and CYP3A4 mRNA and catalytic activity were increased to 100% and 10% of the positive control, respectively. These data suggest the potential for Vitrakvi® to increase the clearance of CYP3A4 substrates. Vitrakvi® (30 μM) did not inhibit P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), OATP1B1, OATP1B3, bile salt export pump, or multidrug and toxin extrusion (MATE1, or MATE2-K), thus interactions with substrates of these transporters is unlikely. Effect of Other Drugs on Vitrakvi® *In vitro*, Vitrakvi® is a substrate for CYP3A4/5. In human liver microsomes, metabolism of Vitrakvi® is reduced by 75-80% by the CYP3A4/5 inhibitor ketoconazole. No other CYP isoform selective inhibitor affected the metabolism of Vitrakvi®. Furthermore, Vitrakvi® was metabolized by recombinant human CYP3A4 and CYP3A5, but not CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6; and, in a panel of human liver microsomes, metabolism of Vitrakvi® correlated most strongly with testosterone 6β-hydroxylation and midazolam 1'hydroxylation, which are marker reactions of CYP3A4/5 activity. The formation of all of the human-relevant metabolites was also suppressed by ketoconazole (CYP3A4 inhibitor), but not by selective inhibitors of the other CYP isoforms. Thus, CYP3A4/5 appears to contribute significantly to the clearance of Vitrakvi® and there is the potential for co-administered inhibitors and inducers of CYP3A4/5 to affect the pharmacokinetics (PK) of Vitrakvi®. Vitrakvi® is not a significant substrate of OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3, but is a substrate of P-gp and BCRP. Thus, strong inhibitors of P-gp or BCRP could affect the PK and distribution of	Related label notifications include the following: 1. **Drugs That May Increase Vitrakvi® Plasma Concentrations**: When dosing concomitantly with strong CYP3A, P-gp or BCRP inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, or voriconazole) monitor patients for adverse reactions. Adverse reactions may be managed by dose modification. Avoid grapefruit or grapefruit juice as these may also increase plasma concentrations of Vitrakvi®. **2. Drugs That May Decrease Vitrakvi® Plasma Concentrations**: Avoid concomitant use of strong CYP3A inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, or St. John's Wort). **3. Drugs Whose Plasma Concentrations May Be Altered by Vitrakvi®**: When dosing Vitrakvi® concomitantly with CYP3A substrates with narrow therapeutic range (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus) monitor patients for adverse reactions and if necessary, adjust dose of the CYP3A substrate. Coadministration of

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Vitrakvi®.	larotrectinib with CYP2B6 substrates (e.g. Bupropion, Efavirenz) may alter their exposure.

SII.2 Conclusions on Non-Clinical Data

The following list of safety concerns has been identified from non-clinical data and will be included as important identified/potential risk or missing information in Part II: Module SVII - Identified and Potential Risks:

Table SII.2: List of safety concerns identified from non-clinical data

Safety concerns
Important identified risk (confirmed by clinical data) • None identified Important potential risks (not refuted by clinical data or which are of unknown significance) • Severe neurologic reactions • Severe drug-induced liver injury • Serious infections secondary to neutropenia • Impairment of neurodevelopment in paediatric patients Missing information • Use in pregnancy and lactation • Long-term safety

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SIII - Clinical trial exposure

Part II: Module SIII - Clinical trial exposure

SIII.1 Overall Exposure

Table SIII.1: Overview of clinical studies of Vitrakvi® supporting the integrated summary of safety and the integrated summary of efficacy

Study ID	Phase	Country	Study Title	Dosing Regimen	Study Population	Enrolment by 20 JUL 2022
20288 (formerly LOXO-TRK-14001)	1	USA 8 sites	A Phase 1 Study of the Oral TRK Inhibitor Larotrectinib in Adult Patients with Solid Tumours	**Escalation Phase**: Dosing schedule: Continuous, 28-day cycles until PD or intolerability Dose levels: 50 mg QD, 100 mg QD, 200 mg QD; 100 mg BID, 150 mg BID, 200 mg BID **Expansion Phase**: Dose: 100 mg BID	**Escalation Phase**: Adult Solid Tumours **Expansion Phase**: Evidence of the *NTRK* or TRK molecular characteristic such as an *NTRK* translocation or amplification	75
20289 (NAVIGATE; formerly LOXO-TRK-15002)	2	USA, EU, Australia, China, Japan, South Korea, Singapore, Taiwan 36 sites	A Phase 2 Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects with TRK Fusion cancer	**Dosing schedule**: Continuous, 28-day cycles until PD or intolerability **Dose**: 100 mg BID	≥12 years Solid Tumours – TRK fusion+ Consists of 8 baskets	200

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.1: Overview of clinical studies of Vitrakvi® supporting the integrated summary of safety and the integrated summary of efficacy

Study ID	Phase	Country	Study Title	Dosing Regimen	Study Population	Enrolment by 20 JUL 2022
20290 (SCOUT; formerly LOXO-TRK-15003)	1/2	USA, EU, Australia, Canada, China, Israel, Japan, South Korea, Switzerland 34 sites	A Phase 1/2 Study of the Oral TRK Inhibitor Larotrectinib in Paediatric Patients with Advanced Solid or Primary Central Nervous System Tumours	**Dosing schedule**: Continuous, 28-day cycles until PD or intolerability **Escalation Phase**: Adult equivalent doses: 100 mg BID, 150 mg BID, 100 mg/m^2 [a], 150 mg/m^2 [a], 200 mg/m^2 [a] [a] maximum of 100 mg BID **Expansion Phase**: 100 mg/m^2 BID (maximum of 100 mg BID) Phase 2: 100 mg/m^2 BID (maximum of 100 mg BID)	**Phase 1**: Paediatric Advanced Solid or Primary Central Nervous System Tumours Expansion: Same as above to further explore dose **Phase 2**: 3 cohorts-infantile fibrosarcoma, solid tumours with *NTRK* gene fusions, and primary CNS tumours with *NTRK* gene fusions	143

BID = Two times a day (bis in die); CNS = Central nervous system; NTRK = Neurotrophic tropomyosin receptor kinase; PD = Progressive disease; QD = Once daily (quaque die); TRK = Tropomyosin-related kinase; USA = United States of America. Source: Table 14.1.1

The Overall Safety (OS) Analysis Set (n=418) includes all paediatric and adult cancer patients who were enrolled in Studies 20288 (formerly LOXO-TRK-14001), 20289 (NAVIGATE; formerly LOXO-TRK-15002), and 20290 (SCOUT; formerly LOXO-TRK-15003) and received 1 or more doses of Vitrakvi® as of the cut-off date of 20 JUL 2022. This analysis set includes patients with and without documented TRK fusion cancer.

The Overall *NTRK* Fusion (O-NF) Cancers Safety Analysis Set (n=347) includes all paediatric and adult patients with documented TRK fusion cancers who were enrolled in Studies 20288, 20289, and 20290 and received 1 or more doses of Vitrakvi® as of the cut-off date of 20 JUL 2022.

The Efficacy-evaluable *NTRK* Fusion (EE-NF) Cancers Safety Analysis Set includes the first 272 patients (both paediatric and adult) enrolled in Studies 20288, 20289, and 20290.

Baseline tumour characteristics are presented in Table SIII.2, duration of exposure in Table SIII.3, initial Vitrakvi® dose and dosage modifications in Table SIII.4, and patient demographics in Table SIII.5.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.2: Baseline disease characteristics by analysis set

	EE-NF (n=272)	O-NF (n=347)	OS (n=418)
Primary tumour type, n (%)			
Soft tissue sarcoma	68 (25)	69 (20)	78 (19)
Salivary gland	25 (9)	26 (7)	28 (7)
Lung	27 (10)	31 (9)	41 (10)
Colon	18 (7)	23 (7)	31 (7)
Infantile fibrosarcoma	49 (18)	49 (14)	49 (12)
Thyroid	30 (11)	37 (11)	39 (9)
Primary CNS	0 (0)	49 (14)	55 (13)
Melanoma	9 (3)	11 (3)	13 (3)
Breast	11 (4)	14 (4)	18 (4)
GIST	5 (2)	5 (1)	5 (1)
Pancreas	6 (2)	7 (2)	11 (3)
Bone sarcoma	3 (1)	3 (<1)	6 (1)
Cholangiocarcinoma	4 (1)	4 (1)	6 (1)
Thymus	1 (<1)	1 (<1)	5 (1)
Appendix	1 (<1)	1 (<1)	2 (<1)
Gastric	1 (<1)	3 (<1)	5 (1)
Hepatic	1 (<1)	1 (<1)	3 (<1)
Neuroblastoma	0 (0)	0 (0)	2 (<1)
Anal	0 (0)	0 (0)	1 (<1)
Cancer of unknown primary	2 (<1)	2 (<1)	3 (<1)
Congenital mesoblastic nephroma	2 (<1)	2 (<1)	2 (<1)
Endometrial	0 (0)	0 (0)	1 (<1)
Ewing’s sarcoma	0 (0)	0 (0)	1 (<1)
Larynx	0 (0)	0 (0)	1 (<1)
Oral	0 (0)	0 (0)	1 (<1)
Ovarian	0 (0)	0 (0)	1 (<1)
Renal	0 (0)	0 (0)	1 (<1)
Cervix	1 (<1)	1 (<1)	1 (<1)
Prostate	2 (<1)	2 (<1)	2 (<1)
Rectal	1 (<1)	1 (<1)	1 (<1)
External auditory canal	1 (<1)	1 (<1)	1 (<1)
Uterus	1 (<1)	1 (<1)	1 (<1)
Esophageal	1 (<1)	1 (<1)	1 (<1)
Congenital mesoblastic nephroma	2 (<1%)	2 (<1%)	2 (<1%)
Duodenal	1 (<1%)	1 (<1%)	1 (<1%)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.2: Baseline disease characteristics by analysis set

	EE-NF (n=272)	O-NF (n=347)	OS (n=418)
Urothelial	1 (<1%)	1 (<1%)	1 (<1%)
Stage at diagnosis, n (%)			
0	0 (0)	1 (<1)	1 (<1)
I	27 (10)	34 (10)	42 (10)
II	40 (15)	47 (14)	57 (14)
III	70 (26)	79 (23)	94 (22)
IV	89 (33)	102 (29)	135 (32)
Unknown/Not reported	46 (17)	84 (24)	89 (21)
Time from diagnosis, years			
Median	1.175	1.229	1.487
Range	0.02, 45.88	0.02, 45.88	0.02, 45.88
Disease extent at enrolment, n (%)			
Locally advanced	74 (27)	76 (22)	78 (19)
Metastatic	198 (73)	222 (64)	285 (68)
Other	0 (0)	49 (14)	55 (13)
***NTRK* gene fusion, n (%)**	272 (100)	347 (100)	347 (83)

EE-NF = Efficacy-evaluable NTRK Fusion (Analysis Set); O NF = Overall NTRK Fusion (Analysis Set); OS = Overall Safety (Analysis Set).
Source: Tables 14.1 / 4, 14.1 / 5, Integrated Summary of Safety (Visit Cut-off 20 JUL 2022)

Table SIII.3: Duration of exposure

	Analysis Set		
	EE-NF (n=272)	**O-NF (n=347)**	**OS (n=418)**
Time on treatment, months			
Mean (SD)	21.21 (18.38)	20.32 (18.62)	17.32 (18.28)
Median	15.67	14.72	9.35
Range	0.10, 75.5	0.0, 75.5	0.0, 75.5
Total number of cycles initiated (%); 1 cycle ≈ 28 days			
Median	17.0	15.0	10.0
Range	1; 83	1; 83	1; 83
1-3 cycles	39 (14%)	63 (18%)	118 (28%)
4-6 cycles	25 (9%)	38 (11%)	47 (11%)
7-9 cycles	29 (11%)	33 (10%)	37 (9%)
10-12 cycles	19 (7%)	22 (6%)	24 (6%)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.3: Duration of exposure

	Analysis Set		
	EE-NF (n=272)	**O-NF (n=347)**	**OS (n=418)**
13-15 cycles	15 (6%)	18 (5%)	18 (4%)
16-18 cycles	14 (5%)	15 (4%)	15 (4%)
19-21 cycles	12 (4%)	13 (4%)	13 (3%)
22-24 cycles	19 (7%)	22 (6%)	22 (5%)
25-27 cycles	12 (4%)	13 (4%)	13 (3%)
28-30 cycles	11 (4%)	14 (4%)	15 (4%)
31-33 cycles	10 (4%)	10 (3%)	10 (2%)
34-36 cycles	3 (1%)	6 (2%)	6 (1%)
37-39 cycles	8 (3%)	10 (3%)	10 (2%)
40-42 cycles	7 (3%)	9 (3%)	9 (2%)
43-45 cycles	4 (1%)	6 (2%)	6 (1%)
46-48 cycles	6 (2%)	9 (3%)	9 (2%)
49-51 cycles	7 (3%)	7 (2%)	7 (2%)
52-54 cycles	6 (2%)	6 (2%)	6 (1%)
55-57 cycles	3 (1%)	5 (1%)	5 (1%)
58-60 cycles	6 (2%)	6 (2%)	6 (1%)
61-63 cycles	3 (1%)	4 (1%)	4 (<1%)
64-66 cycles	3 (1%)	5 (1%)	5 (1%)
>66 cycles	11 (4%)	13 (4%)	13 (3%)

EE-NF = Efficacy-evaluable NTRK Fusion (Analysis Set); O-NF = Overall NTRK Fusion (Analysis Set); OS = Overall Safety (Analysis Set).
Source: Tables 14.1 / 6, Integrated Summary of Safety (Visit Cut-off 20 JUL 2022)

Table SIII.4: Initial Vitrakvi® dose and dosage modifications

Starting dose, n (%)	**Analysis Set**		
	EE-NF (n=272)	**O-NF (n=347)**	**OS (n=418)**
Adult patients (18 years and older)			
Number (%) of adult patients	178 (65)	213 (61)	275 (66)
50 mg QD	0 (0)	0 (0)	4 (<1)
100 mg QD	0 (0)	0 (0)	5 (1)
100 mg BID	176 (65)	211 (61)	248 (59)
200 mg QD	0 (0)	0 (0)	5 (1)
150 mg BID	2 (<1)	2 (<1)	7 (2)
200 mg BID	0 (0)	0 (0)	6 (1)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.4: Initial Vitrakvi® dose and dosage modifications

Starting dose, n (%)	Analysis Set		
	EE-NF (n=272)	O-NF (n=347)	OS (n=418)
Paediatric patients (Less than 18 years)			
Number (%) of paediatric patients	94 (35)	134 (39)	143 (34)
Cohort 1 (9.6–55.0 mg/m^2 BID)	3 (1)	3 (<1)	4 (<1)
Cohort 2 (17.3–120.0 mg/m^2 BID)	6 (2)	7 (2)	10 (2)
Cohort 3 (100 mg/m^2 BID)[a]	85 (31)	124 (36)	129 (31)
Dosage modifications[b, c]	**232 (85)**	**285 (82)**	**339 (81)**
Dose missed, skipped, or delayed	230 (85)	281 (81)	335 (80)
Dose reduced	58 (21)	74 (21)	84 (20)
Dose increased	65 (24)	81 (23)	82 (20)
Reason for dose reduction			
Adverse event	37 (14)	41 (12)	50 (12)
Protocol violation	1 (<1)	2 (<1)	2 (<1)
Other reason	29 (11)	42 (12)	43 (10)
Pharmacokinetics	0 (0)	1 (<1)	1 (<1)
Reason for dose increase			
Protocol violation	3 (1)	5 (1)	5 (1)
Pharmacokinetics	5 (2)	6 (2)	6 (1)
Adverse event	1 (<1)	2 (<1)	2 (<1)
Other reason	59 (22)	74 (21)	75 (18)

[a] Not to exceed 100 mg per dose; [b] Patients may be counted in more than one row; c Modifications include dose skipped, missed, delayed, reduced.
BID = Two times a day (bis in die); EE-NF = Efficacy-evaluable NTRK Fusion (Analysis Set); O-NF = Overall NTRK Fusion (Analysis Set); OS = Overall Safety (Analysis Set); QD = Once daily (quaque die).
Source: Tables 14.1 / 2; 14.1 / 3; 4.1 / 7, (Visit Cut-off 20 JUL 2022)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.5: Demographics by analysis set

Demographic Parameter	Analysis Set		
	EE-NF (n=272)	O-NF (n=347)	OS (n=418)
Age, years			
Mean (SD)	36.82 (26.82)	35.60 (27.09)	38.44 (26.67)
Median	41.0	38.0	45.0
Range	0.1, 90.0	0.1, 90.0	0.1, 90.0
<1 month	2 (<1%)	2 (<1%)	2 (<1%)
1 month - <1 year	33 (12%)	34 (10%)	34 (8%)
1 - <2 years	8 (3%)	10 (3%)	10 (2%)
2 - <6 years	20 (7%)	31 (9%)	33 (8%)
6 - <12 years	17 (6%)	33 (10%)	34 (8%)
12 - <16 years	10 (4%)	19 (5%)	23 (6%)
16 - <18 years	4 (1%)	5 (1%)	7 (2%)
18 - <45 years	50 (18%)	57 (16%)	65 (16%)
45 - <65 years	77 (28%)	91 (26%)	126 (30%)
65 - <75 years	36 (13%)	45 (13%)	61 (15%)
≥ 75 years	15 (6%)	20 (6%)	23 (6%)
Sex, n (%)			
Female	138 (51)	178 (51)	216 (52)
Male	134 (49)	169 (49)	202 (48)
Race, n (%)			
White	154 (57)	198 (57)	250 (60)
Other	25 (9)	35 (10)	40 (10)
Black or African American	6 (2)	8 (2)	17 (4)
Not reported	6 (2)	7 (2)	11 (3)
Asian	78 (29)	96 (28)	97 (23)
American Indian or Alaska Native	1 (<1)	1 (<1)	1 (<1)
Multiple	1 (<1)	1 (<1)	1 (<1)
Native Hawaiian or other Pacific Islander	1 (<1)	1 (<1)	1 (<1)
Ethnicity, n (%)			
Not Hispanic or Latino	228 (84)	292 (84)	349 (83)
Hispanic or Latino	17 (6)	21 (6)	31 (7)
Not reported	24 (9)	29 (8)	33 (8)
Unknown	3 (1)	5 (1)	5 (1)
Baseline ECOG, n (%)			
0: Normal activity	138 (51)	177 (51)	197 (47)
1: Symptoms, but ambulatory	103 (38)	130 (37)	178 (43)

Table SIII.5: Demographics by analysis set

Demographic Parameter	Analysis Set		
	EE-NF (n=272)	O-NF (n=347)	OS (n=418)
2: In bed less than 50% of time	25 (9)	33 (10)	36 (9)
3: In bed greater than 50% of time	6 (2)	6 (2)	6 (1)
Not reported	0 (0)	1 (<1)	1 (<1)

ECOG = Eastern Cooperative Oncology Group (Performance Status); EE-NF = Efficacy-evaluable NTRK Fusion (Analysis Set); O-NF = Overall NTRK Fusion (Analysis Set); OS = Overall Safety (Analysis Set); SD = Standard deviation.
Source: Table 14.1 / 3 Integrated Summary of Safety (Visit Cut-off 20 JUL 2022).

SIII.2 Special Populations

Single-dose clinical studies LOXO-TRK-16013 and LOXO-TRK-17014 were conducted to evaluate the safety profile of Vitrakvi® in adult subjects with impaired hepatic function, and in subjects with end-stage renal disease, respectively.

Studies overview and patient demographics characteristics for both studies are presented in Table SIII.6 and Table SIII.7. Pharmacokinetic parameters and exposure data for study LOXO-TRK-16013 are available in Table SIII.8 and in Table SIII.11 and Table SIII.12 for study LOXO-TRK-17014. Table SIII.9 and Table SIII.10 list adverse event data for study LOXO-TRK-16013. There were no deaths, serious adverse events (SAEs), or adverse events (AEs) leading to study discontinuation and no AEs were reported by any of the subjects in study LOXO-TRK-17014.

Table SIII.6: Overview of clinical studies of Vitrakvi® in special populations

Study ID	Phase	Country	Study Title	Dosing Regimen	Study Population	Enrolment
LOXO-TRK-16013	1	USA	Open-label, nonrandomized, single-dose, parallel-group, safety, tolerance, and pharmacokinetic study of LOXO-101 administered at 100 mg in fasted hepatically impaired male and female subjects and fasted matched-control healthy subjects	A single 100 mg dose, administered in the morning	Healthy controls	11
					Mild hepatic impairment	8
					Moderate hepatic impairment	8
					Severe hepatic impairment	8

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.6: Overview of clinical studies of Vitrakvi® in special populations

Study ID	Phase	Country	Study Title	Dosing Regimen	Study Population	Enrolment
LOXO-TRK-17014	1	USA	A phase 1, open-label, parallel-cohort, single-dose study to evaluate the pharmacokinetics of LOXO-101 in subjects with end-stage renal disease.	A single 100 mg dose, administered in the morning	Healthy controls	8
					End-stage renal disease requiring haemodialysis	8

USA = United States of America

Table SIII.7: Demographics by study

Demographic Parameter	LOXO-TRK-16013 (n=35)				LOXO-TRK-17014 (n=16)	
	Normal HF (n=11)	Mild HI[a] (n=8)	Moderate HI[a] (n=8)	Severe HI[a] (n=8)[b]	ESRD (n=8)	Healthy (n=8)
Age, years						
Mean (SD)	59 (4.6)	57 (4.6)	57 (5.8)	56 (5.9)	51.5 (8.3)	51.8 (6.6)
Median	60	57	58	58	51.5	52.0
Range	49, 65	50, 64	49, 65	48, 62	40, 61	43, 60
Sex, n (%)						
Female	4 (36.4)	3 (37.5)	1 (12.5)	2 (25.0)	1 (13)	1 (13)
Male	7 (63.6)	5 (62.5)	7 (87.5)	6 (75.0)	7 (88)	7 (88)
Race, n (%)						
White	8 (72.7)	7 (87.5)	6 (75.0)	8 (100)	2 (25)	4 (50)
Black or African American	2 (18.2)	1 (12.5)	1 (12.5)	0 (0)	6 (75)	4 (50)
Asian	1 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
American Indian or Alaska Native	0 (0)	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)
Ethnicity, n (%)						
Not Hispanic or Latino	7 (64)	6 (75)	4 (50)	1 (12.5)	7 (88)	6 (75)
Hispanic or Latino	4 (36)	2 (25)	4 (50)	7 (87.5)	1 (13)	2 (25)

[a] To be classified as having hepatic impairment, subjects must have had a Child Pugh (CP) score of 5 to 6 (mild), 7 to 9 (moderate), or 10 to 14 (severe), with known medical history of liver disease
[b] One subject had a Child-Pugh (CP) score of 10 at screening (consistent with severe hepatic impairment), however at check in (Day -1) had a CP score of 9 (consistent with moderate hepatic impairment). Per the Protocol, impaired subjects were to be assigned to groups per their CP scores at Screening and thus this subject was included in the severe hepatic impairment group.
CP: Child Pugh; ESRD = End-stage renal disease; HF = Hepatic function; HI = Hepatic impairment; SD = Standard deviation.
Sources: Table 14-1-2, LOXO-TRK-16013 Clinical Study Report (Report Date: 17 MAY 2018); Table 11-1, LOXO-

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.7: Demographics by study

Demographic Parameter	LOXO-TRK-16013 (n=35)				LOXO-TRK-17014 (n=16)	
	Normal HF (n=11)	Mild HI[a] (n=8)	Moderate HI[a] (n=8)	Severe HI[a] (n=8)[b]	ESRD (n=8)	Healthy (n=8)

TRK-17014 Clinical Study Report (Report Date: 09 MAR 2018)

Table SIII.8: Summary of the pharmacokinetic parameters of Vitrakvi® following single oral administration of 100 mg Vitrakvi® to subjects with normal hepatic function and subjects with mild, moderate, or severe hepatic impairment

Parameter	LOXO-TRK-16013 (n=35)			
	Normal HF (n=11)	Mild HI (n=8)	Moderate HI (n=8)	Severe HI (n=8)
Bound				
AUC_{0-t} (h*ng/mL)	1,100 (50.5)	1,390 (16.5)	2,300 (41.7)	3,500 (44.5)
$AUC_{0-\infty}$ (h*ng/mL)	1,110 (50.6)	1,410 (16.5)	2,320 (41.4)	3,530 (43.9)
C_{max} (ng/mL)	518 (49.4)	567 (22.0)	654 (30.5)	799 (53.5)
tmax[a] (h)	0.500 (0.417-2.0)	1.00 (0.50-1.03)	1.00 (0.50-2.0)	0.500 (0.50-3.0)
$t_{1/2}$[b] (h)	5.39 (5.12)	8.19 (4.63)	8.13 (3.61)	7.92 (3.31)
t_{last}[a] (h)	24.0 (12.0-48.0)	24.0 (24.0-48.0)	36.0 (24.0-48.0)	48.0 (36.0-48.0)
CL/F (L/h)	90.3 (50.6)	71.1 (16.5)	43.0 (41.4)	28.3 (43.9)
V_d/F (L)	504 (65.6)	737 (56.5)	468 (67.8)	301 (65.9)
Unbound				
$AUC_{0-\infty,u}$ (h*ng/mL)	344 (48.4)	469 (22.1)	728 (44.3)	1,220 (47.3)
$C_{max,u}$ (ng/mL)	161 (46.8)	189 (21.6)	205 (29.0)	276 (55.8)
CL/F_u (L/h)	291 (48.4)	213 (22.1)	137 (44.3)	82.0 (47.3)
V_d/F_u (L)	1,620 (61.1)	2,210 (57.9)	1,490 (66.2)	873 (67.4)

AUC_{0-t} = area under the concentration-time curve from Hour 0 to the time of last measurable concentration (t_{last}); $AUC_{0-\infty}$ = area under the concentration-time curve extrapolated to infinity; C_{max} = maximum observed concentration; CL/F = apparent systemic clearance; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time to maximum observed concentration; t_{last} = time of last measurable concentration; V_d/F = apparent volume of distribution during the terminal phase.
$AUC_{0-\infty,u}$ = unbound area under the concentration-time curve extrapolated to infinity; $C_{max,u}$ = unbound maximum observed concentration; CL/F_u = unbound CL/F; V_d/F_u = unbound V_d/F.
Note: Geometric mean (CV%) data are presented; [a] Median (Min-Max) data are provided for t_{max} and t_{last}; [b] Arithmetic mean (SD) data are provided for $t_{1/2}$.
Sources: Table 6, 7 LOXO-TRK-16013 Clinical Study Report (Report Date: 17 MAY 2018).

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.9: Summary of Treatment-Emergent Adverse Events (TEAEs)

	LOXO-TRK-16013 (n=35)				
	Normal HF (n=11)	**Mild HI (n=8)**	**Moderate HI (n=8)**	**Severe HI (n=8)**	**Overall (n=35)**
Severity (All Causalities)					
Grade 1/Mild	1 (9.1%) [1]	4 (50.0%) [4]	1 (12.5%) [1]	1 (12.5%) [1]	7 (20.0%) [7]
Grade 2/Moderate		1 (12.5%) [1]	1 (12.5%) [1]		2 (5.7%) [2]
Total	1 (9.1%) [1]	4 (50.0%) [5]	2 (25.0%) [2]	1 (12.5%) [1]	8 (22.9%) [9]
Severity (Related)					
Grade 1/Mild		3 (37.5%) [3]	1 (12.5%) [1]	1 (12.5%) [1]	5 (14.3%) [5]
Grade 2/Moderate		1 (12.5%) [1]			1 (2.9%) [1]
Total		3 (37.5%) [4]	1 (12.5%) [1]	1 (12.5%) [1]	5 (14.3%) [6]

n = number of subjects; TEAE = treatment-emergent adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events. Note: ( ) = percentage of subjects with adverse events; [ ] = number of adverse events.
For adverse events that changed severity rating, the adverse event was included only once, under the maximum severity rating.
Severity of events was categorized based on the NCI CTCAE Version 4.03
Sources: Table 14.3.1-1, LOXO-TRK-16013 Clinical Study Report (Report Date: 17 MAY 2018).

Table SIII.10: Frequency of Treatment-emergent Adverse Events (all causalities)

MedDRA System Organ Class **Preferred Term**	LOXO-TRK-16013 (n=35)				
	Normal HF (n=11)	**Mild HI (n=8)**	**Moderate HI (n=8)**	**Severe HI (n=8)**	**Overall (n=35)**
Overall Total	1 (9.1%) [1]	4 (50.0%) [5]	2 (25.0%) [2]	1 (12.5%) [1]	8 (22.9%) [9]
Nervous system disorders					
Somnolence		1 (12.5%) [1]	1 (12.5%) [1]	1 (12.5%) [1]	3 (8.6%) [3]
Headache		1 (12.5%) [1]			1 (2.9%) [1]
Presyncope		1 (12.5%) [1]			1 (2.9%) [1]
Total		2 (25.0%) [3]	1 (12.5%) [1]	1 (12.5%) [1]	4 (11.4%) [5]
General disorders and administration site conditions					
Fatigue		1 (12.5%) [1]			1 (2.9%) [1]
Malaise		1 (12.5%) [1]			1 (2.9%) [1]
Vessel puncture site haemorrhage	1 (9.1%) [				1 (2.9%) [1]
Total	1 (9.1%) [	2 (25.0%) [2]			3 (8.6%) [3]
Metabolism and nutrition disorders					
Hypoalbuminaemia			1 (12.5%) [1]		1 (2.9%) [1]
Total			1 (12.5%) [1]		1 (2.9%) [1]

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.10: Frequency of Treatment-emergent Adverse Events (all causalities)

MedDRA System Organ Class Preferred Term	LOXO-TRK-16013 (n=35)				
	Normal HF (n=11)	Mild HI (n=8)	Moderate HI (n=8)	Severe HI (n=8)	Overall (n=35)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.
Note: ( ) = percentage of subjects with adverse events; [ ] = number of adverse events; events were coded using MedDRA (Version 18.1).
For adverse events that changed severity rating, the adverse event was included only once, under the maximum severity rating.
Source: Table 14.3.1-2, LOXO-TRK-16013 Clinical Study Report (Report Date: 17 MAY 2018).

Table SIII.11: Summary of plasma Vitrakvi® pharmacokinetics following administration of a single oral dose of 100 mg Vitrakvi® to subjects with end stage renal disease and to healthy matched control subjects under fasted conditions (PK population) – LOXO-TRK-17014.

Pharmacokinetic Parameters	ESRD	Healthy
AUC_{0-t} (ng*hr/mL)	1,680 (85.4) [n=8]	1,204 (29.5) [n=8]
AUC_{0-inf} (ng*hr/mL)	1,701 (84.8) [n=8]	1,167 (26.5) [n=7]
AUC% extrap	1.223 ± 1.1632 [n=8]	1.826 ± 1.5678 [n=7]
C_{max} (ng/mL)	534.0 (67.2) [n=8]	425.7 (55.1) [n=8]
T_{max} (hr)	1.000 (0.50, 2.00) [n=8]	0.750 (0.50, 3.00) [n=8]
K_{el} (1/hr)	0.1826 ± 0.18270 [n=8]	0.1466 ± 0.089707 [n=7]
$t_{1/2}$ (hr)	7.159 ± 5.3580 [n=8]	6.347 ± 3.3119 [n=7]
CL/F (L/hr)	76.15 ± 67.250 [n=8]	88.18 ± 22.646 [n=7]
Vd/F (L)	676.2 ± 780.50 [n=8]	836.0 ± 577.43 [n=7]
MTT (hr)	4.128 ± 1.3257 [n=8]	4.899 ± 2.7379 [n=7]

ESRD (end-stage renal disease): Administration of a single oral dose of 100 mg Vitrakvi® to subjects with ESRD on non-HD days following an overnight fast
Healthy: Administration of a single oral dose of 100 mg Vitrakvi® to healthy match control subjects following an overnight fast
. = Value missing or not reportable
AUCs and C_{max} are presented as geometric mean and geometric CV%
Tmax are presented as median (min, max).
Other parameters are presented as arithmetic mean (± SD)
Sources: Tables 14.2.1.3 and 14.2.1.4, LOXO-TRK-17014 Clinical Study Report (Report Date: 09 MAR 2018).

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module - SIII: Clinical trial exposure

Table SIII.12: Summary of statistical comparisons of plasma Vitrakvi® pharmacokinetic parameters following administration of a single oral dose of 100 mg Vitrakvi® to subjects with end stage renal disease versus healthy matched control subjects under fasted conditions (PK population) – LOXO-TRK-17014

Parameter	ESRD		Healthy			
	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	90% Confidence Interval
AUC_{0-t} (ng*hr/mL)	1,680	8	1,204	8	139.56	85.09 - 228.88
AUC_{0-inf} (ng*hr/mL)	1,701	8	1,167	7	145.77	86.59 - 245.38
C_{max} (ng/mL)	534.0	8	425.7	8	125.43	76.28 - 206.23

ESRD (end-stage renal disease): Administration of a single oral dose of 100 mg Vitrakvi® to subjects with ESRD on non-HD days following an overnight fast
Healthy: Administration of a single oral dose of 100 mg Vitrakvi® to healthy match control subjects following an overnight fast
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANCOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Sources: Table 14.2.1.6, LOXO-TRK-17014 Clinical Study Report (Report Date: 09 MAR 2018).

Part II: Module SIV - Populations not studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table SIV.1: Exclusion criteria in pivotal studies in the Vitrakvi® (larotrectinib; LOXO-101) development program. Studies 20288, 20289, and 20290 (formerly LOXO-TRK-14001, LOXO-TRK-15002 and LOXO-TRK-15003)

Exclusion Criteria	Reasons for Exclusion	Included as missing information?	Rationale for not including as Missing Information
Investigational agent or anticancer therapy within 2 weeks prior to planned start of Vitrakvi®.	Inclusion of these patients would have affected the efficacy and safety endpoints of the study.	No	Use in this patient population is not predicted to be associated with additional risks of clinical significance.
Major surgery within 4 weeks prior to planned start of Vitrakvi®.	Inclusion of these patients would have affected the efficacy and safety endpoints of the study.	No	Use in this patient population is not predicted to be associated with additional risks of clinical significance.
Patients with unstable primary central nervous system (CNS) tumours or metastasis. Exception: Patients with primary CNS tumours or metastasis, whether they have a documented neurotrophic tropomyosin receptor kinase (*NTRK*) 1, 2, or 3 gene translocation or not, may be enrolled if they have been neurologically stable for 14 days, and have not required increasing doses of steroids within the 14 days prior to study entry (C1D1) to manage CNS symptoms.	Inclusion of these patients would have affected the efficacy and safety endpoints of the study.	No	Use in this patient population is not predicted to be associated with additional risks of clinical significance relative to the seriousness of the disease.
Clinically significant active cardiovascular disease or history of myocardial infarction (within 6 months) or stroke (within 3 months) prior to planned start of Vitrakvi®, cardiomyopathy; current or history within past 6 months of prolonged QTc interval >480 milliseconds.	Inclusion of these patients would have affected the safety endpoints of the study.	No	Use in this patient population is not predicted to be associated with additional risks of clinical significance relative to the seriousness of the disease.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SIV - Populations not studied in clinical trials

Table SIV.1: Exclusion criteria in pivotal studies in the Vitrakvi® (larotrectinib; LOXO-101) development program. Studies 20288, 20289, and 20290 (formerly LOXO-TRK-14001, LOXO-TRK-15002 and LOXO-TRK-15003)

Exclusion Criteria	Reasons for Exclusion	Included as missing information?	Rationale for not including as Missing Information
Active uncontrolled systemic bacterial, viral, or fungal infection, or other systemic disease that would limit compliance with study procedures.	Inclusion of these patients would have affected the safety endpoints of the study.	No	Use in this patient population is not predicted to be associated with additional risks of clinical significance.
Malabsorption syndrome or other condition affecting oral absorption.	Inclusion of these patients would have affected efficacy endpoints of the study.	No	Conditions which may cause in malabsorption may result in diminished absorption of Vitrakvi® which may result in reduced efficacy. However, this is the case for all orally administered medicinal products and can be anticipated. Accordingly, use in this patient population is not missing information.
Current treatment with a strong CYP3A4 inhibitor or inducer	Inclusion of these patients would have affected the efficacy and safety endpoints of the study.	No	Drug-drug interaction (DDI) studies showed that Vitrakvi® is a substrate for CYP3A4/5.
Pregnancy or lactation	Excluded for safety reasons based on results of toxicology studies. No human data are available.	Yes	Not applicable.
Prior progression while receiving approved or investigational tyrosine kinase inhibitors targeting TRK. Subjects who received less than 28 days of treatment and discontinued because of intolerance or toxicity are eligible.	Inclusion of these patients would have affected efficacy endpoints of the study.	No	Use in this patient population is not predicted to be associated with additional risks of clinical significance.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SIV - Populations not studied in clinical trials

Table SIV.1: Exclusion criteria in pivotal studies in the Vitrakvi® (larotrectinib; LOXO-101) development program. Studies 20288, 20289, and 20290 (formerly LOXO-TRK-14001, LOXO-TRK-15002 and LOXO-TRK-15003)

Exclusion Criteria	Reasons for Exclusion	Included as missing information?	Rationale for not including as Missing Information
Uncontrolled concurrent malignancy that would limit assessment of efficacy of Vitrakvi®. Allowed conditions may include but are not limited to in situ cancers of cervix, breast, or skin, superficial bladder cancer, limited stage prostate cancer, basal or squamous cancers of the skin.	Inclusion of these patients would have affected efficacy endpoints of the study.	No	Use in this patient population is not predicted to be associated with additional risks of clinical significance.

SIV.2 Limitations to Detect Adverse reactions in Clinical Trial Development Programmes

The safety of Vitrakvi® described in this section was evaluated in 418 patients (overall safety population) with unresectable or metastatic solid tumours, irrespective of NTRK gene fusion status, who received at least one dose of Vitrakvi® in one of three ongoing clinical trials. Median time on treatment with Vitrakvi® for the overall safety population in ongoing clinical trials was 9.35 months (range: 0.00 to 75.5, cut-off 20 JUL 2022).

The clinical development program is unlikely to detect certain types of adverse reactions such as uncommon (1/100 to 1/1,000) adverse reactions or adverse reactions with a long latency, or those caused by prolonged exposure (Table SIV.2).

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SIV - Populations not studied in clinical trials

Table SIV.2: Limitations to detect adverse reactions

Ability to detect adverse reaction	Limitation of trial program	Discussion of implications for target population
Which are rare	418 patients were treated with Vitrakvi® in the development program.	It is unlikely that a rare adverse reaction will impact the benefit/risk balance of Vitrakvi® in a target population with a life-threatening disease.
Due to prolonged exposure Due to cumulative effects	Vitrakvi® was evaluated for up to 75.2 months (SmPC) in ongoing clinical trials.	Based on the available safety data, prolonged and high cumulative exposure may result in increased liver, hematologic and CNS toxicity and increase the risk of neurologic reactions, hepatotoxicity and myelosuppression.
Which have a long latency	Long term follow-up for Adverse Events of Special Interest (AESIs), and paediatric development in ongoing clinical trials.	Considering the reduced life-expectancy of the target population the implications are limited.

SIV.3 Limitations in Respect to Populations Typically under-represented in Clinical Trial Development Programmes

Table SIV.3: Exposure of special populations included or not in clinical trial development programs

Type of Special Population	Exposure (n=418)[a]
Elderly population	61 (15.0%) of the patients were 65 - <75 years of age, and 23 (6%) were ≥75 years of age.
Paediatric population	143 (34%) of the patients were paediatric patients (<18 years old).
Pregnant women	None
Breastfeeding women	None
Patients with relevant comorbidities:	24[b]
Patients with hepatic impairment	8[c]
Patients with renal impairment	None
Patients with cardiac impairment	
Population with relevant different ethnic origin	Most of the patients were White (60%), Black or African American (4%), Asian (23%), and other (10%).
Subpopulations carrying relevant genetic polymorphisms	347 (83%) of the patients were documented *NTRK* gene fusion carriers

[a] Excluding patients exposed in single-dose studies LOXO-TRK-16013 and LOXO-TRK17014.
[b] LOXO-TRK-16013: a single-dose study in patients with hepatic impairment; 11 healthy controls, and subjects with mild (n=8), moderate (n=8), and severe (n=8) hepatic impairment.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SIV - Populations not studied in clinical trials

Table SIV.3: Exposure of special populations included or not in clinical trial development programs

Type of Special Population	Exposure (n=418)[a]

[c] LOXO-TRK-17014: a single dose study in patients with end-stage renal disease; 8 healthy controls, and 8 subjects with end-stage renal disease.

Part II: Module SV - Post-authorisation Experience

SV.1 Post-authorisation exposure

SVI.1 Method used to calculate exposure

The method to estimate patient exposure is a very high / conservative estimate based on the assumption that the patients took the maximum recommended dose of 100 mg BID (assuming every patient will take the drug *200 mg/day *365 days/year).

The patient exposure to the marketed product Vitrakvi® was calculated using the number of sold units of Vitrakvi® capsule and solution divided by the estimated maximum recommended daily dose.

Number of patient-years of exposure to the marketed product equals:

- For 100 mg capsules,
  100 mg * number capsules sold

  [200 mg/d * 365 d/year]
- For 25 mg capsules,
  25 mg * number capsules sold

  [200 mg/d * 365 d/year]
- For 20 mg/ml solution,
  20 mg/ml * number of ml sold

  [200 mg/d * 365 d/year]

SVI.1 Exposure

Vitrakvi® was approved by the US FDA on 26 NOV 2018. The distributed volume of Vitrakvi® between 26 NOV 2018 (Date of first marketing authorisation in the USA) and 30 APR 2023 was 337,878 100 mg capsules, 33,645 25 mg capsules, and 123,245 ml of Vitrakvi® (100 ml bottle, 20 mg/ml solution). The number of capsules and bottles of Vitrakvi® solution sold represents an estimated post-marketing exposure of 1,355.53 patient-years (see Table SV.1).

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SV - Post-authorisation experience

Table SV.1: Larotrectinib (Vitrakvi®) – Sales volume in estimated daily doses and estimated post-marketing exposure.

Dosage form and strength	Estimated daily doses distributed[a]	Estimated exposure Patient-years
100 mg capsule	337,878	925.69
20 mg/ml oral solution	123,245	337.66
25 mg capsule	33,645	92.18
Total	**494,768**	**1,355.53**

[a]Dosing for paediatric patients with a body surface area of <1.0 m^2 is based on body surface area, the data presented in this table is an estimate based on the maximum recommended daily dose (100 mg BID). Sales data from the International birth date (26 NOV 2018) and until 30 APR 2023.

BID: twice daily.

Part II: Module SVI - Additional EU requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

The established pharmacological profile of the active ingredients in the product Vitrakvi® does not give reason to assume any risk for misuse for illegal purposes.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

All the adverse reactions outlined in Table SVII.1 are reflected as ADRs in the Vitrakvi® Summary of medicinal product characteristics (SmPC).

Table SVII.1: Adverse reactions and laboratory abnormalities reported for ≥5% of all grades in patients treated with Vitrakvi®

Adverse Reaction / Laboratory abnormality	Patient Incidence, n (%); **N = 208**				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**All**
Blood and Lymphatic System Disorders					
Anaemia	20 (10)	15 (7)	20 (10)	0 (0)	55 (26)
Neutrophil count decreased (Neutropenia)	5 (2)	9 (4)	9 (4)	2 (1)	25 (12)
Leucocyte count decreased (Leukopenia)	17 (8)	3 (1)	2 (1)	0 (0)	22 (11)
Nervous System Disorders					
Dizziness	52 (25)	7 (3)	2 (1)	na	61 (29)
Paraesthesia	11 (5)	2 (1)	2 (1)	na	15 (7)
Gait Disturbance	7 (3)	4 (2)	2 (1)	na	13 (6)
Gastrointestinal Disorders					
Nausea	50 (24)	7 (3)	2 (1)	na	59 (28)
Constipation	45 (22)	10 (5)	1 (0)	0 (0)	56 (27)
Vomiting	36 (17)	12 (6)	1 (0)	0 (0)	49 (24)
Dysgeusia	18 (9)	0 (0)	na	na	18 (9)
Musculoskeletal and Connective Tissue Disorders					
Myalgia	24 (12)	8 (4)	2 (1)	na	34 (16)
Muscular weakness	16 (8)	10 (5)	0 (0)	na	26 (13)
General Disorders and Administrative Site Conditions					
Fatigue	37 (18)	31 (15)	6 (3)	na	74 (36)
Investigations					
Aspartate aminotransferase (AST) increased	38 (18)	11 (5)	6 (3)	0 (0)	55 (26)
Alanine aminotransferase (ALT) increased	37 (18)	11 (5)	6 (3)	1 (0)	55 (26)
Weight increased (abnormal weight gain)	13 (6)	10 (5)	7 (3)	na	30 (14)
Blood alkaline phosphatase increased	10 (5)	6 (3)	1 (0)	0 (0)	17 (8)

na = not applicable, i.e. no Grade 3/4 severity denoted in NCI-CTCAE v4.03

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.1: Adverse reactions and laboratory abnormalities reported for ≥5% of all grades in patients treated with Vitrakvi®

Adverse Reaction / Laboratory abnormality	Patient Incidence, n (%); N = 208				
	Grade 1	Grade 2	Grade 3	Grade 4	All

Sources: Table 14.4.4: TEAEs by PT and maximum severity Integrated Summary of Safety (Data Exported 27 NOV 2018, Visit Cut-off 30 JUL 2018)

The risks presented in table above are not considered as important identified risks by themselves as their clinical impact on patients is considered minimal in relation to the severity of the indication and do not substantially impact on Vitrakvi® benefit risk profile. However, PTs “dizziness”, “paraesthesia” and “gait disturbance” are evaluated in the context of important potential risk “severe neurologic reactions”. Likewise, PTs “Blood alkaline phosphatase increased”, “AST increased”, and “ALT increased” are evaluated in the context of important potential risk “severe drug-induced liver injury”.

Overall, this assessment is based on the fact that:

- The majority of adverse reactions were Grade 1 or 2.
- Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (1%) and ALT increased (<1%).
- The highest reported grade was Grade 3 for adverse reactions anaemia, weight increased, fatigue, increased AST, dizziness, gait disturbance, paraesthesia, nausea, myalgia, leukocyte count decreased, vomiting, constipation, and blood alkaline phosphatase increased.
- All the reported Grade 3 adverse reactions occurred in less than 5% of patients with the exception of anaemia (10%).

Further detailed justification for adverse reactions outlined in Table SVII.1 is provided in section SVII.1.1.1 below.

SVII.1.1.1 Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Table SVII.2: List of adverse reactions and the justification for non-Inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-Inclusion
Blood and lymphatic system disorders	
Anaemia	Frequency / Seriousness: Anaemia has been reported as TEAE in 26% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as very common ADR in the proposed SmPC. However, confounded by underlying malignancies, i.e. tumour-associated anaemia as also reflected by the fact that the majority of events have been

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.2: List of adverse reactions and the justification for non-Inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-Inclusion
	reported as unrelated. - Mainly events of Grade 1 and Grade 2 severity. - Grade 3 events (i.e. *"Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated"* according to NCI-CTCAE v4.03 severity grading) reported in 10% of patients. - No respective Grade 4/5 events, two serious adverse events and 5 anaemia-associated dose modifications (no permanent discontinuations), one of them related to study drug were reported. - Also, no reported events like shortness of breath or heart beat increases which might be associated with clinically relevant anaemia. Clinical and benefit/risk impact: Taking into account that the majority of patients do have primarily a decrease in haemoglobin values without associated clinical signs/symptoms, the risk of Vitrakvi®-associated anaemia is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Therefore, reflection as very common ADR in proposed SmPC is considered as sufficient.
General disorders and administration site conditions	
Fatigue	Frequency / Seriousness: Fatigue has been reported as TEAE in 36% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as very common ADR in the proposed SmPC. However, confounded by underlying malignancies, i.e., tumour-associated fatigue as also reflected by the fact that the vast majority of events have been reported as unrelated. - Mainly events of Grade 1 and Grade 2 severity. - Grade 3 events (i.e., *"Fatigue not relieved by rest, limiting self-care activities of daily living (ADL)"* according to NCI-CTCAE v4.03 severity grading) reported in 3% of patients (Please note: For fatigue no Grade 4/5 severity denoted in NCI-CTCAE v4.03). - Two serious adverse events, both reported as unrelated. - Dose modifications due to fatigue in 2% of patients. - Permanent discontinuations due to fatigue in <1% of patients, reported as unrelated. Clinical and benefit/risk impact: Taking into account that the vast majority of patients do have fatigue events not impacting on self-care ADL, the risk of Vitrakvi®-associated fatigue is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Therefore, reflection as very common ADR in proposed SmPC is considered as sufficient.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.2: List of adverse reactions and the justification for non-Inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-Inclusion
Gastrointestinal disorders	
Nausea	Frequency / Seriousness: Nausea has been reported as TEAE in 28% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as very common ADR in the proposed SmPC. - Mainly events of Grade 1 and Grade 2 severity. - Grade 3 events (i.e., *"Inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition (TPN), or hospitalization indicated"* according to NCI-CTCAE v4.03 severity grading) reported in 1% of patients (Please note: For nausea no Grade 4/5 severity denoted in NCI-CTCAE v4.03). - Two reported serious adverse events. - Dose modifications due to nausea in 2% of patients. - Permanent discontinuations due to nausea in <1% of patients. Clinical and benefit/risk impact: Taking into account that the vast majority of patients do have nausea events of Grade 1 (i.e. *"Loss of appetite without alteration in eating habits"*) or Grade 2 (i.e. *"Oral intake decreased without significant weight loss, dehydration or malnutrition"*) according to NCI-CTCAE v4.03 severity grading, the risk of Vitrakvi®-associated nausea is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Therefore, reflection as very common ADR in proposed SmPC is considered as sufficient.
Vomiting	Frequency / Seriousness: Vomiting has been reported as TEAE in 24% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as very common ADR in the proposed SmPC. - Mainly events of Grade 1 and Grade 2 severity. - One reported Grade 3 event (i.e., *">=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated"* according to NCI-CTCAE v4.03 severity grading) – No reported Grade 4 event (Please note: For vomiting no Grade 5 severity denoted in NCI-CTCAE v4.03). – Three reported serious adverse events. – Dose modifications in 2% of the patients due to vomiting, that was reported as unrelated. – Permanent discontinuations in <1% of the patients due to vomiting, that was reported as unrelated. Clinical and benefit/risk impact: Taking into account that only one Grade 3 vomiting event has been reported, the risk of Vitrakvi®-associated vomiting is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Therefore, reflection as very common ADR in proposed SmPC is considered

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.2: List of adverse reactions and the justification for non-Inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-Inclusion
	as sufficient.
Constipation	Frequency / Seriousness: Vomiting has been reported as TEAE in 27% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as very common ADR in the proposed SmPC. - Mainly events of Grade 1 and Grade 2 severity. - One reported Grade 3 event (i.e., *"Obstipation with manual evacuation indicated; limiting self-care ADL"* according to NCI-CTCAE v4.03 severity grading) - No reported Grade 4 event (Please note: For constipation no Grade 5 severity denoted in NCI-CTCAE v4.03). - Two reported serious adverse events. - Dose modifications due to constipation in <1% of patients, reported as unrelated. - No permanent discontinuations due to constipation. Clinical and benefit/risk impact: Taking into account that only one Grade 3 constipation event has been reported, the risk of Vitrakvi®-associated constipation is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Therefore, reflection as very common ADR in proposed SmPC is considered as sufficient.
Dysgeusia	Frequency / Seriousness: Dysgeusia has been reported as TEAE in 9% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as common ADR in the proposed SmPC. - All of Grade 1, i.e. *"Altered taste but no change in diet"* according to NCI-CTCAE v4.03 severity grading (Please note: For dysgeusia no Grade 3/4/5 severity denoted in NCI-CTCAE v4.03). - No reported serious adverse events, no dose modifications (including permanent discontinuations) due to dysgeusia. Clinical and benefit/risk impact: Taking into account that only Grade 1 dysgeusia events have been reported, the risk of Vitrakvi®-associated dysgeusia is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Therefore, reflection as common ADR in proposed SmPC is considered as sufficient.
Musculoskeletal and connective tissue disorders	
Myalgia	Frequency / Seriousness: Myalgia has been reported as TEAE in 16% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as very common ADR in the proposed SmPC. - Mainly events of Grade 1 and Grade 2 severity

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.2: List of adverse reactions and the justification for non-Inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-Inclusion
	- Grade 3 events (i.e. "*Severe pain; limiting self-care ADL"* according to NCI-CTCAE v4.03 severity grading) reported in 1% of patients (Please note: For myalgia no Grade 4/5 severity denoted in NCI-CTCAE v4.03). – One reported serious adverse event – Dose modifications due to myalgia in <1% of patients. – No permanent discontinuations due to myalgia. Clinical and benefit/risk impact: Taking into account that most of reported myalgia events have been reported as of Grade 1 or Grade 2 severity, the risk of Vitrakvi®-associated myalgia is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Therefore, reflection as very common ADR in proposed SmPC is considered as sufficient.
Muscular weakness	Frequency / Seriousness: Muscular weakness has been reported as TEAE in 13% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as very common ADR in the proposed SmPC. - All events of Grade 1 and Grade 2 severity (Please note: For muscular weakness no Grade 4/5 severity denoted in NCI-CTCAE v4.03). - Two reported serious adverse events. - Dose modifications due to muscular weakness in 1% of patients. - Permanent discontinuations due to muscular weakness in <1% of patients. Clinical and benefit/risk impact: Taking into account that none of the reported muscular weakness events has been of Grade 3 severity (i.e. *"Limiting self-care ADL; disabling"* according to NCI-CTCAE v4.03 severity grading), the risk of Vitrakvi®-associated muscular weakness is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Therefore, reflection as very common ADR in proposed SmPC is considered as sufficient.
Investigations	
Weight increase	Frequency / Seriousness: Weight increase has been reported as TEAE in 14% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as very common ADR in the proposed SmPC. - Majority of reported events of Grade 1 and Grade 2 severity – Grade 3 events (i.e. *"≥20% from baseline"* according to NCI-CTCAE v4.03 severity grading) reported in 3% of patients (Please note: For weight increase/gain no Grade 4/5 severity denoted in NCI-CTCAE v4.03). - No reported serious adverse events, no dose modifications (including permanent discontinuations) due to weight increase. Clinical and benefit/risk impact:

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.2: List of adverse reactions and the justification for non-Inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-Inclusion
	On-target CNS effects are potentially mediated via the inhibition of the NTRKB, a receptor thought to regulate body weight (290). A potential class effect cannot be excluded, an observation supported by clinical trial data for entrectinib, with weight gain reported with a similar frequency as for Vitrakvi® (14% vs 10% for entrectinib) (291, 292). The methodology for the calculation of changes in body weight and analysis of adverse event of weight increase differs in paediatric and adult patients. The Centers for Disease Control (CDC) growth charts were used as reference material for the determination of age- and sex-adjusted body weight percentiles in paediatric patients. For adults, the percentage change from absolute values recorded at baseline was used in the analysis. In the overall safety analysis set, a total of 10/56 (18%) of paediatric and 20/152 (13%) of adult patients reported "weight increased" as an adverse event. Relatedness rate for "weight increased" was 47%. Due to confounding by other concurrent and/or pre-existing medical conditions, real aetiology of weight increase in oncological patients is multifactorial by nature. Taking into account that most of reported weight increase events have been reported as of Grade 1 or Grade 2 severity, the risk of Vitrakvi®-associated weight increases is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Therefore, reflection as very common ADR in proposed SmPC is considered as sufficient.
Laboratory abnormalities	
Leukocyte count decrease	Frequency / Seriousness: Leukocyte count decrease has been reported as TEAE in 11% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as common ADR in the proposed SmPC. - Majority of reported events are of Grade 1 and Grade 2 severity, i.e. no decrease <2,000/mm^3; <2.0 x 10^9 /L according to NCI-CTCAE v4.03 severity grading (). - Grade 3 events (i.e., according to NCI-CTCAE v4.03 severity grading) reported in 1% of patients (Please note: For leukocyte count decrease/white blood cell decrease no Grade 5 severity denoted in NCI-CTCAE v4.03). - One reported serious adverse event. - Dose modifications due to leukocyte count decrease in <1% of patients - No permanent discontinuations due to leukocyte count decrease. - Associated events of "lymphocyte count decreased" and "neutrophil count decreased" have been reported as TEAEs in 10% and 12% of patients, respectively. Clinical and benefit/risk impact: Taking into account that most leukocyte count decrease events have been reported as of Grade 1 or Grade 2 severity, the risk of Vitrakvi®-associated leukocyte count decreases is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Therefore,

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.2: List of adverse reactions and the justification for non-Inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-Inclusion
	reflection as common ADR in proposed SmPC is considered as sufficient. Reported neutropenia events are further presented and discussed in context of the important potential risk *"Serious infections secondary to neutropenia"*.
Blood alkaline phosphatase (ALP) increase	Frequency / Seriousness: ALP increase has been reported as TEAE in 8% of the overall 208 Vitrakvi®-treated patients in the clinical database and is reflected as common ADR in the proposed SmPC. - Vast majority of reported events of Grade 1 and Grade 2 severity – One reported Grade 3 event, i.e. *"> 5.0 – 20.0 x Upper limit of normal (ULN)"* according to NCI-CTCAE v4.03 severity grading (Please note: For ALP increase no Grade 5 severity denoted in NCI-CTCAE v4.03). - No reported serious adverse events, no dose modifications (including permanent discontinuations) due to ALP increase. Clinical and benefit/risk impact: Taking into account that most of reported ALP increase events have been of Grade 1 or Grade 2 severity, the risk of Vitrakvi®-associated ALP increases is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Moreover, confounding factors like (progressive) liver or bone metastases might also impact on ALP count. Therefore, reflection as common ADR in proposed SmPC is considered as sufficient.

Source: Table 14.4.4, Table 14.4.8, Table 14.4.9, Table 14.4.10, Table 14.4.11, and Table 14.4.12, Integrated Summary of Safety (Data Exported 27 NOV 2018, Visit Cut-off 30 JUL 2018)

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII.3: Risks considered important for inclusion in the list of safety concerns in the RMP and the reasons for risk classification

Safety Concern	Reason for Risk Classification
Important Identified Risks	
None identified	Not applicable
Important Potential Risks	
Severe neurologic reactions	Animal data: Neuromuscular reactions were observed in juvenile male rats. Low-to-negligible penetration of the blood-brain barrier (BBB) confirmed in rodents. Clinical data: In the overall clinical safety database (n=208), regardless of attribution, central nervous system (CNS)--related signs (≥5% of patients) were mostly

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.3: Risks considered important for inclusion in the list of safety concerns in the RMP and the reasons for risk classification

Safety Concern	Reason for Risk Classification
	of Grade 1 and 2, including the most commonly reported: dizziness (29%), gait disturbance (6%), and paraesthesia (7%). For each of these three events, Grade 3 severities were reported in only 1% of patients and almost all these events were documented as non-serious. Confusional state, lethargy, delirium and somnolence were reported each in 2% of patients (with no reported Grade 5 events). Events of aggression and cognitive disorder were each reported in 1% of patients. One Grade 1 (partial) seizure event and one Grade 4 encephalopathy not related to drug were reported. The majority of these events were reported of Grade 1 or 2 with no reported Grade 4, except for encephalopathy, and 5 events. There were 15 patients with primary or metastatic brain tumours (Module 2.7.4., section 2.1.5.2. Neurologic events) included in the clinical studies as noted in the cancer history listings for each study. Neurologic TEAEs were reported by 10 of these patients, with 4 patients reporting more than 1 neurologic TEAE: the TEAEs reported were dizziness (2 patients), vertigo, (2 patients), dysarthria (2 patients), hypoaesthesia (2 patients), balance disorder, paraesthesia, sensory disturbance, agitation, gait disturbance, extrapyramidal disorder, neuralgia, peripheral sensory neuropathy, cognitive disorder, memory impairment, mental status changes, delirium, dyskinesia (each 1 patient). Two of these TEAEs (sensory disturbance Grade 1 and delirium Grade 2) were considered by the investigator to be related to study treatment. Neurologic reactions are monitored in the proposed Non-Interventional PASS (ON-TRK) and in post-marketing experience. Neurologic reactions are followed as adverse events of special interest (AESI) in all three ongoing clinical trials: LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003. <u>Impact on benefit risk if confirmed</u>: Current clinical data indicate an overall mild effect of Vitrakvi® on (central) nervous system and most reactions resolved under continued Vitrakvi® treatment, in the vast majority without any dose reduction. This current data doesn't substantially impact on Vitrakvi® benefit-risk balance. Reflection of respective most frequently observed reactions (i.e. dizziness, paraesthesia, gait disturbance) as ADRs together with dosing guidance for severe events in proposed Vitrakvi® label is considered adequate. However, taking the currently limited number of Vitrakvi®-treated patients into account, "severe neurological reactions" is included as important potential risk as the potential future occurrence of such reactions with greater severity (i.e. primarily Grade 3 or higher; events reported as serious) might impact on current benefit-risk balance. Dizziness has potential impact on patient safety, especially for activities such as driving and working with machinery. On-target central effect cannot be excluded due to Vitrakvi® MOA affecting neurotrophins signalling. No human data are currently available on the extent of CNS penetration.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.3: Risks considered important for inclusion in the list of safety concerns in the RMP and the reasons for risk classification

Safety Concern	Reason for Risk Classification
Severe drug-induced liver injury	Animal data: Elevation of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in pre-clinical studies with two species. Clinical data: In the overall clinical safety database (n=208), regardless of attribution, elevated AST and ALT were reported as TEAEs in 26% and 26% of patients, respectively; mostly Grade 1 and 2. One case was reported as Grade 4 ALT elevation, related to drug. Permanent treatment discontinuations due to ALT and/or AST increases were reported as related in two and one patients, respectively. Based on laboratory test data, Grade 1, 2, 3 and 4 ALT increases were observed in 70 (34%), 14 (7%), 6 (3%), and 1 (0%), respectively, of the overall 208 Vitrakvi®-treated patients. Transaminases increase of Grade 1, Grade 2 and Grade 3 was reported each for one patient. The Grade 1 case was related to the study drug. Severe drug-induced liver injury is monitored in the proposed Non-Interventional PASS (ON-TRK) and in post-marketing experience. Hepatotoxicity is defined as AESI in all 3 ongoing clinical trials: LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003. Impact on benefit risk if confirmed: Current clinical data indicate an overall mild effect of Vitrakvi® on liver, primarily within first 3 treatment cycles with transient increases in transaminases which resolved under continued Vitrakvi® treatment in the majority of cases without any dose reduction. According to drug-induced liver injury (DILI) criteria of the international DILI expert working group (293). This current liver data doesn't substantially impact on Vitrakvi® benefit-risk balance. Reflection of observed ALT/AST increases as ADRs together with dosing guidance for severe events in proposed Vitrakvi® label is considered adequate. However, taking the currently limited number of Vitrakvi®-treated patients into account, Vitrakvi®-induced *"severe drug-induced liver injury"* (i.e. concurrent relevant increases in transaminases and bilirubin together with signs/symptoms of severe liver impairment like coagulation disturbances, hepatic encephalopathy and/or other organ failures (293)) is included as important potential risk as the potential future occurrence of such severe reactions might impact on current benefit-risk balance.
Serious Infections secondary to neutropenia[a]	Animal data: Neutropenia was not directly observed in pre-clinical studies. Clinical data: In the overall clinical safety database (n=208), a total of 34 SAEs from SOC "Infections" were reported, and none were assessed as related to study medication. None of the cases of infections were reported in combination with neutropenia with the exception of a single patient (neutropenia and

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.3: Risks considered important for inclusion in the list of safety concerns in the RMP and the reasons for risk classification

Safety Concern	Reason for Risk Classification
	sepsis). Neutropenia was reported as TEAE in 25 (12%) of the patients, with 9 reported cases of Grade 3, and 2 reported cases of Grade 4. Two of the Grade 3 and one of the Grade 4 cases were drug-related. There was also one case of febrile neutropenia, reported as serious, not related, Grade 3 event. Relatedness rate (percentage of cases reported as drug-related) was 52% for neutropenia. A disproportion of neutropenia incidence was noted between the paediatric population (32%) and the adults (5%). Neutropenia is monitored in the proposed Non-Interventional PASS (ON-TRK) and in post-marketing experience. Neutropenia is defined as an AESI in all 3 ongoing clinical trials: LOXO-TRK-14001, LOXO-TRK-15002, and LOXO-TRK-15003. Impact on benefit risk if confirmed: Current clinical data indicate an overall mild myelosuppressive effect of Vitrakvi® with neutropenia as the primarily reported associated event. Of note, 46% and 37% of enrolled patients had received 1 or 2 and at least 3 prior systemic therapies, respectively. Hence, a certain effect on baseline bone marrow reserve in these patients, particular in the paediatric population, cannot be excluded. Generally, the neutropenia events were mainly laboratory changes without any clinical presentation (except of febrile neutropenia case), reported in the first 3 cycles of treatment and resolved in the majority of cases under continued treatment. Two events of Grade 4 neutropenia (i.e. <500/mm^3 acc. to NCI-CTCAE v4.03) and one event of febrile neutropenia (reported as non-serious Grade 3 event) were reported. This current data doesn't substantially impact on Vitrakvi® benefit-risk balance. Reflection of respective observed laboratory test abnormalities together with dosing guidance for severe events in proposed Vitrakvi® label is considered adequate. However, taking the currently limited number of Vitrakvi®-treated patients into account, *"Serious infections secondary to neutropenia*[a]" is included as important potential risk as the potential future occurrence of such clinically potentially life-threatening reactions might impact on current benefit-risk balance.
Impairment of neurodevelopment in paediatric patients	Animal data: Larotrectinib had no neurobehavioral findings or effects on respiratory function at up to100 mg/kg in rats and did not affect neuromuscular function in mice given 60 mg/kg/day for 48 days. Neuromuscular reactions were observed in juvenile male rats. Low-to-negligible penetration of the BBB was detected in rodents. Clinical data: No adverse events pertaining to HLGT: "Cognitive and attention disorders and disturbances", HLT: "Developmental motor skills disorders", HLT: "Developmental disorders cognitive", HLT: "Memory loss (excl dementia)", and HLT: "Mental impairment (excl dementia and memory loss" were

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.3: Risks considered important for inclusion in the list of safety concerns in the RMP and the reasons for risk classification

Safety Concern	Reason for Risk Classification
	reported in any of the Vitrakvi® clinical trials to date. TRAEs also evaluated in the context of important potential risk "severe neurologic reactions" including PTs dizziness, gait disturbance, and paresthesia were observed in clinical studies with the following frequencies: dizziness in 44 (21%) of patients, with one case of Grade 3 (<1%); gait disturbance in 7 (3%) of patients, with no Grade 3 cases; paresthesia in 10 (5%) of patients, with no Grade 3 cases. Delirium and somnolence were reported in 1 % and 2% of patients (with no reported Grade 4 and 5 events). No further paediatric neurodevelopment data is currently available. Impairment of neurodevelopment in paediatric patients is monitored in the proposed Non-Interventional PASS (ON-TRK) and in post-marketing experience. Impact on the risk-benefit balance of the product: Current clinical data indicate an overall mild effect of Vitrakvi® on (central) nervous system and most reactions resolved under continued Vitrakvi® treatment, in the vast majority without any dose reduction. This current data doesn't substantially impact on Vitrakvi® benefit-risk balance. Reflection of respective most frequently observed reactions (i.e. dizziness, paraesthesia, gait disturbance) as ADRs together with dosing guidance for severe events in proposed Vitrakvi® label is considered adequate. However, taking the currently limited number of Vitrakvi®-treated patients into account, "impairment of neurodevelopment in paediatric patients" is included as important potential risk as the potential future occurrence of such reactions with greater severity (i.e. primarily Grade 3 or higher; events reported as serious) might impact on current benefit-risk balance. Pharmacovigilance activities will further characterise the risk with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by routine risk minimisation measures such that the benefit-risk for the product is positive.
Missing Information	
Use in pregnancy and lactation	No human data available. Use in pregnancy and lactation is considered missing information.
Long-term safety	Preliminary analysis of safety data on the 16 patients (N=208) who reached the exposure to Vitrakvi of >2 years in on-going clinical studies, suggests that the majority of TEAEs are reported during the first 2 years of exposure. No further long-term safety data is available. Long-term safety is considered missing information

[a] according to NCI-CTCAE v4.03 Grade 3 and Grade 4 severity definitions; i.e.
- Grade 3: ANC <1,000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour;
- Grade 4: ANC <1,000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Potential Risks

Unless stated otherwise, TEAE frequencies from clinical trials are based on the "NTRK Gene Fusion Treated at Recommended Dose Analysis Set (N=335)". This includes all paediatric (N=124) and adult (N=211) patients with documented *NTRK* gene fusion who were enrolled in studies 20288, 20289, and 20290 (formerly LOXO TRK 14001, LOXO TRK 15002, and LOXO TRK 15003) and were assigned to the recommended dose (i.e., 100 mg BID for adults and 100 mg/m^2 BID, not to exceed 100 mg BID regardless of the patient's BSA for paediatric patients) of larotrectinib and received 1 or more doses of larotrectinib as of 20 JUL 2022. Patients with multiple severity ratings for a given adverse event (AE) are counted once under the maximum severity for each preferred term (PT). Reported AE terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 25.0). Severity grade assignment was based on Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03). Selected PTs corresponding to ADRs as defined in Section SVII.1.1 as well as PTs of further interest are presented, as applicable.

SVII.3.1.1 Severe Neurologic Reactions

The following list of MedDRA PTs comprises aside the three PTs (dizziness, gait disturbance, paraesthesia) reflected as ADRs in Vitrakvi® SmPC also PTs which are used for signal detection:

Aggression, Agitation, Anxiety, Ataxia, Balance disorder, Burning sensation, Cerebellar syndrome, Cognitive disorder, Confusional state, Coordination abnormal, Delirium, Dizziness, Dysaesthesia, Dysarthria, Dyskinesia, Encephalopathy, Extrapyramidal disorder, Facial pain, Feeling jittery, Gait disturbance, Hyperaesthesia, Hypoaesthesia, Loss of consciousness, Memory impairment, Mental status changes, Neuralgia, Neuropathy peripheral, Paraesthesia, Partial seizures, Peripheral motor neuropathy, Peripheral sensory neuropathy, Polyneuropathy, Psychomotor hyperactivity, Restless legs syndrome, Restlessness, Seizure, Sensory disturbance, Skin burning sensation, Skin sensitisation, Somnolence, Tremor, Vertigo, Vibratory sense increased

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.4: Presentation of the MedDRA PTs for severe neurologic reactions

MedDRA PTs	Definition acc. to NCI-CTCAE v4.03	Severity grading acc. to NCI-CTCAE v4.03
Dizziness*	A disorder characterised by a disturbing sensation of light-headedness, unsteadiness, giddiness, spinning or rocking.	Grade 1: Mild unsteadiness or sensation of movement Grade 2: Moderate unsteadiness or sensation of movement; limiting instrumental activities of daily living (ADL) Grade 3: Severe unsteadiness or sensation of movement; limiting self-care ADL No Grade 4 and Grade 5 events denoted in CTCAE v4.03
Gait disturbance*	A disorder characterised by walking difficulties.	Grade 1: Mild change in gait (e.g., wide-based, limping or hobbling) Grade 2. Moderate change in gait (e.g., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL Grade 3: Disabling; limiting self-care ADL No Grade 4 and Grade 5 events denoted in CTCAE v4.03
Paraesthesia*	A disorder characterised by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.	Grade 1: Mild symptoms Grade 2: Moderate symptoms; limiting instrumental ADL Grade 3. Severe symptoms; limiting self-care ADL No Grade 4 and Grade 5 events denoted in CTCAE v4.03
Encephalopathy	A disorder characterised by a pathologic process involving the brain.	Grade 1: Mild symptoms Grade 2: Moderate symptoms; limiting instrumental ADL Grade 3: Severe symptoms; limiting self-care ADL Grade 4: Life-threatening consequences; urgent intervention indicated Grade 5: Death
Delirium	A disorder characterised by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition.	Grade 1: Mild acute confusional state Grade 2: Moderate and acute confusional state; limiting instrumental ADL Grade 3: Severe and acute confusional state; limiting self-care ADL; hospitalization indicated Grade 4: Life-threatening consequences, threats of harm to self or others; hospitalization indicated Grade 5: Death

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.4: Presentation of the MedDRA PTs for severe neurologic reactions

MedDRA PTs	Definition acc. to NCI-CTCAE v4.03	Severity grading acc. to NCI-CTCAE v4.03
Somnolence	A disorder characterised by excessive sleepiness and drowsiness.	Grade 1: Mild but more than usual drowsiness or sleepiness Grade 2: Moderate sedation; limiting instrumental ADL Grade 3: Obtundation or stupor Grade 4: Life-threatening consequences; urgent intervention indicated Grade 5: Death
Seizures	A disorder characterised by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.	Grade 1: Brief partial seizure; no loss of consciousness Grade 2: Brief generalized seizure Grade 3: Multiple seizures despite medical intervention Grade 4: Life-threatening; prolonged repetitive seizures Grade 5: Death

* Neurological events reflected as ADRs in Vitrakvi® SmPC

Potential mechanisms:

On-target central effect cannot be excluded (MOA: neurotrophins signalling). In the postnatal period, TRK receptors are expressed in the brain and nervous system and are thought to regulate mood, memory, cognition, and proprioception. No human data are currently available on CNS penetration.

Evidence source(s) and strength of evidence:

Non-clinical studies:

Vitrakvi® had no neurobehavioral findings or effects on respiratory function at up to100 mg/kg in rats and did not affect neuromuscular function in mice given 60 mg/kg/day for 48 days. Neuromuscular reactions were observed in juvenile male rats. Low-to-negligible penetration of the BBB was detected in rodents.

Clinical studies:

Treatment-related adverse events (TRAE) at recommended dose; dizziness, gait disturbance, paraesthesia were observed in clinical studies with the following frequencies: Dizziness in 43 (13%) of patients, with one case of Grade 3 (<1%); gait disturbance in 5 (1%) patients, with no Grade 3 cases; paraesthesia in 11 (3%) patients, with one case of Grade 3 (<1%).

Delirium and somnolence as a TEAE were reported in 1% and 3% of patients, respectively (with no reported Grade 4 + 5 events).

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Potential class effect: TRAE dizziness was reported in 23% of patients treated with entrectinib, mostly Grade 1 and 2; TRAE paraesthesia – in 16% of patients; Grade 1 exclusively (n=203) (294).

Characterisation of the risk:

Frequency and severity

Neurologic reactions (by Preferred Term) reported in the clinical trials are presented in Table SVII.5.

Table SVII.5: Frequency and severity of relevant TEAEs at recommended dose in clinical studies with Vitrakvi®

Preferred Term (PT)	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose; number (percent); n=335;
Agitation	
Grade 1	9 (3)
Grade 2	2 (<1)
Total	**11 (3)**
Anxiety	
Grade 1	7 (2)
Grade 2	5 (1)
Grade 3	3 (<1)
Total	**15 (4)**
Ataxia	
Grade 1	3 (<1)
Grade 2	3 (<1)
Grade 3	1 (<1)
Total	**7 (2)**
Balance disorder	
Grade 1	4 (1)
Grade 2	2 (<1)
Grade 3	2 (<1)
Total	**8 (2)**
Burning sensation	
Grade 1	2 (<1)
Total	**2 (<1)**
Cognitive disorder	
Grade 1	2 (<1)
Grade 2	1 (<1)
Grade 3	1 (<1)
Total	**4 (1)**

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.5: Frequency and severity of relevant TEAEs at recommended dose in clinical studies with Vitrakvi®

Preferred Term (PT)	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose; number (percent); n=335;
Confusional state	
Grade 1	5 (1)
Grade 3	1 (<1)
Grade 4	1 (<1)
Total	**7 (2)**
Coordination abnormal	
Grade 1	1 (<1)
Total	**1 (<1)**
Delirium	
Grade 1	1 (<1)
Grade 3	1 (<1)
Total	**2 (<1)**
Dizziness	
Grade 1	57 (17)
Grade 2	8 (2)
Grade 3	3 (<1)
Total	**68 (20)**
Dysaesthesia	
Grade 1	6 (2)
Total	**6 (2)**
Dysarthria	
Grade 1	2 (<1)
Grade 3	1 (<1)
Total	**3 (<1)**
Dyskinesia	
Grade 1	1 (<1)
Grade 2	1 (<1)
Total	**2 (<1)**
Encephalopathy	
Grade 4	1 (<1)
Total	**1 (<1)**
Extrapyramidal disorder	
Grade 3	1 (<1)
Total	**1 (<1)**

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.5: Frequency and severity of relevant TEAEs at recommended dose in clinical studies with Vitrakvi®

Preferred Term (PT)	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose; number (percent); n=335;
Facial pain	
Grade 1	2 (<1)
Total	**2 (<1)**
Feeling jittery	
Grade 1	1 (<1)
Total	**1 (<1)**
Gait disturbance	
Grade 1	8 (2)
Grade 2	4 (1)
Grade 3	4 (1)
Total	**16 (5)**
Hyperaesthesia	
Grade 1	4 (1)
Grade 3	1 (<1)
Total	**5 (1)**
Hypoaesthesia	
Grade 1	8 (2)
Total	**8 (2)**
Loss of consciousness	
Grade 1	2 (<1)
Total	**2 (<1)**
Memory impairment	
Grade 1	11 (3)
Grade 2	1 (<1)
Total	**12 (4)**
Mental status changes	
Grade 3	1 (<1)
Total	1 (<1)
Neuralgia	
Grade 1	2 (<1)
Grade 2	3 (<1)
Total	**5 (1)**

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.5: Frequency and severity of relevant TEAEs at recommended dose in clinical studies with Vitrakvi®

Preferred Term (PT)	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose; number (percent); n=335;
Neuropathy peripheral	
Grade 1	11 (3)
Grade 2	5 (1)
Grade 3	1 (<1)
Total	**17 (5)**
Paraesthesia	
Grade 1	16 (5)
Grade 2	3 (<1)
Grade 3	3 (<1)
Total	**22 (7)**
Partial Seizures	
Grade 1	2 (<1)
Total	**2 (<1)**
Peripheral motor neuropathy	
Grade 1	1 (<1)
Grade 2	1 (<1)
Total	**2 (<1)**
Peripheral sensory neuropathy	
Grade 1	11 (3)
Grade 2	6 (2)
Grade 3	1 (<1)
Total	**18 (5)**
Restlessness	
Grade 1	4 (1)
Total	**4 (1)**
Sensory disturbance	
Grade 1	2 (<1)
Total	**2 (<1)**
Somnolence	
Grade 1	8 (2)
Grade 2	3 (<1)
Total	**11 (3)**

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.5: Frequency and severity of relevant TEAEs at recommended dose in clinical studies with Vitrakvi®

Preferred Term (PT)	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose; number (percent); n=335;
Tremor	
Grade 1	6 (2)
Grade 2	1 (<1)
Grade 3	1 (<1)
Total	**8 (2)**
Vertigo	
Grade 1	2 (<1)
Total	**2 (<1)**

Source: Table 1 / 7 (2731953 20jul2022 Tables for EU RMP part 1) and Table 1 / 3 (2731953 20jul2022 Tables for EU RMP part 3); Visit Cut-off 20 JUL 2022).

Post-marketing data:

Retrieval criteria

A cumulative search of Bayer's Global Safety Database was performed for relevant cases of severe neurologic reactions from all post-marketing sources, excluding trials (20288, 20289 and 20290). The MedDRA search strategy for severe neurological reactions consisted of all PTs included in the SOCs "Nervous system disorders" and "Psychiatric disorders".

Overview of cases

The search strategy yielded 870 cases that met the above search criteria, received *cumulatively* from post marketing sources since market launch (26 NOV 2018) up to 25 MAY 2023. Out of 870 cases, 293 cases (33.7%) were medically confirmed. Out of 870 cases, 412 cases (47.3%) were serious. Out of 870 cases, 441 cases were received in female patients, 401 cases in male, and for 28 cases, the gender was unknown. Out of 870 cases, 175 cases were spontaneously reported, eight cases were from literature, 38 cases were received from compassionate use programs, eight cases were from interventional clinical studies, 10 cases were from investigator sponsored studies, 4 cases from market research programs, 46 cases from observational studies, 548 cases from patient support programs, 30 cases from reimbursement programs, and 3 cases were from interventional non-Bayer studies.

In total, 300 SAEs were reported. Table SVII.6 presents a list of all PTs (SAEs which were reported in at least 10 patients) reported from all sources, excluding clinical trials (20288, 20289, and 20290).

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.6: Tabulation for all events evaluated in the context of Severe neurological reactions (reported as serious in ≥10 patients) reported cumulatively until 25 MAY 2023.

Preferred Term	Non-serious AEs	Serious AEs	Total AEs
Total	**258**	**111**	**369**
Seizure	1	35	36
Neuropathy peripheral	5	34	39
Loss of consciousness	-	17	17
Dizziness	227	15	242
Confusional state	25	10	35

AEs: Adverse events, PT: Preferred Term, SOC: System Organ Class (MedDRA).
MedDRA version 26.0.

The most frequently reported PTs for SAEs reported in ≥10 patients were seizure (n=35), neuropathy peripheral (n=34), loss of consciousness (n=17), dizziness (n=15), and confusional state (n=10).

Conclusion

Overall, no new or relevant safety information was identified which would warrant or conclude a causal association between severe neurological events and Vitrakvi®. The evaluation of the risk remains consistent with the previous information from clinical studies.

Risk factors and risk groups:

Primary CNS tumours or metastatic lesions, medical history of brain tumours, surgeries or trauma, underlying neurological conditions, neuro-infections, concomitant use of certain agents known for neurotoxicity.

Preventability:

Withholding, reducing, or discontinuing Vitrakvi® dosing should be considered, depending on the severity and persistence of neurologic symptoms.

Impact on the risk-benefit balance of the product:

Current clinical data indicate an overall mild effect of Vitrakvi® on (central) nervous system and most reactions resolved under continued Vitrakvi® treatment, in the vast majority without any dose reduction. This current data doesn't substantially impact on Vitrakvi® benefit-risk balance. Reflection of respective most frequently observed reactions (i.e., dizziness, paraesthesia, gait disturbance) as ADRs together with dosing guidance for severe events in Vitrakvi® label is considered adequate. However, taking the currently limited number of Vitrakvi®-treated patients into account, "severe neurological reactions" is included as important potential risk as the potential future occurrence of such reactions with greater severity (i.e., primarily Grade 3 or higher; events reported as serious) might impact on current benefit-risk balance.

Pharmacovigilance activities will further characterise the risk with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by routine risk minimisation measures such that the benefit-risk for the product is positive.

Public health impact:

Dizziness has been reported in patients receiving Vitrakvi® which may influence the ability to drive and use machines. Advice patients not to drive and use machines, until they are reasonably certain Vitrakvi® therapy does not affect them adversely.

SVII.3.1.2 Severe Drug-induced Liver Injury

Definition of severe drug-induced liver injury as per the international DILI expert working group (293):

ALT ≥5 x ULN or ALP ≥2 x ULN (in the absence of known bone pathology) and TBIL ≥2 x ULN, or symptomatic hepatitis and 1 of the following criteria:

- International normalized ratio (INR) ≥1.5
- Ascites and/or encephalopathy, disease duration <26 weeks, no underlying cirrhosis
- Other organ failure due to DILI.

Associated MedDRA terms: Alanine aminotransferase increased, Ascites, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Drug-induced liver injury, Hepatic encephalopathy, (acute) Hepatic failure, Hepatitis (fulminant), Hepatotoxicity, Hyperbilirubinaemia, Jaundice, Transaminases increased.

Table SVII.7: Presentation of the MedDRA PTs for severe drug-induced liver injury

MedDRA PTs	Definition acc. to NCI-CTCAE v4.03, if available	Severity grading acc. to NCI-CTCAE v4.03, if available/applicable
Alanine aminotransferase increased	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT [Serum glutamic pyruvic transaminase]) in the blood specimen.	Grade 1: >ULN - 3.0 x ULN Grade 2. >3.0 - 5.0 x ULN Grade 3: >5.0 - 20.0 x ULN Grade 4: >20.0 x ULN No Grade 5 event denoted in CTCAE v4.03
Aspartate aminotransferase increased	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT [Serum glutamic oxaloacetic transaminase]) in a blood specimen.	Grade 1: >ULN - 3.0 x ULN Grade 2. >3.0 - 5.0 x ULN Grade 3: >5.0 - 20.0 x ULN Grade 4: >20.0 x ULN No Grade 5 event denoted in CTCAE v4.03

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.7: Presentation of the MedDRA PTs for severe drug-induced liver injury

MedDRA PTs	Definition acc. to NCI-CTCAE v4.03, if available	Severity grading acc. to NCI-CTCAE v4.03, if available/applicable
Blood bilirubin increased	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.	Grade 1: >ULN – 1.5 x ULN Grade 2. >1.5 - 3.0 x ULN Grade 3: >3.0 - 10.0 x ULN Grade 4: >10.0 x ULN No Grade 5 event denoted in CTCAE v4.03
Hyperbilirubinaemia	No specific definition in CTCAE v4.03 - reflected in context of "Blood bilirubin increased"	
Jaundice	No specific definition in CTCAE v4.03 - reflected in context of "Blood bilirubin increased" Classic definition of jaundice is a serum bilirubin level greater than 2.5 to 3 mg per dL (42.8 to 51.3 µmol per L) in conjunction with a clinical picture of yellow skin and sclera (295).	
Blood alkaline phosphatase increased	A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.	Grade 1: >ULN – 2.5 x ULN Grade 2. >2.5 - 5.0 x ULN Grade 3: >5.0 - 20.0 x ULN Grade 4: >20.0 x ULN No Grade 5 event denoted in CTCAE v4.03
(Acute) hepatic failure	A disorder characterised by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, and alkaline phosphatase.	No Grade 1/2 events denoted in CTCAE v4.03 Grade 3: Asterixis; mild encephalopathy; limiting self-care ADL Grade 4: Moderate to severe encephalopathy; coma; life-threatening consequences Grade 5: Death
Ascites	A disorder characterised by accumulation of serous or haemorrhagic fluid in the peritoneal cavity.	Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated Grade 2: Symptomatic; medical intervention indicated Grade 3: Severe symptoms; invasive intervention indicated Grade 4: Life-threatening consequences; urgent operative intervention indicated Grade 5: Death
Drug-induced liver injury (DILI), Hepatitis (fulminant), Hepatic encephalopathy, Hepatotoxicity	No specific definitions in CTCAE v4.03 but they reflect further associated MedDRA PTs of interest indicating – if reported – potentially clinically relevant liver injury, i.e., cases to be further assessed	

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Potential mechanisms:

No potential mechanism has yet been identified.

Evidence source(s) and strength of evidence:

Non-clinical studies:

Increases in serum transaminases, ALT (rat, monkey) AST (monkey), in the 28-day repeat dose studies (from <2-fold in rat to 4-fold in monkey) were observed and were reversible. Single cell necrosis was a minor histologic change in the liver. It was difficult to attribute elevated transaminases solely to single cell necrosis. Liver effects in both species were fully reversible.

Clinical studies:

Elevation of liver enzymes AST/ALT was observed in ongoing clinical trials (31%/33%). Mostly Grade 1 and 2, three reported cases of Grade 4 ALT increase and two reported cases of Grade 4 AST increase. ALT and AST increases leading to dose modifications occurred in 18 (5%) patients and 17 (5%) patients, respectively.

Blood bilirubin increase was reported in 11 (3%) patients: Grade 1 – six cases, Grade 2 – four cases, Grade 3 – one case. One case of each, Grade 1, Grade 2, and Grade 3 were drug-related. Jaundice was reported in 1 patient (Grade 4 and not related to drug). Transaminases increase of Grade 1 was reported for two patients, and of Grade 2 and 4 for one patient each. The two Grade 1 and the one Grade 4 cases were related to the study drug.

Characterisation of the risk:

Frequency and severity

Table SVII.8: Frequency and severity of relevant TEAEs at recommended dose in clinical studies with Vitrakvi®

Preferred Term (PT)	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose; number (percent); n=335;
Alanine aminotransferase increased	
Grade 1	71 (21)
Grade 2	24 (7)
Grade 3	12 (4)
Grade 4	3 (<1)
Total	**110 (33)**
Ascites	
Grade 2	1 (<1)
Grade 3	2 (<1)
Grade 4	1 (<1)
Total	**4 (1)**

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.8: Frequency and severity of relevant TEAEs at recommended dose in clinical studies with Vitrakvi®

Preferred Term (PT)	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose; number (percent); n=335;
Aspartate aminotransferase increased	
Grade 1	73 (22)
Grade 2	18 (5)
Grade 3	10 (3)
Grade 4	2 (<1)
Total	**103 (31)**
Blood alkaline phosphatase increased	
Grade 1	17 (5)
Grade 2	6 (2)
Grade 3	2 (<1)
Grade 4	2 (<1)
Total	**27 (8)**
Blood bilirubin increased	
Grade 1	6 (2)
Grade 2	4 (1)
Grade 3	1 (<1)
Total	**11 (3)**
Hepatitis	
Grade 4	1 (<1)
Total	**1 (<1)**
Hyperbilirubinaemia	
Grade 2	1 (<1)
Grade 3	3 (<1)
Total	**4 (1)**
Jaundice	
Grade 4	1 (<1)
Total	**1 (<1)**
Transaminases increased	
Grade 1	2 (<1)
Grade 2	1 (<1)
Grade 4	1 (<1)
Total	**4 (1)**

Source: Table 1 / 7 (2731953 20jul2022 Tables for EU RMP part 1, Visit Cut-off 20 JUL 2022).

None of the other above outlined associated MedDRA PTs of potential further interest, i.e., "(Acute) hepatic failure", "Drug-induced liver injury (DILI)", "Hepatitis (fulminant)", "Hepatic encephalopathy", and "Hepatotoxicity" have been reported in the overall 335 Vitrakvi®-treated patients.

Hy's law cases

As of the data cut-off 20 JUL 2022, among all patients exposed to larotrectinib in the Overall Safety Analysis Set (N=418, this includes all paediatric and adult cancer patients with or without a documented NTRK gene fusion who received one or more doses of larotrectinib), 8 patients (1.9%, manually calculated) were identified who fulfilled Hy's Law laboratory criteria. These cases were assessed further based on the third component of Hy's Law i.e., other causes for the laboratory abnormality. Although these patients fulfilled the laboratory criteria, there was no definite or 'highly likely' case of Hy's Law, but one case was considered a probable Hy's Law case, according to the drug-induced liver injury network (DILIN) causality assessment score (296).

- [redacted] This patient (50mg QD – once daily) terminated the study due to disease progression. On the EoT visit, laboratory abnormalities elevated AST Grade 1 and elevated ALP Grade 2 were observed but not considered clinically significant by the Investigator. During the safety follow-up period, the patient experienced AEs of AST increased Grade 2 and blood bilirubin increased Grade 2 (2.0 × ULN). The Investigator considered these AEs as not related to the study drug. At the safety follow-up visit, elevated AST worsened to Grade 3 (5.9 × ULN) but the change in grade was not reported. The patient was presenting with progressive disease at the same time and had liver metastases already at the time of study enrolment. With the alternative explanation of progressive disease, this case did not meet the definition for Hy's Law.
- [redacted]This potential case of moderate DILI was highly confounded by sepsis and liver hypoperfusion which provide an alternative explanation for the reported liver injury. Based on the clinical course of events and temporal relationship, causality cannot be fully excluded. However, the case is confounded by sepsis, hypotensive state, liver hypoperfusion, and recent prior treatments with immune checkpoint inhibitors. As alternative explanations are present, the case is considered not to meet the criteria for Hy's Law.
- [redacted]This patient with metastatic hepatocellular carcinoma also had ongoing hepatic cirrhosis. At screening, the patient had laboratory values that met Hy's Law criteria: AST elevation (Grade 2) and bilirubin elevation (Grade 2) but were within the values set by the protocol inclusion criteria. These values remained elevated during treatment. Although the patient had the requisite increases in the lab values associated with Hy's Law, they had documented progression in liver metastases at the same time and the elevations were not treatment-emergent, and thus did not meet Hy's Law criteria.

- [redacted]This patient with metastatic intrahepatic cholangiocarcinoma was admitted to hospital with a severe, Grade 3 SAE hip fracture following a fall. At screening this patient presented with AST (Grade 1) elevation; ALT and bilirubin were within the normal range. While in hospital, the patient reported a Grade 3, non-serious AE of hyperbilirubinemia. On 11 MAR 2020 TB was 10.3 mg/dL (≥2 x ULN) and AST was 186 U/L (≥3 x ULN). Although the patient had the requisite increases in AST and TB values associated with Hy's Law, they had documented cholangiocarcinoma and elevations in AST were not treatment-emergent, and thus did not meet Hy's Law criteria.
- [redacted] This patient with metastatic biliary tract adenocarcinoma presented with baseline AST (Grade 1) and bilirubin (Grade 2) elevation. During treatment, AST and bilirubin increased (Grade 2 and Grade 3, respectively) which was attributed to disease progression (liver metastases), therefore this case did not meet the definition of Hy's Law.
- [redacted] This patient had metastatic melanoma. On Study Day 27, the patient was reported with Grade 4 ALT and AST increased, and Grade 2 TB increased. Treatment was interrupted. The events were not considered serious by the Investigator. On Study Day 28, ALT level was 1131 U/L (28.3x ULN), AST level was 1,228 U/L (35.1 x ULN), ALP level was 523 U/L (4.4 x ULN), and TB level was 51.6 µmol/L (2.5 x ULN). On study Day 42, ALT was 46 U/L (1.2 x ULN), AST was 35 U/L, ALP was 244 U/L (1.8 x ULN) and TB was 16. µmol/L (in the normal range). On Study Day 44 treatment was restarted at a reduced dose (75 mg BID). On Study Day 55, study drug treatment was discontinued due to disease progression. At the EoT visit (on Study Day 57), ALT was 388 U/L (9.7 x ULN), AST was 385 U/L (8.6 x ULN), ALP was 276 U/L (1.7 x ULN) and TB was 38.7 µmol/L (1.9 x ULN). The interpretation of this case with respect to Hy's Law definition is confounded by alternative explanations, including an ongoing medical history of intrahepatic bile duct stones, progressive metastasis to the pancreas, and previous treatment with a checkpoint inhibitor in the last three months. However, based on the positive rechallenge with larotrectinib, a larotrectinib causality of the laboratory elevations cannot be fully excluded. This case is considered a probable Hy's Law case.
- [redacted] This patient with metastatic duodenal adenocarcinoma was also hepatitis B core antibody positive and had cholelithiasis at baseline. During study treatment, the patient had an SAE of biliary obstruction (Grade 3); at the time of onset of the SAE the patient had ALT (Grade 1), AST (Grade 2), and bilirubin (Grade 3) elevation. The SAE of biliary obstruction was attributed to disease progression (liver metastases); therefore, this case did not meet the definition of Hy's Law.
- [redacted]This patient with pancreatic cancer also had bile duct stenosis, cholecystitis chronic, hepatic cyst, hepatic failure, and jaundice cholestatic, at baseline. During study treatment, on Study Day 29, the patient was reported with the first event of an SAE hepatic function abnormal (Grade 4), which lasted until study treatment discontinuation; at the time of onset of the SAE the patient had elevated ALT of 1,359 U/L (Grade 4) and AST of 774 U/L (Grade 3), and normal bilirubin

(21.9 µmol/L) (Module 5.3.5.2, [redacted] Listing 16.2.8.2). On Study Day 35, the event improved to Grade 3, and on Study Day 46 further to Grade 1, but on Study Day 67 the event worsened again to Grade 4 with ALT 1,075 U/L (Grade 4), AST 750 U/L (Grade 3), and bilirubin 166.7 µmol/L (Grade 3). On Study Day 91, the event improved to Grade 2 with ALT 41 U/L (normal), AST 42 U/L (Grade 1), and bilirubin 77.3 µmol/L (Grade 2). Based on the multiple events of hepatic function abnormalities reported in combination with the biliary complications, although in a patient with pancreatic cancer, and a reported positive dechallenge and rechallenge, causality cannot be fully excluded. However, bile duct obstruction secondary to pancreatic cancer provides an alternative explanation. As alternative explanations are present, the case is considered not to meet the criteria for Hy's Law.

Summary assessment:

Current clinical data indicate an overall mild effect of Vitrakvi® on liver, primarily within first 3 treatment cycles. Generally, the elevations did not increase in grade as the patients continued on study and the majority of Grade 3 elevations were transient, appearing in cycles 1-2 of study treatment and resolving to Grade 1 by cycles 3-4. Majority of the abnormalities regarding transaminases were low-grade and transient.

In clinical trials, there were 8 patients who fulfilled Hy's Law laboratory criteria (ALT or AST ≥3x upper limit of normal [ULN] and total bilirubin ≥2xULN). Importantly, confounders were present in all 8 cases.

None of the so far reported cases with liver events qualify as severe liver injury according to (DILI) criteria of the international DILI expert working group (293).

Post-marketing data:

Retrieval criteria:

A cumulative search of Bayer's Global Safety Database was performed for relevant cases of severe drug-induced liver injury received from all post-marketing sources, excluding trials (20288, 20289 and 20290). The MedDRA search strategy for severe DILI cases consisted of associated MedDRA terms: Alanine aminotransferase increased, Ascites, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Drug-induced liver injury, Hepatic encephalopathy, (acute) Hepatic failure, Hepatitis, Hepatitis fulminant, Hepatotoxicity, Hyperbilirubinaemia, Jaundice, Transaminases increased.

Overview of cases:

The search strategy yielded 129 cases that met the above search criteria, received *cumulatively* from post marketing sources since market launch (26 NOV 2018) until 25 MAY 2023. Out of 129 cases, 99 cases (76.7%) were medically confirmed. Out of 129 cases, 53 cases (41.1%) were serious.

Out of 129 cases, 51 cases were spontaneously reported, 2 cases were from literature, 19 cases were received from compassionate use programs, 3 cases were from interventional clinical studies, 3 cases from investigator-sponsored studies, one case from market research, 22 cases

from observational studies, 26 cases from patient support programs, and 2 cases from reimbursement programs.

Table SVII.9 presents a list of all PTs reported from all sources, excluding clinical trials (20288, 20289, and 20290) for the severe drug- induced liver injury.

Table SVII.9: Tabulation by Preferred Term for the events evaluated in the context of severe DILI reported cumulatively until 25 MAY 2023.

Preferred Term	Non-serious AEs	Serious AEs	Total AEs
Alanine aminotransferase increased	68	16	84
Aspartate aminotransferase increased	53	18	71
Transaminases increased	12	4	16
Blood alkaline phosphatase increased	11	1	12
Ascites	0	9	9
Blood bilirubin increased	8	1	9
Hepatotoxicity	1	6	7
Jaundice	2	1	3
Hepatitis	0	2	2
Drug-induced liver injury	0	2	2
Hepatic encephalopathy	0	1	1
Grand total	**155**	**61**	**216**

AEs: Adverse events, DILI: Drug-induced liver injury, PT: Preferred Term.
MedDRA version 26.0

A total of 216 events of interest were received, 61 events (28.2%) were serious and 155 events (71.8%) were non-serious. Out of 61 serious events, 29 events were related, 4 events were unrelated, and for 28 events reporter causality was not reported. Out of 29 serious and related events, the most commonly reported PTs were Aspartate aminotransferase increased (10 events), Alanine aminotransferase increased (8 events), Hepatotoxicity (5 events), Hepatitis, Ascites, Jaundice, Transaminases increased, Drug-induced liver injury, and Hepatic encephalopathy (one event each). Upon the data review, no cases of severe DILI were identified. The PTs reported with the highest frequency were Alanine aminotransferase increased (84 events), Aspartate aminotransferase increased (71 events), and Transaminase increased (16 events). Two events of PT Drug-induced liver injury were reported, both serious. For details, please refer to Table SVII.9.

Conclusion

Based on the review of the data, there were no severe DILI cases identified.

Overall, no new or relevant safety information has been identified which would warrant or conclude a causal association between severe DILI and Vitrakvi®. The evaluation of the risk remains consistent with the previous information from clinical studies.

Risk factors and risk groups:

Patients with impaired liver function at baseline, chronic liver conditions, concomitant administration of agents, and medications with known adverse hepatic effects.

Patients with liver metastases or primary hepatic malignancies might be also at an increased risk due to potentially impaired liver function at baseline. However, so far available data concerning Vitrakvi®-treated patients with liver metastases don't show any respective specific finding.

Preventability:

Liver function including ALT, AST, ALP and bilirubin should be monitored before the first dose, then every 2 weeks during the first month of treatment, then monthly for the next 6 months of treatment, then periodically during treatment. In patients who develop transaminase elevations, more frequent testing is needed. In patients with hepatic transaminase elevations, withhold, modify dose or permanently discontinue Vitrakvi® based on the severity.

Impact on the risk-benefit balance of the product:

The current liver data doesn't substantially impact on Vitrakvi® benefit-risk balance. Reflection of observed ALT/AST increases as ADRs together with dosing guidance for severe events in Vitrakvi® label is considered adequate. However, taking the currently limited number of Vitrakvi®-treated patients into account, Vitrakvi®-induced "severe drug-induced liver injury" (i.e. concurrent relevant increases in transaminases and bilirubin together with signs/symptoms of severe liver impairment like coagulation disturbances, hepatic encephalopathy and/or other organ failures (293)) is included as important potential risk as the potential future occurrence of such severe reactions might impact on current benefit-risk balance.

Pharmacovigilance activities will further characterise the risk with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by routine risk minimisation measures such that the benefit-risk for the product is positive.

Public health impact:

The public health impact is expected to be low.

SVII.3.1.3 Serious infections secondary to neutropenia

MedDRA terms: Febrile neutropenia, Neutrophil count decreased, Neutropenia; SOC: Infections and infestations.

Table SVII.10: Presentation of the MedDRA PTs for Serious infections secondary to neutropenia

MedDRA PTs	Definition acc. to NCI-CTCAE v4.03, if available	Severity grading acc. to NCI-CTCAE v4.03, if available/applicable
Febrile neutropenia	A disorder characterised by an Absolute neutrophil count (ANC) <1,000/mm^3 and a	No Grade 1/2 events denoted in CTCAE v4.03 Grade 3: ANC <1,000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.10: Presentation of the MedDRA PTs for Serious infections secondary to neutropenia

MedDRA PTs	Definition acc. to NCI-CTCAE v4.03, if available	Severity grading acc. to NCI-CTCAE v4.03, if available/applicable
	single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour. Grade 4: Life-threatening consequences; urgent intervention indicated Grade 5: Death
Neutrophil count decreased	A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.	Grade 1: < Lower limit of normal (LLN) – 1,500/mm^3; <LLN - 1.5 x 10^9 /L Grade 2: <1,500 – 1,000/mm^3; <1.5 - 1.0 x 10^9 /L Grade 3: <1,000 - 500/mm^3; <1.0 - 0.5 x 10^9 /L Grade 4: <500/mm^3; <0.5 x 10^9 /L No Grade 5 event denoted in CTCAE v4.03
Neutropenia	No specific definition in CTCAE v4.03 - reflected in context of "Neutrophil count decreased"	
Sepsis	A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock.	No Grade 1-3 events denoted in CTCAE v4.03 Grade 4: Life-threatening consequences; urgent intervention indicated Grade 5: Death
Skin infection	A disorder characterised by an infectious process involving the skin.	Grade 1: Localized, local intervention indicated Grade 2: Oral intervention indicated (e.g., antibiotic, antifungal, antiviral) Grade 3 IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated Grade 5: Death
Wound infection	A disorder characterized by an infectious process involving the wound.	No Grade 1 events denoted in CTCAE v4.03 Grade 2: Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) Grade 3: IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated Grade 5: Death
Other Infections and infestations	For all other PTs included in SOC: Infections and infestations no individual definitions are available in	Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated Grade 2: Moderate; minimal, local or non-invasive

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.10: Presentation of the MedDRA PTs for Serious infections secondary to neutropenia

MedDRA PTs	Definition acc. to NCI-CTCAE v4.03, if available	Severity grading acc. to NCI-CTCAE v4.03, if available/applicable
	NCI-CTCAE v4.03	intervention indicated; limiting age appropriate instrumental ADL Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL Grade 4: Life-threatening consequences; urgent intervention indicated Grade 5: Death

Potential mechanisms:

Neutropenia increasing susceptibility to infections.

Evidence source(s) and strength of evidence:

Non-clinical studies:

Neutropenia was not directly observed in pre-clinical studies.

Clinical studies:

Neutropenia was reported as TEAE at recommended dose, in 56 (17%) of the patients (Table SVII.11), with 22 reported cases of Grade 3, and 7 reported cases of Grade 4. Fourteen of the Grade 3 and four of the Grade 4 cases were drug-related. Relatedness rate was 77% for neutropenia.

Generally, the neutropenia events were mainly laboratory changes without any clinical presentation (except for the one reported case of PT “febrile neutropenia”, and one reported case of PT “neutrophil count decreased” described below), occurred in the first 3 cycles of treatment and resolved in the majority of cases under continued treatment:

- one reported case of PT “febrile neutropenia” in a [redacted] female patient (event occurred on study Day 234); Grade 3, non-serious, not related. No related infections were reported.
- One reported case of febrile neutropenia and sepsis (coded with PT “neutrophil count decreased” and PT “sepsis”) in a [redacted] male patient (reported on Study Day 783); Grade 4, serious, not related.

A disproportion of neutropenia incidence was noted between the paediatric population (29%) and the adults (9%). Dose interruptions or modifications due to neutropenia were reported in 20 patients with two permanent treatment discontinuations due to neutropenia. In the clinical safety database at recommended dose (n=335; Data cut-off 20 JUL 2022), a total of 49 SAEs from SOC “Infections and infestations” were reported. None of the cases of serious infections were co-reported in combination with neutropenia with the exception of a single patient

(febrile neutropenia and sepsis). Table SVII.12 lists all SAEs reported in the SOC: Infections and infestations at the data cut-off of 20 JUL 2022. All of the reported SAEs occurred at a frequency of 4% or less, and the majority of the reported events were of Grade 3 or below, apart from five Grade 4 cases (four cases of sepsis and one case of COVID-19 pneumonia) and three Grade 5 cases (pneumonia, sepsis, pneumonia aspiration, one case each).

Characterisation of the risk:

Frequency and Severity

Table SVII.11: Frequency and severity of relevant TEAEs at recommended dose in clinical studies with Vitrakvi®

Preferred Term PT	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose (n=335)
Febrile neutropenia	
Grade 4	1 (<1%)
Total	**1 (<1%)**
Neutrophil count decreased	
Grade 1	11 (3%)
Grade 2	16 (5%)
Grade 3	22 (7%)
Grade 4	7 (2%)
Total	**56 (17%)**

Source: Table 1 / 7 (2731953 20jul2022 Tables for EU RMP part 1, Visit Cut-off 20 JUL 2022).

Table SVII.12: Frequency and severity of all treatment-emergent SAEs at recommended dose reported in SOC: Infections and infestations in clinical studies with Vitrakvi®

Preferred Term PT	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose (n=335)
Pneumonia	
Grade 2	4 (1%)
Grade 3	8 (2%)
Grade 5	1 (<1%)
Total	**13 (4%)**
Sepsis	
Grade 3	1 (<1%)
Grade 4	4 (1%)
Grade 5	1 (<1%)
Total	**6 (2%)**

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.12: Frequency and severity of all treatment-emergent SAEs at recommended dose reported in SOC: Infections and infestations in clinical studies with Vitrakvi®

Preferred Term PT	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose (n=335)
Cellulitis	
Grade 3	3 (<1%)
Total	**3 (<1%)**
Pneumonia aspiration	
Grade 3	2 (<1%)
Grade 5	1 (<1%)
Total	**3 (<1%)**
Pyelonephritis	
Grade 2	1 (<1%)
Grade 3	2 (<1%)
Total	**3 (<1%)**
Urinary tract infection	
Grade 2	1 (<1%)
Grade 3	2 (<1%)
Total	**3 (<1%)**
Viral infection	
Grade 1	1 (<1%)
Grade 3	2 (<1%)
Total	**3 (<1%)**
Wound infection	
Grade 3	3 (<1%)
Total	**3 (<1%)**
Bronchiolitis	
Grade 2	1 (<1%)
Grade 3	1 (<1%)
Total	**2 (<1%)**
Device related infection	
Grade 3	2 (<1%)
Total	**2 (<1%)**
Gastroenteritis	
Grade 2	1 (<1%)
Grade 3	1 (<1%)
Total	**2 (<1%)**

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.12: Frequency and severity of all treatment-emergent SAEs at recommended dose reported in SOC: Infections and infestations in clinical studies with Vitrakvi®

Preferred Term PT	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose (n=335)
Influenza	
Grade 2	1 (<1%)
Grade 3	1 (<1%)
Total	**2 (<1%)**
Osteomyelitis	
Grade 3	2 (<1%)
Total	**2 (<1%)**
Skin infection	
Grade 3	2 (<1%)
Total	**2 (<1%)**
Vascular device infection	
Grade 3	2 (<1%)
Total	**2 (<1%)**
Abscess soft tissue	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Bacteraemia	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Bronchitis	
Grade 2	1 (<1%)
Total	**1 (<1%)**
Campylobacter gastroenteritis	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Clostridium difficile infection	
Grade 2	1 (<1%)
Total	**1 (<1%)**
COVID-19	
Grade 1	1 (<1%)
Total	**1 (<1%)**

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.12: Frequency and severity of all treatment-emergent SAEs at recommended dose reported in SOC: Infections and infestations in clinical studies with Vitrakvi®

Preferred Term PT	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose (n=335)
COVID-19 pneumonia	
Grade 4	1 (<1%)
Total	**1 (<1%)**
Device-related bacteraemia	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Diarrhoea infectious	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Enterocolitis viral	
Grade 1	1 (<1%)
Total	**1 (<1%)**
Gastritis viral	
Grade 2	1 (<1%)
Total	**1 (<1%)**
Herpangina	
Grade 1	1 (<1%)
Total	**1 (<1%)**
Infection	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Pneumonia bacterial	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Pneumonia viral	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Pyelonephritis acute	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Pyelonephritis chronic	
Grade 2	1 (<1%)
Total	**1 (<1%)**

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.12: Frequency and severity of all treatment-emergent SAEs at recommended dose reported in SOC: Infections and infestations in clinical studies with Vitrakvi®

Preferred Term PT	Overall NTRK Fusion Cancers Safety (Analysis Set) at recommended dose (n=335)
Respiratory syncytial virus infection	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Soft tissue infection	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Systemic infection	
Grade 3	1 (<1%)
Total	**1 (<1%)**
Upper respiratory tract infection	
Grade 2	1 (<1%)
Total	**1 (<1%)**
Varicella	
Grade 3	1 (<1%)
Total	**1 (<1%)**

Patients are counted once with each preferred term.
Source: Table 1 / 3 (2731953 20jul2022 Tables for EU RMP part 1, Visit Cut-off 20 JUL 2022).

Post-marketing data:

Retrieval criteria:

A cumulative search of Bayer's Global Safety Database was performed for relevant cases of serious infections secondary to neutropenia received from all post-marketing sources, excluding clinical trials (20288, 20289 and 20290). The MedDRA search strategy for serious infections secondary to neutropenia retrieved cases reporting any of the following MedDRA PTs: Febrile neutropenia, Neutrophil count decreased, Neutropenia, in combination with any PT under the SOC: Infections and infestations.

Overview of cases

The search strategy yielded 2 cases that met the above search criteria, received *cumulatively* from post-marketing sources since market launch (26 NOV 2018) up to 25 MAY 2023. Both cases were serious. Out of 2 cases, one case was medically-confirmed. Out of 2 cases, one case was related to the study drug.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

A brief description of 2 cases is provided below:

- One reported case (PTs Neutropenia, Pyrexia, and Sepsis) in a [redacted] male patient. The case describes the occurrence of Sepsis (Grade 3), Neutropenia (Grade 4), and Pyrexia ('Fever (Grade 3)'). Forty-two days after the start of larotrectinib treatment the patient experienced the events of Sepsis, and Pyrexia. Three days later the patient experienced the event of Neutropenia. The patient was hospitalized. Larotrectinib was interrupted. At the time of the report, the events of Sepsis, Pyrexia and Neutropenia were resolving. The investigator considered all events to be unrelated to larotrectinib.
- One reported case (PTs Infection, Neutropenia) in a [redacted] male patient. Fifty-eight days after the start of larotrectinib treatment, the patient experienced Neutropenia. On an unknown date, the patient experienced Infection. The patient was hospitalized and treated with antibiotics. The dose of Vitrakvi® was reduced. The events did not improve after the dosage reduction. At the time of the report, the event of Neutropenia had not resolved and the outcome for the event of Infection was not provided. Neutropenia was considered to be related to Vitrakvi®; other events were not assessed.

Conclusion

Overall, no new or relevant safety information was identified which would warrant or conclude a causal association between serious infections secondary to neutropenia and Vitrakvi®.

The evaluation of the risk remains consistent with the previous information from clinical studies.

Risk factors and risk groups:

Underlying haematological conditions, concomitant administration of agents with known haematotoxicity effects, immunosuppression, chronic infectious and inflammatory disease, exposure to infectious agents. Paediatric patients with complex past medical histories and / or neutropenia observable at baseline. Of note, 47% of Vitrakvi®-treated patients had received 1 or 2 prior systemic therapies, with 28% of patients having received 3 or more. Hence, a certain effect on baseline bone marrow reserve in these patients, particular in the paediatric population, cannot be excluded.

Preventability:

Standard of care management of neutropenic cancer patients should be followed.

Impact on the risk-benefit balance of the product:

Current clinical data indicate an overall mild myelosuppressive effect of Vitrakvi® with neutropenia as the primarily reported associated event. Generally, the neutropenia events occurred in the first 3 cycles of treatment and resolved in majority of cases under continued treatment. Current data doesn't substantially impact on Vitrakvi® benefit-risk balance. Reflection of respective observed laboratory test abnormalities together with dosing guidance for severe events in Vitrakvi® label is considered adequate. However, taking the currently

limited number of Vitrakvi®-treated patients into account, "Serious infections secondary to neutropenia" is included as important potential risk as the potential future occurrence of such clinically potentially life-threatening- reactions might impact on current benefit-risk balance.

Pharmacovigilance activities will further characterise the risk with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by routine risk minimisation measures such that the benefit-risk for the product is positive.

Public health impact:

The public health impact is expected to be low. Patients may be at an increased risk of infection.

SVII.3.1.4 Impairment of Neurodevelopment in Paediatric Patients

MedDRA terms: In addition to the MedDRA PTs included in signal evaluation of the important potential risk "Severe neurologic reactions" (see Section SVII.3.1.1), the following HLGT (High-level group terms) and HLTs (High-level terms) are included in the context of important potential risk "Impairment of neurodevelopment in paediatric patients":

SOC "Psychiatric disorders": HLGT: "Cognitive and attention disorders and disturbances", HLT: "Developmental motor skills disorders".

SOC "Nervous System disorders": HLT: "Developmental disorders cognitive", HLT: "Memory loss (excl. dementia)", HLT: "Mental impairment (excl. dementia and memory loss".

Potential mechanisms:

On-target central effect cannot be excluded (MOA: neurotrophins signaling). In the postnatal period, TRK receptors are expressed in the brain and nervous system and are thought to regulate mood, memory, cognition, and proprioception. No human data are currently available on CNS penetration.

Evidence source(s) and strength of evidence:

Non-clinical studies:

Larotrectinib had no neurobehavioral findings or effects on respiratory function at up to100 mg/kg in rats and did not affect neuromuscular function in mice given 60 mg/kg/day for 48 days. Neuromuscular reactions were observed in juvenile male rats. Low-to-negligible penetration of the BBB was detected in rodents.

Clinical studies (N=335):

TRAEs also evaluated in the context of important potential risk "severe neurologic reactions" including PTs dizziness, gait disturbance, and paraesthesia were observed in clinical studies with the following frequencies: dizziness in 43 (13%) of all patients, and 3 (2%) in paediatric patients; gait disturbance in 5 (1%) of all patients, and no cases in paediatric patients; paraesthesia in 11 (3%) of all patients, and one case (<1%) in paediatric patients.

Delirium and somnolence as a TEAE were reported in <1 % and 3% of patients (with no reported Grade 4 and 5 events); no case of delirium and five cases (4%) of somnolence (none related) reported in paediatric patients. Three cases (5%) of memory impairment (one related) were captured in the paediatric population.

TEAEs cognitive disorder and disturbance in attention from HLT: “Mental impairment (excl. dementia and memory loss” were reported in 1 (<1%) and 6 (5%) paediatric patients. One case of disturbance in attention was related to the study drug. No additional adverse events pertaining to HLGT: “Cognitive and attention disorders and disturbances”, HLT: “Developmental motor skills disorders”, HLT: “Developmental disorders cognitive”, HLT: “Memory loss (excl. dementia)”, and HLT: “Mental impairment (excl. dementia and memory loss” were reported in paediatric patients in any of the Vitrakvi® clinical trials to date. No further neuro-developmental data is currently available.

Post-marketing data:

Retrieval criteria:

A cumulative search of Bayer’s Global Safety Database was performed for relevant cases of impairment of neurodevelopment in paediatric patients received from all post-marketing sources, excluding trials (20288, 20289 and 20290). The MedDRA search strategy for impairment of neurodevelopment in patients up to 21 years of age consisted of the following MedDRA terms:

HLGT (High level group terms) and HLTs (High level terms) are included in the context of important potential risk “Impairment of neurodevelopment in paediatric patients”:

SOC “Psychiatric disorders”: HLGT: “Cognitive and attention disorders and disturbances”, HLT: “Developmental motor skills disorders”.

SOC “Nervous System disorders”: HLT: “Developmental disorders cognitive”, HLT: “Memory loss (excl. dementia)”, HLT: “Mental impairment (excl. dementia and memory loss”.

Overview of cases

The search strategy yielded 5 cases that met the above search criteria, received *cumulatively* from post marketing sources since market launch (26 NOV 2018) until 25 MAY 2023. All cases were received from patient support programs and were non-medically confirmed. All 5 cases were non-serious. Out of 5 cases, 3 cases were reported in male patients and 2 cases in female patients.

Table SVII.13 presents the list of all PTs received cumulatively from 5 cases.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.13: Tabulation by Preferred Term for all events evaluated in the context of the Impairment in neurodevelopment in paediatric patients reported cumulatively until 25 MAY 2023.

Preferred Term	Non-serious AEs	Serious AEs	Total AEs
Total	**7**	**0**	**7**
Memory impairment	2	0	2
Disturbance in attention	2	0	2
Hypersomnia	1	0	1
Aphasia	1	0	1
Dizziness	1	0	1

AEs: Adverse events, PT: Preferred Term, SOC: System Organ Class (MedDRA).
MedDRA version 26.0

Cumulatively, 7 events of interest were received from post-marketing sources, all of them were non-serious. For details, please refer to Table SVII.13.

Conclusion

Overall, no new or relevant safety information was identified which would warrant or conclude a causal association between impairment of neurodevelopment in paediatric patients and Vitrakvi®. The evaluation of the risk remains consistent with the previous information from clinical studies.

Characterisation of the risk:

Frequency and Severity

Risk factors and risk groups:

Malnutrition, prematurity, perinatal asphyxia (e.g., cerebral palsy), genetic disorders, chronic infections and severe medical conditions - brain tumours (including benign), broncho-pulmonary dysplasia, microcephaly, hydrocephalus, sepsis, intranatal infections (e.g., Zika virus), environmental enteropathy and toxins, cardiac surgery, congenital heart disease, severe head trauma, neurodevelopment disruption (including psychosocial stress, violence).

Preventability:

Monitoring of developmental milestones, adequate nutrition, vaccination, treatment of medical conditions.

Impact on the risk-benefit balance of the product:

Current clinical data indicate an overall mild effect of Vitrakvi® on (central) nervous system and most reactions resolved under continued Vitrakvi® treatment, in the vast majority without any dose reduction. This current data does not substantially impact on Vitrakvi® benefit-risk balance. However, taking the currently limited number of Vitrakvi®-treated patients into account, “impairment of neurodevelopment in paediatric patients” is included as important

potential risk as the potential future occurrence of such reactions with greater severity (i.e., primarily Grade 3 or higher; events reported as serious) might impact on current benefit-risk balance.

Pharmacovigilance activities will further characterise the risk with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by routine risk minimisation measures such that the benefit-risk for the product is positive.

Public health impact:

If confirmed, the public health impact is expected to be substantial.

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Use in Pregnancy and Lactation

Evidence source:

Patient population has not been studied.

Population in need of further characterisation:

No data are available and thus the safety profile will be derived from routine pharmacovigilance activities.

Anticipated risk / consequence of the missing information:

Increased risk of maternal toxicity, damage to the foetus, and breastfed infants.

SVII.3.2.2 Long-Term Safety

Evidence source:

Overview of exposure versus TEAE data for 109 patients who reached more than 2 years of treatment at recommended dose is summarized in Table SVII.14. Mean age of patients who reached more than 2 years of treatment with larotrectinib was 34 years at baseline. The mean total treatment duration exceeded 3 years on treatment (1,279 +/- 374 days). Preliminary analysis is reassuring and suggests that the majority of TEAEs are reported during the first 2 years of exposure to Vitrakvi®, with the overall reported monthly AE frequency reducing by approximately two-fold following 2 years of exposure (1.19 versus 0.69 AEs reported per month on average). Detailed information of the number and the frequency of AEs (both < and ≥2 years of larotrectinib treatment), for each individual patient is presented in Annex 7.2.

Most common TEAEs reported after 24 months from the start of larotrectnib treatment regardless of attribution are upper respiratory tract infection (59%), vomiting (59%), cough (56%), and pyrexia (56%) for paediatric population, and alanine aminotransferase increased (50%), cough (49%), dizziness (46%), and aspartate aminotransferase increased (43%) or myalgia (43%) for adult population. Detailed information about most common TEAEs (>30% of patients) reported after 2 years from the start of larotrectinib treatment by age group is presented in Table SVII.15.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.14: Overview of exposure data for patients who reached more than two years of treatment at recommended dose (Overall Safety Set; N=377)

No. of patients treated for ≥ 2 years	Total (N=109)	
Age (years)	Mean (at baseline)	34
Total number of AEs	Average +/- SD	40 +/- 35
AE frequency (patient months)	Average	0.97
Number of AEs <2 years from treatment start	Average +/- SD	28 +/- 22
AE frequency (patient months)	Average	1.19
Number of AEs ≥2 years from treatment start	Average +/- SD	12 +/- 17
AE frequency (patient months)	Average	0.69
Total treatment duration (days)	Mean +/- SD	1,279 +/- 375

Source: 2731953 20jul2022 Tables for EU RMP part 3 (Visit Cut-off 20 JUL 2022)
Table 1 / 4: Treatment-emergent Adverse Event Counts for Subjects at Recommended Dose with at least 2 Years of Treatment (N=109)
Same AE can occur multiple times per subject.
Bayer: /var/swan/root/bhc/2731953/ia/stat/main03_q002/prod/pgms/t_teae_exdur_2yrs_update_rec_dos.sas 22JUL2023 9:56
AE: Adverse event, No.: Number, SD: Standard deviation.

Table SVII.15: Most common* TEAEs at recommended dose reported after 24 months from start of treatment by age group (Overall Safety with treatment duration ≥24 months)

Preferred Term	<18 years (N=41)	18+ years (N=68)	Overall (N=109)
Cough	23 (56%)	33 (49%)	56 (51%)
Alanine aminotransferase increased	16 (39%)	34 (50%)	50 (46%)
Aspartate aminotransferase increased	17 (41%)	29 (43%)	46 (42%)
Pyrexia	23 (56%)	20 (29%)	43 (39%)
Upper respiratory tract infection	24 (59%)	18 (26%)	42 (39%)
Diarrhoea	18 (44%)	23 (34%)	41 (38%)
Vomiting	24 (59%)	13 (19%)	37 (34%)
Arthralgia	9 (22%)	28 (41%)	37 (34%)
Constipation	10 (24%)	27 (40%)	37 (34%)
Myalgia	7 (17%)	29 (43%)	36 (33%)
Dizziness	4 (10%)	31 (46%)	35 (32%)
Anaemia	16 (39%)	17 (25%)	33 (30%)
Nausea	9 (22%)	24 (35%)	33 (30%)
Fatigue	4 (10%)	28 (41%)	32 (29%)
Headache	14 (34%)	16 (24%)	30 (28%)
Weight increased	6 (15%)	23 (34%)	29 (27%)
Nasopharyngitis	15 (37%)	13 (19%)	28 (26%)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVII - Identified and potential risks

Table SVII.15: Most common* TEAEs at recommended dose reported after 24 months from start of treatment by age group (Overall Safety with treatment duration ≥24 months)

Preferred Term	<18 years (N=41)	18+ years (N=68)	Overall (N=109)
Leukocyte count decreased	13 (32%)	11 (16%)	24 (22%)
Neutrophil count decreased	14 (34%)	8 (12%)	22 (20%)

*TEAEs reported after 24 months of larotrectinib treatment with a threshold of 30% (either in the paediatric or adult group, sorted in the descending order of frequency in the overall subset of 109 patients treated for 24+months).
Source: Table 1 / 5 (2731953 20jul2022 Tables for EU RMP part 3, Visit Cut-off 20 JUL 2022)
Patients are counted once within each Preferred term.
Reported AEs terms were coded using MedDRA dictionary (version 25.0).
Percentages are calculated based on the number of patients in the column heading as the denominator.
AE: Adverse event, MedDRA: Medical Dictionary for Regulatory Activities, TEAE: Treatment-emergent adverse event.

Population in need of further characterisation:

Adult and paediatric patients exposed to Vitkravi® for a period of 2 years and longer.

Anticipated risk / consequence of the missing information: Long-term exposure may increase the risk of occurrence of additional adverse events.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part II: Module SVIII - Summary of the safety concerns

Part II: Module SVIII - Summary of the Safety Concerns

Table SVIII.1: Summary of safety concerns

Important identified risks	None identified
Important potential risks	Severe neurologic reactions
	Severe drug-induced liver injury
	Serious infections secondary to neutropenia
	Impairment of neurodevelopment in paediatric patients
Missing information	Use in pregnancy and lactation
	Long-term safety

Part III: Pharmacovigilance Plan

III.1 Routine Pharmacovigilance Activities

The global safety database for Vitrakvi® is maintained and operated by Bayer for reporting to regulatory authorities. All newly acquired safety information will continue to be actively monitored in accordance with Good Pharmacovigilance Practices (GVP) including regular review and evaluation of data, routine systematic review of published literature and case reports and both individual case and aggregate safety reviews and analysis.

The objective of pharmacovigilance strategy is to systematically collect and review adverse events (AEs) and safety information from multiple sources and to conduct real-time- and periodic medical assessments of single and aggregate case reports. The purpose of this surveillance is to detect and evaluate changes in reporting frequency of AEs and in overall AE patterns that are suggestive of new safety concerns. Early detection of safety signals enables the Applicant to develop and implement appropriate risk management strategy.

No routine pharmacovigilance activities beyond adverse reaction reporting and signal reporting are planned.

Routine Pharmacovigilance Practices

AE Collection and Single Case Processing

Bayer will collect and process AE reports from multiple sources (spontaneous reporting from healthcare professionals and consumers, regulatory agencies, scientific literature, clinical trials, and post-marketing studies, i.e., registries, safety studies) and store in a centralised and validated company safety database.

Bayer will perform medical reviews to identify important single cases and conduct appropriate follow-up to obtain relevant medical information pertaining to these cases.

Bayer will prepare and submit expedited reports and other reports of interest to relevant Health Authorities and Ethics Committees within specified time frames.

Aggregate Reports

Aggregate reports are prepared and submitted to health authorities as required by regulations. These include Periodic Safety Update Reports (PSURs), Development Safety Update Reports (DSURs) and other reports as required. Ad hoc reports may be prepared upon identification of a potential safety issue and/or upon request by a regulatory agency or other healthcare entity.

Surveillance and Signal Detection

Signals identified during surveillance review will lead to further discussions. Recommendations will be made for further evaluation and action as appropriate. These may include:

- No actions needed as the signal is not confirmed after review of additional data
- Further assessment of the signal

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part III: Pharmacovigilance plan (including post-authorisation safety studies)

- Revision of the product label or other actions

III.2 Additional Pharmacovigilance Activities

Table Part III.1: Non-Interventional PASS (ON-TRK) – Category 3

Study short name and title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Rationale and study objectives	The purpose of this study is to evaluate, under real-world conditions, the safety and effectiveness of Vitrakvi® in patients with locally advanced or metastatic TRK fusion cancer for whom a decision to treat with larotrectinib has been made before enrollment. The primary objective of this study is to evaluate the safety of Vitrakvi® in adult and paediatric patients with locally advanced or metastatic TRK fusion cancer, including incidences of all TEAEs in real-world practice conditions. The secondary objectives of this study are: • To describe the effectiveness of Vitrakvi®, including overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) • To describe the patterns of Vitrakvi® treatment, including actual doses, duration of treatment (DOT), and other dosing parameters • To describe patient characteristics, including demographics, baseline characteristics, and *NTRK* testing • To describe the effectiveness of Vitrakvi® in subgroups of patients, including but not limited to: by age, *NTRK* gene, *NTRK* gene partner, testing methodology, country/region, prior therapy (type and/or number of lines of therapy), and/or by other patient baseline characteristics • To describe long-term effects of Vitrakvi® on growth (height and weight), neurological outcomes, developmental milestones, and sexual development (Tanner scale) in the paediatric cohort Additional exploratory objectives include: • To describe the effectiveness of larotrectinib, including overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), progression-free survival (PFS) based on tumour response data as determined by an Independent Review Committee (IRC) as applicable • To determine procedures avoided because of the use of larotrectinib (e.g., amputation or other disfiguring procedures) in infantile fibrosarcoma • To determine the number of patients who underwent surgery for a curative intent (excluding amputation) because of the use of larotrectinib • To describe systemic treatment prior to larotrectinib treatment, including doses, duration of treatment, best tumour response, and reasons for discontinuation, as appropriate
Study design	International, prospective, open-label, multicenter, single arm, multi-cohort, non-interventional study. Specific cohorts: gastrointestinal (GI), head and neck (H&N), lung, soft tissue sarcoma

	(STS), primary central nervous system (CNS), melanoma, paediatrics, and others. The recruitment period will be 36 months; the end of the study for all cohorts but the paediatric cohort will happen after the final patient has been in the study for at least 24 months, or is no longer under observation owing to being lost to follow-up, withdrawal, or death. For the paediatric cohort, each patient will be followed up for at least 60 months from larotrectinib initiation unless the patient is discontinued due to lost to follow-up, withdrawal, or death
Study population	Adult and paediatric (from birth to 18-year-old) patients with a locally advanced or metastatic solid tumour harbouring an NTRK gene fusion (detected by NGS, FISH, rt-PCR or other genomic testing able to detect NTRK gene fusion) assessed locally for whom a decision to treat with larotrectinib has been made by the treating physician prior to or at the time of study enrolment. The initial study aim was to enrol and collect data from up to 300 patients, which will allow for the observation of at least 1 adverse event for even uncommon occurring events with a 95% probability. Given significant enrolment challenges the protocol will be amended to include a sample size up to 150 patients. The reduction of the sample size from 300 patients to 150 allows to observe at least one AE event with a 95% probability for a true event incidence of 2% within the range of 0.1% to 5%, as per study protocol. Patients will be allocated to one of the cohorts depending on their tumour type or age: gastrointestinal (GI), head and neck (H&N), lung, soft tissue sarcoma (STS), primary central nervous system (CNS), melanoma, paediatric, and 'other'.

The European Reference Network (ERN)-EURACAN for adult rare solid cancers – Category 3

Bayer AG supports a European adult registry (TRacKING) through the European Reference Network (ERN)-EURACAN, a European network focusing on rare adult solid cancers. ((https://euracan.eu/registries/tracking/).

The objective of the TRacKING registry is to describe the management of adult patients with solid cancers harbouring an actionable fusion in real-life practice. The primary goal is the evaluation of overall survival. Among the secondary goals the clinical activity and safety of fusion-targeting treatments will be documented.

The registry was launched in Q2 2021 for a 4-year period (2 years inclusion + 2 years follow-up. Bayer receives annual data updates in return for its support of the EURACAN registry.

Table Part III.2: Study 20289 (NAVIGATE; formerly LOXO-TRK-15002) – Category 2

Study short name and title	Study 20289, a Phase 2 multicentre, open-label study in patients 12 years of age and older with advanced cancer harbouring a fusion of *NTRK1*, *NTRK2*, or *NTRK3*.
Rationale and study objectives	**Primary Objective:** To determine the overall response rate (ORR) as determined by an independent radiology review committee and measured by the proportion of subjects with best overall confirmed response of complete response (CR) or partial response (PR) by the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1), or Response Assessment in

Neuro-Oncology (RANO) criteria, as appropriate, following treatment with Vitrakvi® in subjects age 12 and older with an advanced cancer harbouring a fusion involving *NTRK1*, *NTRK2*, or *NTRK3* (collectively referred to as *NTRK* gene fusions) for each tumour-specific disease cohort.

Secondary Objectives for each tumour-specific disease cohort:

- To determine the ORR based on the treating Investigator's response assessment using RECIST 1.1 or RANO criteria, as appropriate to tumour type.
- To evaluate the duration of response (DOR) in subjects with best overall response of CR or PR as determined by 1) an independent radiology review committee and 2) the treating Investigator.
- To estimate the proportion of subjects that has any tumour regression as a best response.
- To evaluate the duration of progression-free survival (PFS) following initiation of Vitrakvi®.
- To evaluate the duration of overall survival (OS) following initiation of Vitrakvi®.
- To assess the safety profile and tolerability of Vitrakvi®.
- To compare the duration of PFS following initiation of Vitrakvi® to that following the line of therapy immediately preceding Vitrakvi® in subjects who have received prior therapy.
- To evaluate the clinical benefit rate (CBR) based on the proportion of subjects with best overall response of CR, PR, or stable disease lasting 16 or more weeks following initiation of Vitrakvi®.
- To evaluate the concordance of prior molecular profiling that detected an *NTRK* gene fusion within the subject's tumour with the diagnostic test being evaluated by the Sponsor.

Exploratory Objectives:

- To investigate the overall response rate based on positron emission tomography (PET) response criteria.
- To characterise *NTRK1, NTRK2,* and *NTRK3* fusions by next-generation sequencing from tumour biopsies and circulating tumour deoxyribonucleic acid (DNA).
- To characterise activation of the TRKA, TRKB, and TRKC signalling pathways in fresh pre-treatment tumour biopsies, with the aim of elucidating TRK biology and modifiers of response to Vitrakvi®.
- To characterise concurrently activated oncogenic pathways in fresh pre-treatment tumour biopsies with the aim of elucidating TRK, and modifiers of response to Vitrakvi®. To assess changes in tumour molecular status in fresh tumour biopsies and circulating tumour DNA obtained during treatment and after progression on Vitrakvi®, with the aim of elucidating TRK biology, modifiers of response, and mechanisms of acquired resistance to Vitrakvi®.
- To determine the relationship between PK and drug effects, including efficacy and safety.
- To evaluate changes from baseline in quality of life and health utilities measures, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EuroQoL Five Dimension Questionnaire (EQ-5D) for subjects 18 and

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part III: Pharmacovigilance plan (including post-authorisation safety studies)

	older and the PedsQL-Core Module (PedsQL-Core) for subjects age 12 to 17.
Study design	This is a Phase II, multi-centre, open-label study of subjects age 12 and older with advanced cancer harbouring a fusion of *NTRK1*, *NTRK2*, or *NTRK3*. Subjects with *NTRK1*, *NTRK2*, or *NTRK3* gene fusion will be identified through molecular assays as routinely performed at Clinical Laboratory Improvement Amendments of 1988 (CLIA) or other similarly certified laboratories. The study will consist of a screening period, a treatment period, a safety follow-up visit, and long-term follow up assessments. Safety, survival, and subsequent anticancer therapies will be tracked during the long-term follow-up period. Vitrakvi® will be administered at 100 mg BID. Each cycle will consist of 28 days of dosing administered on a continuous basis. One cycle will be defined as 28 days. Subjects will undergo radiographic evaluation of their disease at the end of even-numbered cycles between Cycles 1-12, and every 3 cycles thereafter. Subjects with primary central nervous system (CNS) disease will undergo radiographic evaluation of their disease at the end of each cycle between C1 TO C4, and every 2 cycles between C5 to C12, and every 3 cycles thereafter. Subjects will continue on Vitrakvi® until disease progression (as per RECIST 1.1 or RANO criteria), unacceptable toxicity, subject withdrawal of consent, or death. Subjects who have progressed may be allowed to continue Vitrakvi® if, in the opinion of the Investigator, the subject is deriving clinical benefit from continuing study treatment, and continuation of treatment is approved by the Sponsor. The study will include 9 cohorts of subjects with tumours bearing *NTRK* gene fusions, including non-small cell lung cancer, thyroid cancer, sarcoma, colorectal cancer, salivary gland cancer, biliary cancer, and primary CNS tumour and a cohort that includes all other tumour types and subjects without measurable disease. Subjects are required to have RECIST v1.1 or RANO measurable disease to be enrolled in Cohorts 1 through 7; these subjects and those in Cohort 8 with measurable disease will be evaluated for the primary objective of the trial. Subjects who do not have measurable disease but do have disease that is evaluable, for example by PET, may enrol in Cohort 8, will not be evaluated for the primary objective of the trial and will continue to be evaluated by the same modality until disease progression. Cohort 9 will enrol subjects who qualify for Cohorts 1-8, but where CLIA or similar certification of the lab performing the fusion assay is not confirmed at the time of consent. This study proposes to evaluate the selective TRK inhibitor larotrectinib in patients with NTRK fusion-positive solid tumour cancers using a basket trial design.
Study population	Patient with locally-advanced or metastatic malignancy with an *NTRK1*, *NTRK2* or *NTRK3* gene fusion, identified through molecular assays as routinely performed at CLIA or other similarly-certified laboratories. Subjects who have *NTRK* gene fusion identified in a lab where certification of the lab cannot be confirmed by the Sponsor at the time of consent may enrol to Cohort 9. Subjects must have received prior standard therapy appropriate for their tumour type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part III: Pharmacovigilance plan (including post-authorisation safety studies)

Table Part III.3: Study 20290 (SCOUT; formerly LOXO-TRK-15003) – Category 2

Study short name and title	Study 20290, a Phase 1/2 study of the oral TRK inhibitor LOXO-101 in paediatric patients with advanced solid or primary central nervous system tumours.
Rationale and study objectives	Initial results from the Phase 1, first-in-human dose-escalation clinical study for Vitrakvi® (Study LOXO-TRK-14001) in adult patients with advanced solid tumours demonstrated that Vitrakvi® has been well-tolerated at all dose levels tested. The current study will evaluate Vitrakvi® in paediatric patients. The initial starting dose of Vitrakvi® for this paediatric study was chosen to match exposure to the 100 mg BID dose that has been previously tested in adults and has not exceeded maximum tolerated dose criteria in the adult Phase 1 study. **Phase 1:** **Primary Objective:** To determine the safety of oral Vitrakvi®, including DLT, in paediatric patients with advanced solid or primary CNS tumours. **Secondary Objectives:** • To characterise the PK properties of Vitrakvi® in paediatric patients with advanced solid or primary CNS tumours. • To identify the MTD and/or the appropriate dose of Vitrakvi® for further clinical investigation in this patient population. • To describe the antitumour activity of Vitrakvi® in paediatric patients with advanced solid or primary CNS tumours. • To describe pain and health related quality of life in paediatric patients with advanced solid or primary CNS tumours treated with Vitrakvi®. **Exploratory Objective:** • To evaluate potential biomarkers of response and resistance to Vitrakvi®. **Phase 2:** **Primary Objective:** To determine the ORR as determined by an independent radiology review committee and measured by the proportion of subjects with best overall confirmed response of CR or PR by the RECIST 1.1, or RANO criteria, as appropriate, following treatment with Vitrakvi® in paediatric subjects with an advanced cancer harbouring a fusion involving *NTRK1*, *NTRK2,* or *NTRK3* (collective referred to as *NTRK* gene fusions). **Secondary Objectives:** • To determine the ORR based on the treating Investigator's response assessment using RECIST 1.1 or RANO criteria, as appropriate to tumour type. • To evaluate the DOR in subjects with best overall response of CR or PR as determined by 1) an independent radiology review committee and 2) the treating Investigator. • To estimate the proportion of subjects that have any tumour regression as a best response. • To evaluate the duration of PFS following initiation of Vitrakvi®.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part III: Pharmacovigilance plan (including post-authorisation safety studies)

Table Part III.3: Study 20290 (SCOUT; formerly LOXO-TRK-15003) – Category 2

	• To evaluate the duration of OS following initiation of Vitrakvi®. • To assess the safety profile and tolerability of Vitrakvi®. • To collect long-term use safety and efficacy data in paediatric patients. • To evaluate the CBR based on the proportion of subjects with best overall response of CR, PR, or stable disease lasting 16 or more weeks following initiation of Vitrakvi® as determined by 1) an independent radiology review committee and 2) the treating Investigator. • To evaluate the concordance of prior molecular profiling that detected an *NTRK* fusion within the subject's tumour with diagnostic tests being evaluated by the Sponsor. • To characterise post-operative staging and surgical margin status in patients who have definitive surgery following treatment with Vitrakvi®. • To describe the putative pre-treatment surgical plan and capture the post treatment actual approach with an emphasis on the functional and cosmetic outcome. **Exploratory Objectives:** • To characterise *NTRK1*, *NTRK2*, and *NTRK3* gene fusions by next-generation sequencing from tumour biopsies and circulating tumour DNA. • To determine the relationship between PK and drug effects, including efficacy and safety. • To evaluate changes from baseline in quality of life and health utilities measures, the PedsQL-Core assessment will be used. In patients 3 years of age or older, pain will be assessed by the Wong-Baker Faces Scale. • To evaluate potential biomarkers of response and resistance to Vitrakvi®. • Comparison to historical control with existing and future databases.
Study design	**Phase 1 Dose Escalation:** This part of the study is a multicentre, open-label, Phase 1 study in paediatric patients with advanced solid or primary CNS tumours. Vitrakvi® will be administered orally BID, with the dose adjusted by body surface area (BSA). Escalation will proceed through planned 5 dose levels, or until the MTD is reached, or until the Sponsor determines that a suitable dose has been achieved based on PK exposure. The maximum dose will be no higher than the recommended dose of 100 mg BID in the adult Phase 2 trial (LOXO-TRK-15002), regardless of the patient's BSA. **Phase 1 Expansion Cohort:** To confirm that a safe level of drug exposure has been established, up to 18 additional patients may be enrolled in an expansion cohort, following the formal dose escalation phase of the study. Distinct from the Phase 1 dose escalation cohort, the Phase I expansion cohort will enrol paediatric patients with advanced solid or primary CNS tumours with a documented *NTRK* gene fusion or, in the case of infantile fibrosarcoma (IFS), congenital mesoblastic nephroma (CMN) or secretory breast cancer (SBC) with documented ETV6 rearrangement by fluorescence in situ hybridisation (FISH) or real-time polymerase chain reaction (RT-PCR) or a documented NTRK fusion by NGS. The expansion cohort may accrue in parallel to the Phase 2 portion of the study (e.g., the expansion cohort does not need to complete accrual before the Phase 2 portion of the study opens for accrual).

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part III: Pharmacovigilance plan (including post-authorisation safety studies)

Table Part III.3: Study 20290 (SCOUT; formerly LOXO-TRK-15003) – Category 2

	Phase 2 Efficacy Cohorts: This part of the study is a Phase 2 expansion which will include 3 cohorts of patients with tumours bearing *NTRK* gene fusions (infantile fibrosarcoma, other extra-cranial solid tumours, and primary CNS tumours). Patients with infantile fibrosarcoma will require a documented *NTRK* gene fusion by NGS for eligibility to enrol. Patients with solid tumours with an *NTRK* gene fusion will be locally identified through molecular assays as routinely performed at CLIA or other similarly certified laboratories. Patients are required to have RECIST or RANO measurable disease to be enrolled. Vitrakvi® is administered in oral capsule or liquid formulation at the recommended Phase 2 dose. Each cycle consists of 28 days.
Study population	Paediatric (to 21 years of age) patients with advanced solid or primary CNS tumours as young as 1 month of age (for patients with infantile fibrosarcoma or congenital mesoblastic nephroma with an *NTRK* gene fusion) and patients greater than 1 year of age with or without an *NTRK* gene fusion will be eligible for enrolment. Infantile fibrosarcoma is being considered as a special case for inclusion at a younger age than other malignancies.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.4: Ongoing 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				
Study 20289 (NAVIGATE; formerly LOXO-TRK-15002), a Phase 2 multicentre, open-label study in patients 12 years of age and older with advanced cancer harbouring a fusion of *NTRK1*, *NTRK2*, or *NTRK3*	To determine the ORR as determined by an independent radiology review committee and measured by the proportion of subjects with best overall confirmed response of CR or PR by the RECIST 1.1, or RANO criteria, as appropriate, following treatment with Vitrakvi® in subjects age 12 and older with an advanced cancer	Severe neurologic reactions Severe drug-induced liver injury Serious infections secondary to neutropenia	FPFV LPLV	OCT 2015 31 OCT 2025

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part III: Pharmacovigilance plan (including post-authorisation safety studies)

Table Part III.4: Ongoing and planned additional pharmacovigilance activities

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Ongoing	harbouring a fusion involving *NTRK1*, *NTRK2*, or *NTRK3* (collectively referred to as *NTRK* gene fusions) for each tumour-specific disease cohort.	Impairment of neurodevelopment in paediatric patients Use in pregnancy and lactation Long-term safety	CSR	15 MAY 2026
Study 20290 (SCOUT; formerly LOXO-TRK-15003), a Phase 1/2 study of the oral TRK inhibitor LOXO-101 in paediatric patients with advanced solid or primary central nervous system tumours	Phase 1: To determine the safety of oral Vitrakvi® (larotrectinib; LOXO-101), including DLT, in paediatric patients with advanced solid or primary CNS tumours. Phase 2: To determine the ORR, following treatment with Vitrakvi® in paediatric subjects with an advanced cancer harbouring a fusion involving *NTRK1*, *NTRK2*, or *NTRK3* (collective referred to as *NTRK* gene fusions). To create an updated PopPK model in paediatric patients between 1 month and 6 years of age. To collect long-term use safety and efficacy data in paediatric patients.	Severe neurologic reactions Severe drug-induced liver injury Serious infections secondary to neutropenia	FPFV Update of pop PK model	OCT 2015 SEP 2021
Ongoing		Impairment of neurodevelopment in paediatric patients Use in pregnancy and lactation Long-term safety	LPLV CSR	22 SEP 2026 16 FEB 2027

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part III: Pharmacovigilance plan (including post-authorisation safety studies)

Table Part III.4: Ongoing and planned additional pharmacovigilance activities

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Non-Interventional PASS (ON-TRK) Ongoing	To evaluate, under real-world conditions, the safety and effectiveness of Vitrakvi® in patients with locally advanced or metastatic TRK fusion cancer for whom a decision to treat with larotrectinib has been made before enrolment.	Severe neurologic reactions Severe drug-induced liver injury Serious infections secondary to neutropenia Impairment of neurodevelopment in paediatric patients Use in pregnancy and lactation Long-term safety	FPFV LPFV (all cohorts) LPLV (all cohorts excl. paediatric) LPLV (paediatric) Final CSR excl. paediatric Final CSR (Paediatric)	Q2 2020 Q4 2024 Q4 2026 Q4 2029 Q2 2027 Q2 2030
Patient Registry (EURACAN TRacKING) European Reference Network (ERN)- for adult rare solid cancers EURACAN Ongoing	The objective of the TRacKING registry is to describe the management of adult patients with solid cancers harbouring an actionable fusion in real-life practice. The primary goal is the evaluation of overall survival. Among the secondary goals the clinical activity and safety of fusion-targeting treatments will be documented. The registry was launched in Q2 2021 for a 4-year period (2 years inclusion + 2 years follow-up. Bayer receives annual data updates in return for its support of the EURACAN registry	Severe neurologic reactions Severe drug-induced liver injury Serious infections secondary to neutropenia Use in pregnancy and lactation Long-term safety	Annual summary results	Annualy

Part IV: Plans for Post-authorisation Efficacy Studies

No post-authorisation efficacy studies are currently planned.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Part V: Risk Minimisation Measures

The Module Risk Minimisation Plan for Vitrakvi® comprises the routine risk minimisation measures detailed in Section V.1. No additional risk minimisation measures are currently in place.

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important identified risks	
None identified.	
Important potential risks	
Severe neurologic reactions	**Routine risk communication**: Summary of medicinal Product Characteristics (SmPC) sections: 4.8 (Undesirable effects); 5.3 (Preclinical safety data). **Routine risk minimisation measures recommending specific clinical measures to address the risk**: Patients should be cautioned about driving and using machines, until they are reasonably certain Vitrakvi® therapy does not affect them adversely (SmPC section 4.7: Effects on ability to drive or use machines). Withholding, reducing, or discontinuing Vitrakvi® dosing should be considered depending on severity and persistence of symptoms (SmPC sections 4.2: Posology and method of administration; 4.4: Special warnings and precautions). **Other routine risk minimisation measures beyond the Product Information**: Vitrakvi® is a prescription-only medicine and is administered by a specialist healthcare professional.
Severe drug-induced liver injury	**Routine risk communication**: SmPC sections: 4.2 (Posology and method of administration); 4.8 (Undesirable effects); 5.2 (Pharmacokinetic properties. **Routine risk minimisation measures recommending specific clinical measures to address the risk**: A reduced starting dose by 50% in patients with moderate (Child Pugh B) to severe (Child Pugh C) hepatic impairment is advised. The majority of ALT/AST increases occurred within 3 months of starting VITRAKVI. Cases of hepatotoxicity with increases in ALT and/or AST of Grade 2, 3 or Grade 4 severity and increases in bilirubin ≥ 2 x ULN have been reported in adult patients. In patients with hepatic transaminase elevations, withhold, modify dose or permanently discontinue VITRAKVI based on the severity. Monitor for liver function including ALT, AST, ALP and bilirubin before the first dose, then every 2 weeks during the first month of treatment, then monthly for the next 6 months of treatment, then periodically during

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
	treatment. In patients who develop transaminase elevations, more frequent testing is needed. (SmPC sections 4.2: Posology and method of administration; 4.4: Special warnings and precautions). **Other routine risk minimisation measures beyond the Product Information**: Vitrakvi® is a prescription-only medicine and is administered by a specialist healthcare professional.
Serious infections secondary to neutropenia	**Routine risk communication:** SmPC section 4.8 (Undesirable effects). **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Vitrakvi® is a prescription-only medicine and is administered by a specialist healthcare professional.
Impairment of neurodevelopment in paediatric patients	**Routine risk communication:** 5.3 (Preclinical safety data). **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Vitrakvi® is a prescription-only medicine and is administered by a specialist healthcare professional.
Missing information	
Use in pregnancy and lactation	**Routine risk communication**: SmPC section 5.3 (Preclinical safety data). **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC section 4.6 (Fertility, pregnancy and lactation): It is preferable to avoid the use of Vitrakvi® during pregnancy. Foetal harm cannot be excluded. Women of childbearing potential should have a pregnancy test prior to starting treatment with Vitrakvi®. Advise women of reproductive potential to use highly effective contraception during treatment with Vitrakvi® and for at least one month after the final dose. For males of reproductive potential with a non-pregnant female partner of childbearing potential, advise use of highly effective contraception during treatment with Vitrakvi® and for at least one month after the final dose.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
	Advise a nursing woman to discontinue breastfeeding during treatment with Vitrakvi® and for 3 days following the final dose. **Other routine risk minimisation measures beyond the Product Information**: Vitrakvi® is a prescription-only medicine and is administered by a specialist healthcare professional.
Long-term safety	**Routine risk communication**: SmPC section 4.8 (Undesirable effects). **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None. **Other routine risk minimisation measures beyond the Product Information**: Vitrakvi® is a prescription-only medicine and is administered by a specialist healthcare professional.

SmPC: Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation measures as described in Section V.1 are deemed sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Severe neurologic reactions (Important potential risk)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC Sections 4.8; 5.3) Routine risk communication recommending specific clinical measure to address the risk: • Caution patients about driving and operating machinery (SmPC 4.7) • Consider dose modification/s (SmPC 4.2; 4.4) Prescription-only medicine Specialist healthcare professional	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, and in post-marketing experience. Further evaluation as an Adverse Event of Special Interest (AESI) in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	
Severe drug-induced liver injury (Important potential risk)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC sections: 4.2; 4.8; 5.2) Routine risk communication recommending specific clinical measure to address the risk: • Liver function monitoring (SmPC 4.2; 4.4) • Consider dose modification/s (SmPC 4.2; 4.4) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, and in post-marketing experience. Further evaluation as an AESI in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003)
Serious infections secondary to neutropenia (Important potential risk)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 4.8) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, and in post-marketing experience. Further evaluation in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003)

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Table Part V.2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Impairment of neurodevelopment in paediatric patients (Important potential risk)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 5.3) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK), and in post-marketing experience. Further evaluation in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002, LOXO-TRK-15003)
Use in pregnancy and lactation (Missing information)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 5.3) Routine risk communication recommending specific clinical measure to address the risk: • Highly effective contraception in both males and females (SmPC 4.6) • Pregnancy test prior to treatment initiation (SmPC 4.6) • Discontinuation of breastfeeding in nursing mothers (SmPC 4.6) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK) evaluation of annual summary results obtained from the (ERN)-EURACAN registry, and in post-marketing experience. Further evaluation in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003)
Long-term safety (Missing information)	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 4.8) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities**: Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, and in post-marketing experience. Further evaluation in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003)

VITRAKVI®
(Larotrectinib)

EU Risk Management Plan
Part VI: Summary of the risk management plan

Part VI: Summary of the risk management plan for Vitrakvi®

This is a summary of the risk management plan (RMP) for Vitrakvi® (larotrectinib; LOXO-101). The RMP details important risks of Vitrakvi®, how these risks can be minimised, and how more information will be obtained about Vitrakvi®'s risks and uncertainties (missing information).

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

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

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

I. The Medicine and What it is used for

Vitrakvi® as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display 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**
- who have no satisfactory treatment options.

Further information about the evaluation of the benefits of Vitrakvi®, including its plain-language summary, can be found in in the EPAR for Vitrakvi® (https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi).

II. Risks Associated with the Medicine and Activities to Minimise or further Characterise the Risks

Important risks of Vitrakvi®, together with measures to minimise such risks and the proposed studies for learning more about these risks, are outlined below.

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

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

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part VI: Summary of the risk management plan

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

In addition to these measures, information about adverse reactions is collected continuously and analysed regularly (e.g., via the periodic safety update report [PSUR]) so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Vitrakvi® is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

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

List of important risks and missing information	
Important identified risks	None identified
Important potential risks	Severe neurologic reactions
	Severe drug-induced liver injury
	Serious infections secondary to neutropenia
	Impairment of neurodevelopment in paediatric patients
Missing information	Use in pregnancy and lactation
	Long-term safety

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part VI: Summary of the risk management plan

II.B Summary of Important Risks

Important potential risk: Severe neurologic reactions	
Evidence for linking the risk to the medicine	Treatment-related adverse events (TRAEs) of dizziness, gait disturbance, paraesthesia were frequently observed in clinical studies.
Risk factors and risk groups	Primary central nervous system tumours or metastatic lesions, medical history of brain tumours, surgeries or head trauma, underlying neurological conditions, concomitant use of certain agents known for neurotoxicity.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC sections 4.8; 5.3) Routine risk communication recommending specific clinical measure to address the risk: • Caution patients about driving and operating machinery (SmPC 4.7) • Consider dose modification/s (SmPC 4.2; 4.4) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, in post-marketing experience, and as an Adverse Event of Special Interest (AESI) in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

Important potential risk: Severe drug-induced liver injury	
Evidence for linking the risk to the medicine	Elevation of liver enzymes, hyperbilirubinaemia and jaundice were reported in clinical trials with Vitrakvi®.
Risk factors and risk groups	Patients with impaired liver function at baseline, chronic liver conditions, concomitant administration of agents, and medications with known adverse hepatic effects.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC sections: 4.2; 4.8; 5.2) Routine risk communication recommending specific clinical measure to address the risk: • Liver function monitoring (SmPC 4.2; 4.4) • Consider dose modification/s (SmPC 4.2; 4.4) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures**:

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part VI: Summary of the risk management plan

Important potential risk: Severe drug-induced liver injury	
	None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, in post-marketing experience, and as an AESI in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

Important potential risk: Serious infections secondary to neutropenia	
Evidence for linking the risk to the medicine	In the overall clinical safety database (n=335), a total of 49 SAEs from SOC "Infections" were reported, and none were assessed as related to study medication. None of the cases of infections were reported in combination with neutropenia with the exception of a single patient (febrile neutropenia and sepsis). Neutropenia was observed in ongoing clinical trials in 17% of total cases (paediatric patients 29% vs adults 9%).
Risk factors and risk groups	Underlying haematological conditions, concomitant administration of agents with known haematotoxicity effects, immunosuppression, chronic infectous and inflammatory disease, exposure to infectous agents. Paediatric patients with complex past medical histories and / or neutropenia observable at baseline. Of note, 47% and 28% of so far Vitrakvi®-treated patients had received 1 or 2 and at least 3 prior systemic therapies, respectively. Hence, a certain effect on baseline bone marrow reserve in these patients, in particular in the paediatric population, can't be excluded.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 4.8) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, in post-marketing experience, and in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

Important potential risk: Impairment of neurodevelopment in paediatric patients	
Evidence for linking the risk to the medicine	No adverse events pertaining to HLGT: "Cognitive and attention disorders and disturbances", HLT: "Developmental motor skills disorders", HLT: "Developmental disorders cognitive", HLT: "Memory loss (excl dementia)", and HLT: "Mental impairment (excl dementia and memory loss" were reported in any of the Vitrakvi® clinical trials to date. Risk is also being evaluated in the context of the important potential risk "severe neurologic reactions". No further developmental data is currently available.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part VI: Summary of the risk management plan

Important potential risk: Impairment of neurodevelopment in paediatric patients	
Risk factors and risk groups	Malnutrition, prematurity, perinatal asphyxia (e.g., cerebral palsy), genetic disorders, chronic infections and medical conditions, - brain tumours (including benign), broncho-pulmonary dysplasia, microcephaly, hydrocephalus, sepsis, intranatal infections (e.g., Zika virus), environmental enteropathy and toxins, cardiac surgery, congenital heart disease, severe head trauma, neurodevelopment disruption (including psychosocial stress, violence).
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 5.3) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), in post-marketing experience, and in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

Missing information: Use in pregnancy and lactation	
Evidence for linking the risk to the medicine	Patient population has not been studied.
Risk factors and risk groups	Respective population in need of further characterisation. Potential increased risk of maternal toxicity, damage to the foetus, and nursing infants.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 5.3) Routine risk communication recommending specific clinical measure to address the risk: • Highly effective contraception in both males and females (SmPC 4.6) • Pregnancy test prior to treatment initiation (SmPC 4.6) • Discontinuation of breastfeeding in nursing mothers (SmPC 4.6) Prescription-only medicine Specialist healthcare professional **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, in post-marketing experience and in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part VI: Summary of the risk management plan

Missing information: Long-term safety	
Evidence for linking the risk to the medicine	Preliminary analysis of safety data on the 109 patients who reached the exposure to Vitrakvi® of >2 years, suggests that the majority of TEAEs are reported during the first 2 years of exposure. No further long-term safety data is available.
Risk factors and risk groups	Long-term exposure may increase the risk of occurrence of additional adverse events in adult and paediatric patients exposed to Vitrakvi® for a period of longer than 2 years.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication so that an informed decision can be made (SmPC section: 4.8). Prescription-only medicine. Specialist healthcare professional. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Further evaluation in a Non-Interventional PASS (ON-TRK), evaluation of annual summary results obtained from the (ERN)-EURACAN registry, in post-marketing experience, and in ongoing clinical trials 20289 and 20290 (formerly LOXO-TRK-15002 and LOXO-TRK-15003).

II.C Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

Study name **Status**	**Rationale and study objectives**
Study ON-TRK, A PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib Ongoing	To evaluate, under real-world conditions, the safety and effectiveness of Vitrakvi® in patients with locally advanced or metastatic TRK fusion cancer for whom a decision to treat with larotrectinib has been made before enrolment.
Study 20289 (NAVIGATE; formerly LOXO-TRK-15002), a Phase 2 multicentre, open-label study in patients 12 years of age and older with advanced cancer harbouring a fusion of *NTRK1*, *NTRK2*, or *NTRK3*. Ongoing	To determine the overall response rate as determined by an independent radiology review committee and measured by the proportion of subjects with best overall confirmed response of complete response or partial response by the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1), or Response Assessment in Neuro Oncology (RANO) criteria, as appropriate, following treatment with Vitrakvi® in subjects age 12 and older with an advanced cancer harbouring a fusion involving *NTRK1*, *NTRK2*, or *NTRK3* (collectively referred to as *NTRK* gene fusions) for each tumour-specific disease cohort.

VITRAKVI®
(Larotrectinib)
EU Risk Management Plan
Part VI: Summary of the risk management plan

Study name Status	Rationale and study objectives
	The study will also assess the safety profile and tolerability of Vitrakvi® for each tumour-specific disease cohort.
Study 20290 (SCOUT; formerly LOXO-TRK-15003), A Phase 1/2 study of the oral TRK inhibitor LOXO-101 in paediatric patients with advanced solid or primary central nervous system tumours. Ongoing	Phase I: To determine the safety of oral Vitrakvi®, including dose-limiting toxicity (DLT), in paediatric patients with advanced solid or primary central nervous system (CNS) tumours. Phase II: To determine the overall response rate (ORR) as determined by an independent radiology review committee and measured by the proportion of subjects with best overall confirmed response of complete response (CR) or partial response (PR) by the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1), or Response Assessment in Neuro-Oncology (RANO) criteria for primary CNS tumours, and International Neuroblastoma Response Criteria (INRC) for neuroblastoma as appropriate, following treatment with Vitrakvi® in paediatric subjects with an advanced cancer harbouring a fusion involving *NTRK1*, *NTRK2*, or *NTRK3* (collectively referred to as neurotrophic tyrosine kinase receptor [*NTRK*] fusions). In order to confirm the appropriate dose recommended in paediatric patients an updated PopPK model based on additional PK sampling in paediatric patients between 1 month and 6 years of age will be created. To collect long-term use safety and efficacy data in paediatric patients.

II.C.2 Other studies in Post-authorisation Development Plan

Study name Status	Rationale and study objectives
Patient Registry (EURACAN TRacKING) European Reference Network (ERN)- for adult rare solid cancers EURACAN Ongoing	Bayer AG supports a European adult registry (TRacKING) through the European Reference Network (ERN)-EURACAN, a European network focusing on rare adult solid cancers (http://euracan.eu/registries/tracking/) The objective of the TRacKING registry is to describe the management of adult patients with solid cancers harbouring an actionable fusion in real-life practice. The primary goal is the evaluation of overall survival. Among the secondary goals the clinical activity and safety of fusion-targeting treatments will be documented. The registry was launched in Q2 2021 for a 4-year period (2 years inclusion + 2 years follow-up. Bayer receives annual data updates in return for its support of the EURACAN registry.

PART VII: Annexes

Table of Contents

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities

Not applicable.