ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 25 mg hard capsules
VITRAKVI 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VITRAKVI 25 mg hard capsules
Each hard capsule contains larotrectinib sulfate equivalent to 25 mg of larotrectinib.

VITRAKVI 100 mg hard capsules
Each hard capsule contains larotrectinib sulfate equivalent to 100 mg of larotrectinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

VITRAKVI 25 mg hard capsules
White opaque hard gelatine capsule, size 2 (18 mm long x 6 mm wide), 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 (22 mm long x 7 mm wide), with blue printing of BAYER-cross and “100 mg” on body of capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Treatment with VITRAKVI should be initiated by physicians experienced in the administration of anticancer therapies.

The presence of an *NTRK* gene fusion in a tumour specimen should be confirmed by a validated test prior to initiation of treatment with VITRAKVI.

Posology

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.

Missed dose
If a dose is missed, the patient should not take two doses at the same time to make up for a missed dose. Patients should take the next dose at the next scheduled time. If the patient vomits after taking a dose, the patient should not take an additional dose to make up for vomiting.

Dose modification
For all grade 2 adverse reactions, continued dosing may be appropriate, though close monitoring to ensure no worsening of the toxicity is advised.

For all grade 3 or 4 adverse reactions not referring to liver function test abnormalities:
- VITRAKVI should be withheld until the adverse reaction resolves or improves to baseline or grade 1. Resume at the next dose modification if resolution occurs within 4 weeks.
- VITRAKVI should be permanently discontinued if an adverse reaction does not resolve within 4 weeks.

The recommended dose modifications for VITRAKVI for adverse reactions are provided in Table 1.

Table 1: Recommended dose modifications for VITRAKVI for adverse reactions

Dose modification	Adult and paediatric patients with body surface area of at least 1.0 m^2	Paediatric patients with body surface area less than 1.0 m^2
First	75 mg twice daily	75 mg/m^2 twice daily
Second	50 mg twice daily	50 mg/m^2 twice daily
Third	100 mg once daily	25 mg/m^2 twice daily[a]

[a] Paediatric patients on 25 mg/m² twice daily should remain on this dose even if body surface area becomes greater 1.0 m² during the treatment. Maximum dose should be 25 mg/m² twice daily at the third dose modification.

VITRAKVI should be permanently discontinued in patients who are unable to tolerate VITRAKVI after three dose modifications.

The recommended dose modifications in case of liver function tests abnormalities during treatment with VITRAKVI are provided in Table 2.

Table 2: Recommended dose modifications and management for VITRAKVI for liver function test abnormalities

Laboratory parameters	Recommended measures
Grade 2 ALT and/or AST (>3x ULN and ≤5x ULN)	- Conduct serial laboratory evaluations frequently after the observation of grade 2 toxicity, until resolved, to establish whether a dose interruption or reduction is required.
Grade 3 ALT and/or AST (>5x ULN and ≤20x ULN) or Grade 4 ALT and/or AST (>20x ULN), with bilirubin <2x ULN	- Withhold treatment until the adverse reaction resolves or improves to baseline. Monitor liver function frequently until resolution or return to baseline. Permanently discontinue treatment if an adverse reaction does not resolve. - Resume at the next dose modification if adverse reactions resolve. Treatment should only be resumed in patients where the benefit outweighs the risk. - Permanently discontinue treatment if a grade 4 ALT and/or AST elevation occurs after resuming treatment.
ALT and/or AST ≥3x ULN with bilirubin ≥2x ULN	- Withhold treatment and monitor liver function frequently until resolution or return to baseline. - Consider permanent treatment discontinuation. - Treatment should only be resumed in patients where the benefit outweighs the risk. - If resumed, start at the next lower dose. Monitor liver function frequently upon restart. - Permanently discontinue treatment if adverse reaction recurs after resuming treatment.

ALT Alanine aminotransferase
AST Aspartate aminotransferase
ULN upper limit of normal

Special populations

Elderly
No dose adjustment is recommended in elderly patients (see section 5.2).

Hepatic impairment
The starting dose of VITRAKVI should be reduced by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A) (see section 5.2).

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2).

Co-administration with strong CYP3A4 inhibitors
If co-administration with a strong CYP3A4 inhibitor is necessary, the VITRAKVI dose should be reduced by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, VITRAKVI should be resumed at the dose taken prior to initiating the CYP3A4 inhibitor (see section 4.5).

Method of administration

VITRAKVI is for oral use.

VITRAKVI is available as a capsule or oral solution 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Efficacy across tumour types

The benefit of VITRAKVI has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit *NTRK* gene fusions. Favourable effects of VITRAKVI have been shown on the basis of overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genetic alterations (see section 5.1). For these reasons, VITRAKVI should only be used if there are no treatment options for which clinical benefit has been established, or where such treatment options have been exhausted (i.e., no satisfactory treatment options).

Neurologic reactions

Neurologic reactions including dizziness, gait disturbance and paraesthesia were reported in patients receiving larotrectinib (see section 4.8). For the majority of neurologic reactions, onset occurred within the first three months of treatment. Withholding, reducing, or discontinuing VITRAKVI dosing should be considered, depending on the severity and persistence of these symptoms (see section 4.2).

Hepatotoxicity

Abnormalities of liver function tests including increased ALT, AST, alkaline phosphatase (ALP) and bilirubin have been observed in patients receiving larotrectinib (see section 4.8). The majority of ALT and AST increases occurred within 3 months of starting treatment. Cases of hepatotoxicity with increases in ALT and/or AST of grade 2, 3 or 4 severity and increases in bilirubin ≥ 2x ULN have been reported.
In patients with hepatic transaminase elevations, withhold, modify dose or permanently discontinue VITRAKVI based on the severity (see section 4.2).
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 (see section 4.2).

Co-administration with CYP3A4/P-gp inducers

Avoid co-administration of strong or moderate CYP3A4/P-gp inducers with VITRAKVI due to a risk of decreased exposure (see section 4.5).

Contraception in female and male

Women of childbearing potential must use highly effective contraception while taking VITRAKVI and for at least one month after stopping treatment (see sections 4.5 and 4.6).
Males of reproductive potential with a non-pregnant woman partner of childbearing potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on larotrectinib

Effect of CYP3A, P-gp and BCRP inhibitors on larotrectinib
Larotrectinib is a substrate of cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of VITRAKVI with strong or moderate CYP3A inhibitors, P-gp and BCRP inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole or grapefruit) may increase larotrectinib plasma concentrations (see section 4.2).
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with itraconazole (a strong CYP3A inhibitor and P-gp and BCRP inhibitor) 200 mg once daily for 7 days increased larotrectinib C_{max} and AUC by 2.8-fold and 4.3-fold, respectively.
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with a single dose of 600 mg rifampicin (a P-gp and BCRP inhibitor) increased larotrectinib C_{max} and AUC by 1.8-fold and 1.7-fold, respectively.

Effect of CYP3A and P-gp inducers on larotrectinib
Co-administration of VITRAKVI with strong or moderate CYP3A inducers and strong P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, or St. John's Wort) may decrease larotrectinib plasma concentrations and should be avoided (see section 4.4).
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with rifampicin (a strong CYP3A and P-gp inducer) 600 mg once daily for 11 days decreased larotrectinib C_{max} and AUC by 71% and 81%, respectively. No clinical data is available on the effect of a moderate inducer, but a decrease in larotrectinib exposure is expected.

Effects of larotrectinib on other agents

Effect of larotrectinib on CYP3A substrates
Clinical data in healthy adult subjects indicate that co-administration of VITRAKVI (100 mg twice daily for 10 days) increased the C_{max} and AUC of oral midazolam 1.7-fold compared to midazolam alone, suggesting that larotrectinib is a weak inhibitor of CYP3A.
Exercise caution with concomitant use of CYP3A substrates with narrow therapeutic range (e.g. alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus) in patients taking VITRAKVI. If concomitant use of these CYP3A substrates with narrow therapeutic range is required in patients taking VITRAKVI, dose reductions of the CYP3A substrates may be required due to adverse reactions.

Effect of larotrectinib on CYP2B6 substrates
In vitro studies indicate that larotrectinib induces CYP2B6. Co-administration of larotrectinib with CYP2B6 substrates (e.g. bupropion, efavirenz) may decrease their exposure.

Effect of larotrectinib on other transporter substrates
In vitro studies indicate that larotrectinib is an inhibitor of OATP1B1. No clinical studies have been performed to investigate interactions with OATP1B1 substrates. Therefore, it cannot be excluded whether co-administration of larotrectinib with OATP1B1 substrates (e.g. valsartan, statins) may increase their exposure.

Effect of larotrectinib on substrates of PXR regulated enzymes
In vitro studies indicate that larotrectinib is a weak inducer of PXR regulated enzymes (e.g. CYP2C family and UGT). Co-administration of larotrectinib with CYP2C8, CYP2C9 or CYP2C19 substrates (e.g. repaglinide, warfarin, tolbutamide or omeprazole) may decrease their exposure.

Hormonal contraceptives
It is currently unknown whether larotrectinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should be advised to add a barrier method.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Based on the mechanism of action, foetal harm cannot be excluded when administering larotrectinib to a pregnant woman. Women of childbearing potential should have a pregnancy test prior to starting treatment with VITRAKVI.
Women of reproductive potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose. As it is currently unknown whether larotrectinib may reduce the effectiveness of systemically acting hormonal contraceptives, women using systemically acting hormonal contraceptives should be advised to add a barrier method.
Males of reproductive potential with a non-pregnant woman partner of childbearing potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose.

Pregnancy

There are no data from the use of larotrectinib in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of VITRAKVI during pregnancy.

Breast-feeding

It is unknown whether larotrectinib/metabolites are excreted in human milk.
A risk to newborns/infants cannot be excluded.
Breast-feeding should be discontinued during treatment with VITRAKVI and for 3 days following the final dose.

Fertility

There are no clinical data on the effect of larotrectinib on fertility. No relevant effects on fertility were observed in repeat-dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

VITRAKVI has a moderate influence on the ability to drive and use machines. Dizziness and fatigue have been reported in patients receiving larotrectinib, mostly grade 1 and 2 during the first 3 months of treatment. This may influence the ability to drive and use machines during this time period. Patients should be advised not to drive and use machines, until they are reasonably certain VITRAKVI therapy does not affect them adversely (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (≥ 20%) of VITRAKVI in order of decreasing frequency were increased ALT (36%), increased AST (33%), vomiting (30%), anaemia (28%), constipation (28%), diarrhoea (27%), nausea (24%), fatigue (23%), and dizziness (20%).
The majority of adverse reactions were grade 2 or 3. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (2%), ALT increased (1%), AST increased, leukocyte count decreased, platelet count decreased, muscular weakness and blood alkaline phosphatase increased (each in < 1%). The highest reported grade was grade 3 for adverse reactions anaemia (7%), weight increased (6%), diarrhoea (4%), gait disturbance and vomiting (each 1%), and fatigue, dizziness, paraesthesia, nausea, myalgia, and constipation (each in < 1%).
Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions occurred in 2% of patients (2 cases each of neutrophil count decreased, ALT increased, and AST increased, 1 case each of gait disturbance, and muscular weakness). The majority of adverse reactions leading to dose reduction occurred in the first three months of treatment.

Tabulated list of adverse reactions

The safety of VITRAKVI was evaluated in 361 patients with TRK fusion-positive cancer in one of three on-going clinical trials, Studies 1, 2 ("NAVIGATE"), and 3 ("SCOUT") and post-marketing. The safety population characteristics were comprised of patients with a median age of 39.0 years (range: 0, 90) with 37% of patients being paediatric patients. Median time on treatment for the overall safety population (n=361) was 16.2 months (range: 0.1, 89.1).
The adverse drug reactions reported in patients (n=361) treated with VITRAKVI are shown in Table 3 and Table 4.

The adverse drug reactions are classified according to the System Organ Class.
Frequency groups are defined by the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), and not known (cannot be estimated from available data).
Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (overall safety population, n=361) and post-marketing

System organ class	Frequency	All grades	Grades 3 and 4
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	
	Common	Platelet count decreased (Thrombocytopenia)	Anaemia Neutrophil count decreased (Neutropenia)[a] Leukocyte count decreased (Leukopenia)[a]
	Uncommon		Platelet count decreased (Thrombocytopenia)[a, b]
Nervous system disorders	Very common	Dizziness	
	Common	Gait disturbance Paraesthesia	Gait disturbance
	Uncommon		Dizziness Paraesthesia
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting Diarrhoea	
	Common	Dysgeusia[c]	Diarrhoea Vomiting
	Uncommon		Nausea Constipation
Hepatobiliary disorders	Not known	Liver injury[d]	
Musculoskeletal and connective tissue disorders	Very common	Myalgia	
	Common	Muscular weakness	
	Uncommon		Myalgia Muscular weakness[a, b]
General disorders and administration site conditions	Very common	Fatigue	
	Uncommon		Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain)	
	Common	Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased[a] Aspartate aminotransferase (AST) increased[a] Weight increased (Abnormal weight gain)
	Uncommon		Blood alkaline phosphatase increased[a, b]

[a] grade 4 reactions were reported

[b] each grade frequency was less than <1%

[c] ADR dysgeusia includes the preferred terms “dysgeusia” and “taste disorder”

[d] includes cases with ALT/AST ≥3x ULN and bilirubin ≥2x ULN

Table 4: Adverse drug reactions reported in TRK fusion-positive paediatric cancer patients treated with VITRAKVI at recommended dose (n=135); all grades

System organ class	Frequency	Infants and toddlers (n=43)[a]	Children (n=67)[b]	Adolescents (n=25)[c]	Paediatric patients (n=135)
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) Platelet count decreased (Thrombocytopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) Platelet count decreased (Thrombocytopenia)
	Common		Platelet count decreased (Thrombocytopenia)	Platelet count decreased (Thrombocytopenia)	
Nervous system disorders	Very common			Dizziness	
	Common	Dizziness	Dizziness Paraesthesia Gait disturbance	Paraesthesia Gait disturbance	Dizziness Paraesthesia Gait disturbance
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea
	Common		Dysgeusia		Dysgeusia
Musculoskeletal and connective tissue disorders	Very common		Myalgia	Myalgia	Myalgia
	Common	Muscular weakness	Muscular weakness	Muscular weakness	Muscular weakness
General disorders and administration site conditions	Very common	Fatigue	Fatigue	Fatigue	Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased

[a] Infant/toddlers (28 days to 23 months): 5 grade 4 Neutrophil count decreased (Neutropenia) reactions and 2 Blood alkaline phosphatase increased reported. Grade 3 reactions included 11 cases of Neutrophil count decreased (Neutropenia), 4 cases of ALT increased, 3 cases each of Anaemia, Diarrhoea, and Weight increased (Abnormal weight gain), and 2 cases each of Blood alkaline phosphatase increased, and Vomiting and 1 case of AST increased.

[b] Children (2 to 11 years): 1 grade 4 Leukocytes count decreased reported. 9 reported grade 3 cases of Neutrophil count decreased (Neutropenia), 4 cases of Weight increased (Abnormal weight gain), 2 cases each of ALT increased, Anaemia, Diarrhoea, and Vomiting and 1 case each of AST increased, Gait disturbance, Paraesthesia and Myalgia.

[c] Adolescents (12 to <18 years): no grade 4 reactions were reported. Grade 3 reactions were reported in 1 case each of ALT increased, AST increased, Fatigue, Gait disturbance, and Muscular weakness.

Description of selected adverse reactions

Neurologic reactions
In the overall safety database (n=361), the maximum grade neurologic adverse reaction observed was grade 3 or 4 which was observed in 10 (3%) patients and included gait disturbance (4 patients, 1%), dizziness (3 patients, <1%), and paraesthesia (3 patients, <1%). The overall incidence was 20% for dizziness, 7% for paraesthesia and 5% for gait disturbance. Neurologic reactions leading to dose modification or interruptions included dizziness (1%), gait disturbance (<1%), and paraesthesia (<1%). One patient permanently discontinued the treatment due to grade 3 gait disturbance. In all cases except of one, patients with evidence of anti-tumour activity who required a dose reduction were able to continue dosing at a reduced dose and/or schedule (see section 4.4).

Hepatotoxicity
Abnormalities of liver function tests including ALT, AST, ALP and bilirubin have been observed in patients treated with VITRAKVI.
In the overall safety database (n=361), the maximum grade transaminase elevation observed was grade 4 ALT increase in 7 patients (2%) and AST increase in 4 patients (1%). Grade 3 ALT and AST increases in 26 (7%) and 22 (6%) of patients, respectively. Majority of grade 3 elevations were transient appearing in the first three months of treatment and resolving to grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in 37 (10%) and 33 (9%) of patients, respectively, and grade 1 ALT and AST increases were observed in 173 (48%) and 177 (49%) of patients, respectively. ALT and AST increases leading to dose modifications or interruptions occurred in 25 (7%) patients and 21 (6%) patients, respectively (see section 4.4). Two patients permanently discontinued the treatment with 1 patient due to grade 3 ALT and grade 3 AST increases.
Cases of hepatotoxicity with increases in ALT and/or AST of grade 2, 3 or 4 severity and increases in bilirubin ≥ 2x ULN have been reported. In some cases, the dose of VITRAKVI was withheld and restarted at a reduced dose, while in other cases treatment was permanently discontinued (see section 4.4).

Additional information on special populations

Paediatric patients
Of the 361 patients treated with VITRAKVI, 135 (37%) patients were from birth to < 18 years of age (n=13 from birth to < 3 months, n=4 ≥ 3 months to < 6 months, n=17 ≥ 6 months to < 12 months, n=9 ≥ 12 months to < 2 years, n=30 ≥ 2 years to < 6 years, n=37 ≥ 6 years to < 12 years, n=25 ≥ 12 years to < 18 years). The majority of adverse reactions were grade 1 or 2 in severity and were resolved without VITRAKVI dose modification or discontinuation. Adverse reactions of grade 3 or 4 in severity were generally observed more frequently in patients < 6 years of age. They were reported in 77% of patients from birth to < 3 months and in 47% of patients ≥ 3 months to < 6 years. Decreased neutrophil count has been reported to have led to study drug discontinuation, dose modification and dose interruption.

Elderly
Of the 361 patients in the overall safety population who received VITRAKVI, 69 (19%) patients were 65 years or older and 22 (6%) patients were 75 years or older. The safety profile in elderly patients (≥ 65 years) is consistent with that seen in younger patients. The adverse reaction dizziness (30% versus 28% in all adults), anaemia (36% versus 28% in all adults), diarrhoea (25% versus 23% in all adults), muscular weakness (13% versus 11% in all adults), platelet count decreased (12% versus 6% in all adults), gait disturbance (9% versus 5% in all adults), and dysgeusia (9% versus 6% in all adults) were more frequent in patients of 65 years or older.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited experience of overdose with VITRAKVI. Symptoms of overdose are not established. In the event of overdose, physicians should follow general supportive measures and treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, protein kinase inhibitors, ATC code: L01EX12.

Mechanism of action

Larotrectinib is an adenosine triphosphate (ATP)-competitive and selective tropomyosin receptor kinase (TRK) inhibitor that 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.

Acquired resistance mutations after progression on TRK inhibitors have been observed. Larotrectinib had minimal activity in cell lines with point mutations in the TRKA kinase domain, including the clinically identified acquired resistance mutation, G595R. Point mutations in the TRKC kinase domain with clinically identified acquired resistance to larotrectinib include G623R, G696A, and F617L.

The molecular causes for primary resistance to larotrectinib are not known. It is therefore not known if the presence of a concomitant oncogenic driver in addition to an *NTRK* gene fusion affects the efficacy of TRK inhibition. The measured impact of any concomitant genomic alterations on larotrectinib efficacy is provided below (see clinical efficacy).

Pharmacodynamic effects

Cardiac electrophysiology
In 36 healthy adult subjects receiving single doses ranging from 100 mg to 900 mg, VITRAKVI did not prolong the QT interval to any clinically relevant extent.
The 200 mg dose corresponds to a peak exposure (C_{max}) similar to that observed with larotrectinib 100 mg BID at steady state. A shortening of QTcF was observed with VITRAKVI dosing, with a maximum mean effect observed between 3 and 24 hours after C_{max}, with a geometric mean decrease in QTcF from baseline of -13.2 msec (range -10 to -15.6 msec). Clinical relevance of this finding has not been established.

Clinical efficacy

Overview of studies
The efficacy and safety of VITRAKVI were studied in three multicentre, open-label, single-arm clinical studies in adult and paediatric cancer patients (Table 5). Two studies are still ongoing. Patients with and without documented *NTRK* gene fusion were allowed to participate in Study 1 and Study 3 ("SCOUT"). Patients enrolled to Study 2 ("NAVIGATE") were required to have TRK fusion-positive cancer. The pooled primary analysis set of efficacy includes 364 patients with TRK fusion-positive cancer enrolled across the three studies that had measurable disease assessed by RECIST v1.1, a non-CNS primary tumour and received at least one dose of larotrectinib as of July 2024. These patients were required to have received prior standard therapy appropriate for their tumour type and stage of disease or who, in the opinion of the investigator, would have had to undergo radical surgery (such as limb amputation, facial resection, or paralysis causing procedure), or were unlikely to tolerate, or derive clinically meaningful benefit from available standard of care therapies in the advanced disease setting. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC). In addition, 60 patients with primary CNS tumours and measurable disease at baseline were treated in Study 2 ("NAVIGATE") and in Study 3 ("SCOUT"). Fifty-seven of the 60 primary CNS tumour patients had received prior cancer treatment (surgery, radiotherapy and/or previous systemic therapy). Tumour responses were assessed by the investigator using RANO or RECIST v1.1 criteria.

Identification of *NTRK* gene fusions relied on tissue samples for the molecular test methods: next generation sequencing (NGS) used in 327 patients, polymerase chain reaction (PCR) used in 14 patients, fluorescence *in situ* hybridization (FISH) used in 18 patients, and other testing methods (Sequencing, Nanostring, Sanger sequencing, or Chromosome Microarray) used in 5 patients.

Table 5: Clinical studies contributing to the efficacy analyses in solid and primary CNS tumours

Study name, design and patient population	Dose and formulation	Tumour types included in efficacy analysis	n
Study 1 NCT02122913 • Phase 1, open-label, dose escalation and expansion study; expansion phase required tumours with an *NTRK* gene fusion • Adult patients (≥ 18 years) with advanced solid tumours with an *NTRK* gene fusion	Doses up to 200 mg once or twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Thyroid (n=4) Salivary gland (n=3) GIST (n=2)[a] Soft tissue sarcoma (n=2) NSCLC (n=1)[b, c] Unknown primary cancer (n=1)	13
Study 2 "NAVIGATE" NCT02576431 • Phase 2 multinational, open label, tumour "basket" study • Adult and paediatric patients ≥ 12 years with advanced solid tumours with an *NTRK* gene fusion	100 mg twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	NSCLC (n=29)[b, c] Soft tissue sarcoma (n=28) Thyroid (n=26)[b] Colon (n=25) Salivary gland (n=24) Primary CNS (n=19) Melanoma (n=10)[b] Breast, non-secretory (n=10)[b] Pancreas (n=7) Breast, secretory (n=5) Cholangiocarcinoma (n=4) GIST (n=3)[a] Gastric (n=3) Prostate (n=2) Appendix, Atypical carcinoid lung cancer, Bone sarcoma, Cervix, Hepatic[e], Duodenal, External auditory canal[b], Oesophageal, SCLC[b, d], Rectal, Testes[b], Thymus, Unknown primary cancer, Urothelial, Uterus (n=1 each)	210
Study 3 "SCOUT" NCT02637687 • Phase 1/2 multinational, open-label, dose escalation and expansion study; Phase 2 expansion cohort required advanced solid tumours with an *NTRK* gene fusion, including locally advanced infantile fibrosarcoma • Paediatric patients from birth to 21 years with advanced cancer or with primary CNS tumours	Doses up to 100 mg/m^2 twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Infantile fibrosarcoma (n=49) Soft tissue sarcoma (n=42)[b] Primary CNS (n=41) Congenital mesoblastic nephroma (n=2) Bone sarcoma (n=2) Breast secretory, Cervix, Lipofibromatosis, Melanoma, Thyroid (n=1 each)	141
Total number of patients (n)[*]			364

[*] consist of 304 patients with IRC tumour response assessment and 60 patients with primary CNS tumours (including astrocytoma, ganglioglioma, glioblastoma, glioma, glioneuronal tumours, neuronal and mixed neuronal-glial tumours, oligodendroglioma, and primitive neuro-ectodermal tumour, not specified) with investigator tumour response assessment

[a] GIST: gastrointestinal stromal tumour

[b] brain metastases were observed in some patients in the following tumour types: lung (NSCLC, SCLC), thyroid, melanoma, breast (non-secretory), external auditory canal, soft tissue sarcoma and testes

[c] NSCLC: non-small cell lung cancer
[d] SCLC: small cell lung cancer
[e] hepatocellular carcinoma

Baseline characteristics for the pooled 304 patients with solid tumours with an *NTRK* gene fusion were as follows: median age 44.5 years (range 0-90 years); 33% < 18 years of age, and 67% ≥ 18 years; 55% white and 47% male; and ECOG PS 0-1 (88%), 2 (10%), or 3 (2%). Ninety-one percent of patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. Of these, 72% had received prior systemic therapy with a median of 1 prior systemic treatment regimen. Twenty-eight percent of all patients had received no prior systemic therapy. Of those 304 patients the most common tumour types represented were soft tissue sarcoma (24%), infantile fibrosarcoma (16%), lung cancer (11%), thyroid cancer (10%), salivary gland tumour (9%) and colon cancer (8%).
Baseline characteristics for the 60 patients with primary CNS tumours with an *NTRK* gene fusion assessed by investigator were as follows: median age 9.1 years (range 0-79 years); 43 patients < 18 years of age, and 17 patients ≥ 18 years, and 39 patients white and 28 patients male; and ECOG PS 0-1 (52 patients), or 2 (5 patients). Fifty-seven (95%) patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. There was a median of 1 prior systemic treatment regimen received.

Efficacy results
The pooled efficacy results for overall response rate, duration of response and time to first response, in the primary analysis population (n=304) and with post-hoc addition of primary CNS tumours (n=60) resulting in the pooled population (n=364), are presented in Table 6 and Table 7.

Table 6: Pooled efficacy results in solid tumours including and excluding primary CNS tumours

Efficacy parameter	**Analysis in solid tumours excluding primary CNS tumours (n=304)**[a]	**Analysis in solid tumours including primary CNS tumours (n=364)**[a, b]
Overall response rate (ORR) % (n) [95% CI]	65% (198) [59, 70]	60% (219) [55, 65]
Complete response (CR)	22% (66)	20% (71)
Pathological complete response[c]	7% (20)	5% (20)
Partial response (PR)	37% (112)	35% (128)
Time to first response (median, months) [range]	1.84 [0.89, 22.90]	1.84 [0.89, 49.87]
Duration of response (median, months) [range] % with duration ≥ 12 months % with duration ≥ 24 months % with duration ≥ 36 months % with duration ≥ 48 months	43.3 [0.0+,84.7+] 80% 66% 57% 48%	43.3 [0.0+, 84.7+] 79% 65% 54% 47%

+ denotes ongoing
[a] Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (304 patients).
[b] Evaluated using either RANO or RECIST v1.1 criteria for primary CNS tumours (60 patients).
[c] A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumour cells and negative margins on post-surgical pathology evaluation. The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v.1.1.

Table 7: Overall response rate and duration of response by tumour type*

Tumour type	Patients (n=364)	ORR[a]		DOR			
		%	95% CI	months			Range (months)
				≥ 12	≥ 24	≥ 36	
Soft tissue sarcoma	72	68%	56%, 79%	80%	72%	60%	0.03+, 84.7+
Primary CNS	60	35%	23%, 48%	66%	50%	50%	2.8+, 70.9+
Infantile fibrosarcoma	49	94%	83%, 99%	83%	66%	60%	1.6+, 73.7+
Lung	32	69%	50%, 84%	75%	52%	45%	1.9+, 67.2+
Thyroid	31	65%	45%, 81%	85%	63%	47%	3.7, 83.9+
Salivary gland	27	85%	66%, 96%	91%	86%	76%	2.7, 81.1+
Colon	25	48%	28%, 69%	83%	62%	31%	3.9, 56.3+
Breast	16						
Non-secretory[c]	10	30%	7%, 65%	67%	0%	0%	7.4, 15.3
Secretory[b]	6	83%	36%, 100%	80%	80%	80%	11.1, 69.2+
Melanoma	11	45%	17%, 77%	50%	NR	NR	1.9+, 23.2+
Pancreas	7	14%	0%, 58%	0%	0%	0%	5.8, 5.8
Gastrointestinal stromal tumour	5	80%	28%, 99%	75%	38%	38%	9.5, 50.4+
Bone sarcoma	3	33%	1%, 91%	0%	0%	0%	9.5, 9.5
Congenital mesoblastic nephroma	2	100%	16%, 100%	100%	100%	50%	32.9, 44.5
Cervix	2	50%	1%, 99%	100%	NR	NR	18.7+, 18.7+
Unknown primary cancer	2	100%	16%, 100%	0	0	0	5.6, 7.4
External auditory canal	1	100%	3%, 100%	100%	100%	100%	45.1+, 45.1+
Lipofibromatosis	1	100%	3%, 100%	100%	NR	NR	17.7+, 17.7+

DOR: duration of response
NE: not evaluable
NR: not reached
* no data are available for the following tumour types: cholangiocarcinoma (n=4); gastric (n=3); prostate (n=2); appendix, hepatic, duodenal, oesophageal, rectal, testes, thymus, urothelial, uterus (n=1 each)
+ denotes ongoing response
[a] evaluated per independent review committee analysis by RECIST v1.1 for all tumour types except patients with a primary CNS tumour who were evaluated using either RANO or RECIST v1.1 criteria
[b] with 2 complete, 2 partial response
[c] with 1 complete, 2 partial response

Due to the rarity of TRK fusion-positive cancer, patients were studied across multiple tumour types with a limited number of patients in some tumour types, causing uncertainty in the ORR estimate per tumour type. The ORR in the total population may not reflect the expected response in a specific tumour type.

In the adult sub-population (n=222), the ORR was 51%. In the paediatric sub-population (n=142), the ORR was 74%.

In 257 patients with wide molecular characterisation before larotrectinib treatment, the ORR in 120 patients who had other genomic alterations in addition to *NTRK* gene fusion was 53%, and in 137 patients without other genomic alterations ORR was 68%.

Pooled primary analysis set

The pooled primary analysis set consisted of 304 patients and did not include primary CNS tumours. Median time on treatment before disease progression was 15.9 months (range: 0.1 to 99.4 months) based on July 2024 cut-off. Fifty-five percent of patients had received VITRAKVI for 12 months or more, 37% had received VITRAKVI 24 months or more, and 28% had received VITRAKVI 36 months or more. Follow-up was ongoing at the time of the analysis for 27% of patients.
At the time of analysis, the median duration of response is 43.3 months (range: 0.0+ to 84.7+), an estimated 80% [95% CI: 74, 86] of responses lasted 12 months or longer, 66% [95% CI: 59, 74] of responses lasted 24 months or longer, and 57% [95% CI: 49, 64] of responses lasted 36 months or longer. Eighty-three percent (83%) [95% CI: 79, 88] of patients treated were alive one year after the start of therapy, 73% [95% CI: 68, 78] after two years after the start of therapy, and 68% [95% CI: 63, 74] after three years with the median for overall survival not yet being reached. Median progression free survival was 28.0 months at the time of the analysis, with a progression free survival rate of 63% [95% CI: 57, 69] after 1 year, 54% [95% CI: 48, 60] after 2 years, and 44% [95% CI: 38, 50] after 3 years.
The median change in tumour size in the pooled primary analysis set was a decrease of 66%.

Patients with primary CNS tumours

At the time of data cut-off, of the 60 patients with primary CNS tumours confirmed response was observed in 21 patients (35%) with 5 of the 60 patients (8%) being complete responders and 16 patients (27%) being partial responders. Further 24 patients (40%) had stable disease. 13 patients (22%) had progressive disease. At the time of data cut-off, time on treatment ranged from 1.2 to 67.3 months and was ongoing in 20 out of 60 patients, with all of these patients receiving post-progression treatment.

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

In cancer patients given VITRAKVI capsules, peak plasma levels (C_{max}) of larotrectinib were achieved at approximately 1 hour after dosing. Half-life ($t_{½}$) is approximately 3 hours and steady state is reached within 8 days with a systemic accumulation of 1.6 fold. At the recommended dose of 100 mg taken twice daily, steady-state arithmetic mean (± standard deviation) C_{max} and daily AUC in adults were 914 ± 445 ng/mL and 5410 ± 3813 ng*h/mL, respectively. *In vitro* studies indicate that larotrectinib is not a substrate for either OATP1B1 or OATP1B3.

In vitro studies indicate that larotrectinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations and is unlikely to affect clearance of substrates of these CYPs.
In vitro studies indicate that larotrectinib does not inhibit the transporters BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B3, BSEP, MATE1 and MATE2-K at clinically relevant concentrations and is unlikely to affect clearance of substrates of these transporters.

Absorption

VITRAKVI is available as a capsule and oral solution formulation.
The mean absolute bioavailability of larotrectinib was 34% (range: 32% to 37%) following a single 100 mg oral dose. In healthy adult subjects, the AUC of larotrectinib in the oral solution formulation was similar to the capsule, with C_{max} 36% higher with the oral solution formulation.
Larotrectinib C_{max} was reduced by approximately 35% and there was no effect on AUC in healthy subjects administered VITRAKVI after a high-fat and high-calorie meal compared to the C_{max} and AUC after overnight fasting.

Effect of gastric pH-elevating agents on larotrectinib
Larotrectinib has pH-dependent solubility. *In vitro* studies show that in liquid volumes relevant to the gastrointestinal (GI) tract larotrectinib is fully soluble over entire pH range of the GI tract. Therefore, larotrectinib is unlikely to be affected by pH-modifying agents.

Distribution

The mean volume of distribution of larotrectinib in healthy adult subjects was 48 L following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose. Binding of larotrectinib to human plasma proteins *in vitro* was approximately 70% and was independent of drug concentration. The blood-to-plasma concentration ratio was approximately 0.9.

Biotransformation

Larotrectinib was metabolised predominantly by CYP3A4/5 *in vitro*. Following oral administration of a single 100 mg dose of radiolabelled larotrectinib to healthy adult subjects, unchanged larotrectinib (19%) and an O-glucuronide that is formed following loss of the hydroxypyrrolidine-urea moiety (26%) were the major circulating radioactive drug components.

Elimination

The half-life of larotrectinib in plasma of cancer patients given 100 mg twice daily of VITRAKVI was approximately 3 hours. Mean clearance (CL) of larotrectinib was approximately 34 L/h following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose of VITRAKVI.

Excretion

Following oral administration of 100 mg radiolabelled larotrectinib to healthy adult subjects, 58% of the administered radioactivity was recovered in faeces and 39% was recovered in urine and when an IV microtracer dose was given in conjunction with a 100 mg oral dose of larotrectinib, 35% of the administered radioactivity was recovered in faeces and 53% was recovered in urine. The fraction excreted as unchanged drug in urine was 29% following IV microtracer dose, indicating that direct renal excretion accounted for 29% of total clearance.

Linearity / non-linearity

The area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of larotrectinib after a single dose in healthy adult subjects were dose proportional up to 400 mg and slightly greater than proportional at doses of 600 to 900 mg.

Special populations

Paediatric patients
Based on population pharmacokinetic analyses, exposure (C_{max} and AUC) in paediatric patients at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID was higher than in adults (≥ 18 years of age) given the dose of 100 mg BID (see Table 8).
Data defining exposure in small children (1 month to < 2 years of age) at the recommended dose is limited (n=46).

Table 8: Exposure (C_{max} and AUC[a]) in patients grouped by age group at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID

Age group	n=438[b]	Fold difference compared to patients ≥ 18 years of age[c]	
		C_{max}	AUC[a]
1 to < 3 months	12	3.2	4.5
3 to < 6 months	4	3.0	3.2
6 to < 12 months	19	2.1	1.7
1 to < 2 years	11	1.6	1.1
2 to < 6 years	37	1.6	1.1
6 to < 12 years	38	1.3	1.2
12 to < 18 years	32	0.9	0.8
≥ 18 years	285	1.0	1.0

[a] area under the plasma concentration-time curve at steady-state
[b] number of patients from 23 September 2024 data cut-off
[c] fold difference is the ratio of stated age group to ≥18 years group. A fold-difference of 1 equates to no difference.

Elderly
There is no clinically meaningful difference in larotrectinib exposure in patients > 65 years compared to those in younger patients (< 65 years).

Patients with hepatic impairment
A pharmacokinetic study was conducted in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, and in healthy adult control subjects with normal hepatic function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib $AUC_{0\text{-}inf}$ was observed in subjects with mild, moderate and severe hepatic impairment of 1.3, 2 and 3.2-fold respectively versus those with normal hepatic function. C_{max} was observed to increase slightly by 1.1, 1.1 and 1.5-fold respectively.

Patients with renal impairment
A pharmacokinetic study was conducted in subjects with end stage renal disease requiring dialysis, and in healthy adult control subjects with normal renal function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib C_{max} and $AUC_{0\text{-}inf}$, of 1.25 and 1.46-fold respectively was observed in renally impaired subjects versus those with normal renal function.

Other special populations
Gender and race have no effect on the systemic exposure of larotrectinib based on population pharmacokinetic analysis.

5.3 Preclinical safety data

Systemic toxicity

Systemic toxicity was assessed in studies with daily oral administration up to 3 months in rats and monkeys. Dose limiting skin lesions were only seen in rats and were primarily responsible for mortality and morbidity. Skin lesions were not seen in monkeys.
Clinical signs of gastrointestinal toxicity were dose limiting in monkeys. In rats, severe toxicity (STD10) was observed at doses corresponding to 1- to 2-times the human AUC at the recommended clinical dose. No relevant systemic toxicity was observed in monkeys at doses which correspond to > 10-times the human AUC at the recommended clinical dose.

Embryotoxicity / Teratogenicity

Larotrectinib was not teratogenic and embryotoxic when dosed daily during the period of organogenesis to pregnant rats and rabbits at maternotoxic doses, i.e. corresponding to 32-times (rats) and 16-times (rabbits) the human AUC at the recommended clinical dose. Larotrectinib crosses the placenta in both species.

Reproduction toxicity

Fertility studies with larotrectinib have not been conducted. In 3-months toxicity studies, larotrectinib had no histological effect on the male reproductive organs in rats and monkeys at the highest tested doses corresponding to approximately 7-times (male rats) and 10-times (male monkeys) the human AUC at the recommended clinical dose. In addition, larotrectinib had no effect on spermatogenesis in rats.

In a 1-month repeat-dose study in rats, fewer corpora lutea, increased incidence of anestrus and decreased uterine weight with uterine atrophy were observed and these effects were reversible. No effects on female reproductive organs were seen in the 3-months toxicity studies in rats and monkeys at doses corresponding to approximately 3-times (female rats) and 17-times (female monkeys) the human AUC at the recommended clinical dose.
Larotrectinib was administered to juvenile rats from postnatal day (PND) 7 to 70. Pre-weaning mortality (before PND 21) was observed at the high dose level corresponding to 2.5- to 4-times the AUC at the recommended dose. Growth and nervous system effects were seen at 0.5- to 4-times the AUC at the recommended dose. Body weight gain was decreased in pre-weaning male and female pups, with a post-weaning increase in females at the end of exposure whereas reduced body weight gain was seen in males also post-weaning without recovery. The male growth reduction was associated with delayed puberty. Nervous system effects (i.e. altered hindlimb functionality and, likely, increases in eyelid closure) demonstrated partial recovery. A decrease in pregnancy rate was also reported despite normal mating at the high-dose level.

Genotoxicity and carcinogenicity

Carcinogenicity studies have not been performed with larotrectinib.
Larotrectinib was not mutagenic in bacterial reverse mutation (Ames) assays and in *in vitro* mammalian mutagenesis assays. Larotrectinib was negative in the *in vivo* mouse micronucleus test at the maximum tolerated dose of 500 mg/kg.

Safety pharmacology

The safety pharmacology of larotrectinib was evaluated in several *in vitro* and *in vivo* studies that assessed effects on the CV, CNS, respiratory, and GI systems in various species. Larotrectinib had no adverse effect on haemodynamic parameters and ECG intervals in telemetered monkeys at exposures (C_{max}) which are approximately 6-fold the human therapeutic exposures. Larotrectinib had no neurobehavioural findings in adult animals (rats, mice, cynomolgus monkeys) at exposure (C_{max}) at least 7-fold higher than the human exposure. Larotrectinib had no effect on respiratory function in rats; at exposures (C_{max}) at least 8-times the human therapeutic exposure. In rats, larotrectinib accelerated intestinal transit and increased gastric secretion and acidity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell
Gelatin
Titanium dioxide (E 171)

Printing ink
Shellac, bleached dewaxed
Indigo carmine aluminium lake (E 132)
Titanium dioxide (E 171)
Propylene glycol (E 1520)
Dimeticone 1000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE)-bottles with a child-resistant polypropylene (PP) screw cap with a polyethylene (PE) heat seal layer.

Each carton contains one bottle of 56 hard capsules.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1385/001 – VITRAKVI 25 mg
EU/1/19/1385/002 – VITRAKVI 100 mg

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2019
Date of latest renewal: 22 July 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 20 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral solution contains larotrectinib sulfate equivalent to 20 mg of larotrectinib.

Excipients with known effect:
Each mL of oral solution contains 295 mg sucrose, 22 mg sorbitol, 1.2 mg propylene glycol and 0.2 mg methyl parahydroxybenzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear yellow to orange solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Treatment with VITRAKVI should be initiated by physicians experienced in the administration of anticancer therapies.

The presence of an *NTRK* gene fusion in a tumour specimen should be confirmed by a validated test prior to initiation of treatment with VITRAKVI.

Posology

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.

Missed dose
If a dose is missed, the patient should not take two doses at the same time to make up for a missed dose. Patients should take the next dose at the next scheduled time. If the patient vomits after taking a dose, the patient should not take an additional dose to make up for vomiting.

Dose modification
For all grade 2 adverse reactions, continued dosing may be appropriate, though close monitoring to ensure no worsening of the toxicity is advised.

For all grade 3 or 4 adverse reactions not referring to liver function test abnormalities:
- VITRAKVI should be withheld until the adverse reaction resolves or improves to baseline or grade 1. Resume at the next dose modification if resolution occurs within 4 weeks.
- VITRAKVI should be permanently discontinued if an adverse reaction does not resolve within 4 weeks.

The recommended dose modifications for VITRAKVI for adverse reactions are provided in Table 1.

Table 1: Recommended dose modifications for VITRAKVI for adverse reactions

Dose modification	Adult and paediatric patients with body surface area of at least 1.0 m^2	Paediatric patients with body surface area less than 1.0 m^2
First	75 mg twice daily	75 mg/m^2 twice daily
Second	50 mg twice daily	50 mg/m^2 twice daily
Third	100 mg once daily	25 mg/m^2 twice daily[a]

[a] Paediatric patients on 25 mg/m^2 twice daily should remain on this dose even if body surface area becomes greater 1.0 m^2 during the treatment. Maximum dose should be 25 mg/m^2 twice daily at the third dose modification.

VITRAKVI should be permanently discontinued in patients who are unable to tolerate VITRAKVI after three dose modifications.

The recommended dose modifications in case of liver function tests abnormalities during treatment with VITRAKVI are provided in Table 2.

Table 2: Recommended dose modifications and management for VITRAKVI for liver function test abnormalities

Laboratory parameters	Recommended measures
Grade 2 ALT and/or AST (>3x ULN and ≤5x ULN)	- Conduct serial laboratory evaluations frequently after the observation of grade 2 toxicity, until resolved, to establish whether a dose interruption or reduction is required.
Grade 3 ALT and/or AST (>5x ULN and ≤20x ULN) or Grade 4 ALT and/or AST (>20x ULN), with bilirubin <2x ULN	- Withhold treatment until the adverse reaction resolves or improves to baseline. Monitor liver function frequently until resolution or return to baseline. Permanently discontinue treatment if an adverse reaction does not resolve. - Resume at the next dose modification if adverse reactions resolve. Treatment should only be resumed in patients where the benefit outweighs the risk. - Permanently discontinue treatment if a grade 4 ALT and/or AST elevation occurs after resuming treatment.
ALT and/or AST ≥3x ULN with bilirubin ≥2x ULN	- Withhold treatment and monitor liver function frequently until resolution or return to baseline. - Consider permanent treatment discontinuation. - Treatment should only be resumed in patients where the benefit outweighs the risk. - If resumed, start at the next lower dose. Monitor liver function frequently upon restart. - Permanently discontinue treatment if adverse reaction recurs after resuming treatment.

ALT Alanine aminotransferase
AST Aspartate aminotransferase
ULN upper limit of normal

Special populations

Elderly
No dose adjustment is recommended in elderly patients (see section 5.2).

Hepatic impairment
The starting dose of VITRAKVI should be reduced by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A) (see section 5.2).

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2).

Co-administration with strong CYP3A4 inhibitors
If co-administration with a strong CYP3A4 inhibitor is necessary, the VITRAKVI dose should be reduced by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, VITRAKVI should be resumed at the dose taken prior to initiating the CYP3A4 inhibitor (see section 4.5).

Method of administration

VITRAKVI is for oral use.

VITRAKVI is available as a capsule or oral solution with equivalent oral bioavailability and may be used interchangeably.

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.
- For doses below 1 mL a 1 mL oral syringe should be used. The calculated dose volume should be rounded to the nearest 0.1 mL.
- For doses of 1 mL and higher a 5 mL oral syringe should be used. The dose volume should be calculated to the nearest 0.2 mL.
- VITRAKVI should not be mixed with feeding formulas, if administered via nasogastric feeding tube. Mixing with the feeding formulas could lead to tube blockages.
- For instructions for use of oral syringes and feeding tubes see section 6.6.

The oral solution can be taken with or without food but should not be taken with grapefruit or grapefruit juice.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Efficacy across tumour types

The benefit of VITRAKVI has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit *NTRK* gene fusions. Favourable effects of VITRAKVI have been shown on the basis of overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genetic alterations (see section 5.1). For these reasons, VITRAKVI should only be used if there are no treatment options for which clinical benefit has been established, or where such treatment options have been exhausted (i.e., no satisfactory treatment options).

Neurologic reactions

Neurologic reactions including dizziness, gait disturbance and paraesthesia were reported in patients receiving larotrectinib (see section 4.8). For the majority of neurologic reactions, onset occurred within the first three months of treatment. Withholding, reducing, or discontinuing VITRAKVI dosing should be considered, depending on the severity and persistence of these symptoms (see section 4.2).

Hepatotoxicity

Abnormalities of liver function tests including increased ALT, AST, alkaline phosphatase (ALP) and bilirubin have been observed in patients receiving larotrectinib (see section 4.8). The majority of ALT and AST increases occurred within 3 months of starting treatment. Cases of hepatotoxicity with increases in ALT and/or AST of grade 2, 3 or 4 severity and increases in bilirubin ≥ 2x ULN have been reported.
In patients with hepatic transaminase elevations, withhold, modify dose or permanently discontinue VITRAKVI based on the severity (see section 4.2).
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 (see section 4.2).

Co-administration with CYP3A4/P-gp inducers

Avoid co-administration of strong or moderate CYP3A4/P-gp inducers with VITRAKVI due to a risk of decreased exposure (see section 4.5).

Contraception in female and male

Women of childbearing potential must use highly effective contraception while taking VITRAKVI and for at least one month after stopping treatment (see sections 4.5 and 4.6).
Males of reproductive potential with a non-pregnant woman partner of childbearing potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose (see section 4.6).

Important information about some of the ingredients

Sucrose: may be harmful to the teeth. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicinal product.
Sorbitol: patients with hereditary fructose intolerance (HFI) should not take this medicinal product.
Sodium: this medicinal product contains less than 1 mmol sodium (23 mg) per 5 mL, that is to say essentially 'sodium-free'.
Propylene glycol: co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.
Parahydroxybenzoate: may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on larotrectinib

Effect of CYP3A, P-gp and BCRP inhibitors on larotrectinib
Larotrectinib is a substrate of cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of VITRAKVI with strong or moderate CYP3A inhibitors, P-gp and BCRP inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole or grapefruit) may increase larotrectinib plasma concentrations (see section 4.2).
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with itraconazole (a strong CYP3A inhibitor and P-gp and BCRP inhibitor) 200 mg once daily for 7 days increased larotrectinib C_{max} and AUC by 2.8-fold and 4.3-fold, respectively.
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with a single dose of 600 mg rifampicin (a P-gp and BCRP inhibitor) increased larotrectinib C_{max} and AUC by 1.8-fold and 1.7-fold, respectively.

Effect of CYP3A and P-gp inducers on larotrectinib
Co-administration of VITRAKVI with strong or moderate CYP3A inducers and strong P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, or St. John's Wort) may decrease larotrectinib plasma concentrations and should be avoided (see section 4.4).
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with rifampicin (a strong CYP3A and P-gp inducer) 600 mg once daily for 11 days decreased larotrectinib C_{max} and AUC by 71% and 81%, respectively. No clinical data is available on the effect of a moderate inducer, but a decrease in larotrectinib exposure is expected.

Effects of larotrectinib on other agents

Effect of larotrectinib on CYP3A substrates
Clinical data in healthy adult subjects indicate that co-administration of VITRAKVI (100 mg twice daily for 10 days) increased the C_{max} and AUC of oral midazolam 1.7-fold compared to midazolam alone, suggesting that larotrectinib is a weak inhibitor of CYP3A.
Exercise caution with concomitant use of CYP3A substrates with narrow therapeutic range (e.g. alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus) in patients taking VITRAKVI. If concomitant use of these CYP3A substrates with narrow therapeutic range is required in patients taking VITRAKVI, dose reductions of the CYP3A substrates may be required due to adverse reactions.

Effect of larotrectinib on CYP2B6 substrates
In vitro studies indicate that larotrectinib induces CYP2B6. Co-administration of larotrectinib with CYP2B6 substrates (e.g. bupropion, efavirenz) may decrease their exposure.

Effect of larotrectinib on other transporter substrates
In vitro studies indicate that larotrectinib is an inhibitor of OATP1B1. No clinical studies have been performed to investigate interactions with OATP1B1 substrates. Therefore, it cannot be excluded whether co-administration of larotrectinib with OATP1B1 substrates (e.g. valsartan, statins) may increase their exposure.

Effect of larotrectinib on substrates of PXR regulated enzymes
In vitro studies indicate that larotrectinib is a weak inducer of PXR regulated enzymes (e.g. CYP2C family and UGT). Co-administration of larotrectinib with CYP2C8, CYP2C9 or CYP2C19 substrates (e.g. repaglinide, warfarin, tolbutamide or omeprazole) may decrease their exposure.

Hormonal contraceptives
It is currently unknown whether larotrectinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should be advised to add a barrier method.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Based on the mechanism of action, foetal harm cannot be excluded when administering larotrectinib to a pregnant woman. Women of childbearing potential should have a pregnancy test prior to starting treatment with VITRAKVI.
Women of reproductive potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose. As it is currently unknown whether larotrectinib may reduce the effectiveness of systemically acting hormonal contraceptives, women using systemically acting hormonal contraceptives should be advised to add a barrier method.
Males of reproductive potential with a non-pregnant woman partner of childbearing potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose.

Pregnancy

There are no data from the use of larotrectinib in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of VITRAKVI during pregnancy.

Breast-feeding

It is unknown whether larotrectinib/metabolites are excreted in human milk.
A risk to newborns/infants cannot be excluded.
Breast-feeding should be discontinued during treatment with VITRAKVI and for 3 days following the final dose.

Fertility

There are no clinical data on the effect of larotrectinib on fertility. No relevant effects on fertility were observed in repeat-dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

VITRAKVI has a moderate influence on the ability to drive and use machines. Dizziness and fatigue have been reported in patients receiving larotrectinib, mostly grade 1 and 2 during the first 3 months of treatment. This may influence the ability to drive and use machines during this time period. Patients should be advised not to drive and use machines, until they are reasonably certain VITRAKVI therapy does not affect them adversely (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (≥ 20%) of VITRAKVI in order of decreasing frequency were increased ALT (36%), increased AST (33%), vomiting (30%), anaemia (28%), constipation (28%), diarrhoea (27%), nausea (24%), fatigue (23%), and dizziness (20%).
The majority of adverse reactions were grade 2 or 3. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (2%), ALT increased (1%), AST increased, leukocyte count decreased, platelet count decreased, muscular weakness and blood alkaline phosphatase increased (each in < 1%). The highest reported grade was grade 3 for adverse reactions anaemia (7%), weight increased (6%), diarrhoea (4%), gait disturbance and vomiting (each 1%), and fatigue, dizziness, paraesthesia, nausea, myalgia, and constipation (each in < 1%).
Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions occurred in 2% of patients (2 cases each of neutrophil count decreased, ALT increased, and AST increased, 1 case each of gait disturbance, and muscular weakness). The majority of adverse reactions leading to dose reduction occurred in the first three months of treatment.

Tabulated list of adverse reactions

The safety of VITRAKVI was evaluated in 361 patients with TRK fusion-positive cancer in one of three on-going clinical trials, Studies 1, 2 (“NAVIGATE”), and 3 (“SCOUT”) and post-marketing.
The safety population characteristics were comprised of patients with a median age of 39.0 years (range: 0, 90) with 37% of patients being paediatric patients. Median time on treatment for the overall safety population (n=361) was 16.2 months (range: 0.1, 89.1).
The adverse drug reactions reported in patients (n=361) treated with VITRAKVI are shown in Table 3 and Table 4.

The adverse drug reactions are classified according to the System Organ Class.
Frequency groups are defined by the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), and not known (cannot be estimated from available data).
Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (overall safety population, n=361) and post-marketing

System organ class	Frequency	All grades	Grades 3 and 4
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	
	Common	Platelet count decreased (Thrombocytopenia)	Anaemia Neutrophil count decreased (Neutropenia)[a] Leukocyte count decreased (Leukopenia)[a]
	Uncommon		Platelet count decreased (Thrombocytopenia)[a, b]
Nervous system disorders	Very common	Dizziness	
	Common	Gait disturbance Paraesthesia	Gait disturbance
	Uncommon		Dizziness Paraesthesia
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting Diarrhoea	
	Common	Dysgeusia[c]	Diarrhoea Vomiting
	Uncommon		Nausea Constipation
Hepatobiliary disorders	Not known	Liver injury[d]	
Musculoskeletal and connective tissue disorders	Very common	Myalgia	
	Common	Muscular weakness	
	Uncommon		Myalgia Muscular weakness[a, b]
General disorders and administration site conditions	Very common	Fatigue	
	Uncommon		Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain)	
	Common	Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased[a] Aspartate aminotransferase (AST) increased[a] Weight increased (Abnormal weight gain)
	Uncommon		Blood alkaline phosphatase increased[a, b]

[a] grade 4 reactions were reported
[b] each grade frequency was less than <1%
[c] ADR dysgeusia includes the preferred terms “dysgeusia” and “taste disorder”
[d] includes cases with ALT/AST ≥3x ULN and bilirubin ≥2x ULN

Table 4: Adverse drug reactions reported in TRK fusion-positive paediatric cancer patients treated with VITRAKVI at recommended dose (n=135); all grades

System organ class	Frequency	Infants and toddlers (n=43)[a]	Children (n=67)[b]	Adolescents (n=25)[c]	Paediatric patients (n=135)
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) Platelet count decreased (Thrombocytopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) Platelet count decreased (Thrombocytopenia)
	Common		Platelet count decreased (Thrombocytopenia)	Platelet count decreased (Thrombocytopenia)	
Nervous system disorders	Very common			Dizziness	
	Common	Dizziness	Dizziness Paraesthesia Gait disturbance	Paraesthesia Gait disturbance	Dizziness Paraesthesia Gait disturbance
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea
	Common		Dysgeusia		Dysgeusia
Musculoskeletal and connective tissue disorders	Very common		Myalgia	Myalgia	Myalgia
	Common	Muscular weakness	Muscular weakness	Muscular weakness	Muscular weakness
General disorders and administration site conditions	Very common	Fatigue	Fatigue	Fatigue	Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased

[a] Infant/toddlers (28 days to 23 months): 5 grade 4 Neutrophil count decreased (Neutropenia) reactions and 2 Blood alkaline phosphatase increased reported. Grade 3 reactions included 11 cases of Neutrophil count decreased (Neutropenia), 4 cases of ALT increased, 3 cases each of Anaemia, Diarrhoea, and Weight increased (Abnormal weight gain), and 2 cases each of Blood alkaline phosphatase increased, and Vomiting and 1 case of AST increased.

[b] Children (2 to 11 years): 1 grade 4 Leukocytes count decreased reported. 9 reported grade 3 cases of Neutrophil count decreased (Neutropenia), 4 cases of Weight increased (Abnormal weight gain), 2 cases each of ALT increased, Anaemia, Diarrhoea, and Vomiting and 1 case each of AST increased, Gait disturbance, Paraesthesia and Myalgia.

[c] Adolescents (12 to <18 years): no grade 4 reactions were reported. Grade 3 reactions were reported in 1 case each of ALT increased, AST increased, Fatigue, Gait disturbance, and Muscular weakness.

Description of selected adverse reactions

Neurologic reactions
In the overall safety database (n=361), the maximum grade neurologic adverse reaction observed was grade 3 or 4 which was observed in 10 (3%) patients and included gait disturbance (4 patients, 1%), dizziness (3 patients, <1%), and paraesthesia (3 patients, <1%). The overall incidence was 20% for dizziness, 7% for paraesthesia and 5% for gait disturbance. Neurologic reactions leading to dose modification or interruptions included dizziness (1%), gait disturbance (<1%), and paraesthesia (<1%). One patient permanently discontinued the treatment due to grade 3 gait disturbance. In all cases except of one, patients with evidence of anti-tumour activity who required a dose reduction were able to continue dosing at a reduced dose and/or schedule (see section 4.4).

Hepatotoxicity
Abnormalities of liver function tests including ALT, AST, ALP and bilirubin have been observed in patients treated with VITRAKVI.
In the overall safety database (n=361), the maximum grade transaminase elevation observed was grade 4 ALT increase in 7 patients (2%) and AST increase in 4 patients (1%). Grade 3 ALT and AST increases in 26 (7%) and 22 (6%) of patients, respectively. Majority of grade 3 elevations were transient appearing in the first three months of treatment and resolving to grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in 37 (10%) and 33 (9%) of patients, respectively, and grade 1 ALT and AST increases were observed in 173 (48%) and 177 (49%) of patients, respectively. ALT and AST increases leading to dose modifications or interruptions occurred in 25 (7%) patients and 21 (6%) patients, respectively (see section 4.4). Two patients permanently discontinued the treatment with 1 patient due to grade 3 ALT and grade 3 AST increases.
Cases of hepatotoxicity with increases in ALT and/or AST of grade 2, 3 or 4 severity and increases in bilirubin ≥ 2x ULN have been reported. In some cases, the dose of VITRAKVI was withheld and restarted at a reduced dose, while in other cases treatment was permanently discontinued (see section 4.4).

Additional information on special populations

Paediatric patients
Of the 361 patients treated with VITRAKVI, 135 (37%) patients were from birth to < 18 years of age (n=13 from birth to < 3 months, n=4 ≥ 3 months to < 6 months, n=17 ≥ 6 months to < 12 months, n=9 ≥ 12 months to < 2 years, n=30 ≥ 2 years to < 6 years, n=37 ≥ 6 years to < 12 years, n=25 ≥ 12 years to < 18 years). The majority of adverse reactions were grade 1 or 2 in severity and were resolved without VITRAKVI dose modification or discontinuation. Adverse reactions of grade 3 or 4 in severity were generally observed more frequently in patients < 6 years of age. They were reported in 77% of patients from birth to < 3 months and in 47% of patients ≥ 3 months to < 6 years. Decreased neutrophil count has been reported to have led to study drug discontinuation, dose modification and dose interruption.

Elderly
Of the 361 patients in the overall safety population who received VITRAKVI, 69 (19%) patients were 65 years or older and 22 (6%) patients were 75 years or older. The safety profile in elderly patients (≥ 65 years) is consistent with that seen in younger patients. The adverse reaction dizziness (30% versus 28% in all adults), anaemia (36% versus 28% in all adults), diarrhoea (25% versus 23% in all adults), muscular weakness (13% versus 11% in all adults), platelet count decreased (12% versus 6% in all adults), gait disturbance (9% versus 5% in all adults), and dysgeusia (9% versus 6% in all adults) were more frequent in patients of 65 years or older.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited experience of overdose with VITRAKVI. Symptoms of overdose are not established. In the event of overdose, physicians should follow general supportive measures and treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, protein kinase inhibitors, ATC code: L01EX12.

Mechanism of action

Larotrectinib is an adenosine triphosphate (ATP)-competitive and selective tropomyosin receptor kinase (TRK) inhibitor that 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.

Acquired resistance mutations after progression on TRK inhibitors have been observed. Larotrectinib had minimal activity in cell lines with point mutations in the TRKA kinase domain, including the clinically identified acquired resistance mutation, G595R. Point mutations in the TRKC kinase domain with clinically identified acquired resistance to larotrectinib include G623R, G696A, and F617L.

The molecular causes for primary resistance to larotrectinib are not known. It is therefore not known if the presence of a concomitant oncogenic driver in addition to an *NTRK* gene fusion affects the efficacy of TRK inhibition. The measured impact of any concomitant genomic alterations on larotrectinib efficacy is provided below (see clinical efficacy).

Pharmacodynamic effects

Cardiac electrophysiology
In 36 healthy adult subjects receiving single doses ranging from 100 mg to 900 mg, VITRAKVI did not prolong the QT interval to any clinically relevant extent.
The 200 mg dose corresponds to a peak exposure (C_{max}) similar to that observed with larotrectinib 100 mg BID at steady state. A shortening of QTcF was observed with VITRAKVI dosing, with a maximum mean effect observed between 3 and 24 hours after C_{max}, with a geometric mean decrease in QTcF from baseline of -13.2 msec (range -10 to -15.6 msec). Clinical relevance of this finding has not been established.

Clinical efficacy

Overview of studies
The efficacy and safety of VITRAKVI were studied in three multicentre, open-label, single-arm clinical studies in adult and paediatric cancer patients (Table 5). Two studies are still ongoing. Patients with and without documented *NTRK* gene fusion were allowed to participate in Study 1 and Study 3 ("SCOUT"). Patients enrolled to Study 2 ("NAVIGATE") were required to have TRK fusion-positive cancer. The pooled primary analysis set of efficacy includes 364 patients with TRK fusion-positive cancer enrolled across the three studies that had measurable disease assessed by RECIST v1.1, a non-CNS primary tumour and received at least one dose of larotrectinib as of July 2024. These patients were required to have received prior standard therapy appropriate for their tumour type and stage of disease or who, in the opinion of the investigator, would have had to undergo radical surgery (such as limb amputation, facial resection, or paralysis causing procedure), or were unlikely to tolerate, or derive clinically meaningful benefit from available standard of care therapies in the advanced disease setting. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC). In addition, 60 patients with primary CNS tumours and measurable disease at baseline were treated in Study 2 ("NAVIGATE") and in Study 3 ("SCOUT"). Fifty-seven of the 60 primary CNS tumour patients had received prior cancer treatment (surgery, radiotherapy and/or previous systemic therapy). Tumour responses were assessed by the investigator using RANO or RECIST v1.1 criteria.

Identification of *NTRK* gene fusions relied on tissue samples for the molecular test methods: next generation sequencing (NGS) used in 327 patients, polymerase chain reaction (PCR) used in 14 patients, fluorescence *in situ* hybridization (FISH) used in 18 patients, and other testing methods (Sequencing, Nanostring, Sanger sequencing, or Chromosome Microarray) used in 5 patients.

Table 5: Clinical studies contributing to the efficacy analyses in solid and primary CNS tumours

Study name, design and patient population	Dose and formulation	Tumour types included in efficacy analysis	n
Study 1 NCT02122913 • Phase 1, open-label, dose escalation and expansion study; expansion phase required tumours with an *NTRK* gene fusion • Adult patients (≥ 18 years) with advanced solid tumours with an *NTRK* gene fusion	Doses up to 200 mg once or twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Thyroid (n=4) Salivary gland (n=3) GIST (n=2)[a] Soft tissue sarcoma (n=2) NSCLC (n=1)[b, c] Unknown primary cancer (n=1)	13
Study 2 "NAVIGATE" NCT02576431 • Phase 2 multinational, open label, tumour "basket" study • Adult and paediatric patients ≥ 12 years with advanced solid tumours with an *NTRK* gene fusion	100 mg twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	NSCLC (n=29)[b, c] Soft tissue sarcoma (n=28) Thyroid (n=26)[b] Colon (n=25) Salivary gland (n=24) Primary CNS (n=19) Melanoma (n=10)[b] Breast, non-secretory (n=10)[b] Pancreas (n=7) Breast, secretory (n=5) Cholangiocarcinoma (n=4) GIST (n=3)[a] Gastric (n=3) Prostate (n=2) Appendix, Atypical carcinoid lung cancer, Bone sarcoma, Cervix, Hepatic[e], Duodenal, External auditory canal[b], Oesophageal, SCLC[b, d], Rectal, Testes[b], Thymus, Unknown primary cancer, Urothelial, Uterus (n=1 each)	210
Study 3 "SCOUT" NCT02637687 • Phase 1/2 multinational, open-label, dose escalation and expansion study; Phase 2 expansion cohort required advanced solid tumours with an *NTRK* gene fusion, including locally advanced infantile fibrosarcoma • Paediatric patients from birth to 21 years with advanced cancer or with primary CNS tumours	Doses up to 100 mg/m^2 twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Infantile fibrosarcoma (n=49) Soft tissue sarcoma (n=42)[b] Primary CNS (n=41) Congenital mesoblastic nephroma (n=2) Bone sarcoma (n=2) Breast secretory, Cervix, Lipofibromatosis, Melanoma, Thyroid (n=1 each)	141
Total number of patients (n)[*]			364

[*] consist of 304 patients with IRC tumour response assessment and 60 patients with primary CNS tumours (including astrocytoma, ganglioglioma, glioblastoma, glioma, glioneuronal tumours, neuronal and mixed neuronal-glial tumours, oligodendroglioma, and primitive neuro-ectodermal tumour, not specified) with investigator tumour response assessment

[a] GIST: gastrointestinal stromal tumour

[b] brain metastases were observed in some patients in the following tumour types: lung (NSCLC, SCLC), thyroid, melanoma, breast (non-secretory), external auditory canal, soft tissue sarcoma and testes

[c] NSCLC: non-small cell lung cancer
[d] SCLC: small cell lung cancer
[e] hepatocellular carcinoma

Baseline characteristics for the pooled 304 patients with solid tumours with an *NTRK* gene fusion were as follows: median age 44.5 years (range 0-90 years); 33% < 18 years of age, and 67% ≥ 18 years; 55% white and 47% male; and ECOG PS 0-1 (88%), 2 (10%), or 3 (2%). Ninety-one percent of patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. Of these, 72% had received prior systemic therapy with a median of 1 prior systemic treatment regimen. Twenty-eight percent of all patients had received no prior systemic therapy. Of those 304 patients the most common tumour types represented were soft tissue sarcoma (24%), infantile fibrosarcoma (16%), lung cancer (11%), thyroid cancer (10%), salivary gland tumour (9%) and colon cancer (8%).
Baseline characteristics for the 60 patients with primary CNS tumours with an *NTRK* gene fusion assessed by investigator were as follows: median age 9.1 years (range 0-79 years); 43 patients < 18 years of age, and 17 patients ≥ 18 years, and 39 patients white and 28 patients male; and ECOG PS 0-1 (52 patients), or 2 (5 patients). Fifty-seven (95%) patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. There was a median of 1 prior systemic treatment regimen received.

Efficacy results
The pooled efficacy results for overall response rate, duration of response and time to first response, in the primary analysis population (n=304) and with post-hoc addition of primary CNS tumours (n=60) resulting in the pooled population (n=364), are presented in Table 6 and Table 7.

Table 6: Pooled efficacy results in solid tumours including and excluding primary CNS tumours

Efficacy parameter	**Analysis in solid tumours excluding primary CNS tumours (n=304)**[a]	**Analysis in solid tumours including primary CNS tumours (n=364)**[a, b]
Overall response rate (ORR) % (n) [95% CI]	65% (198) [59, 70]	60% (219) [55, 65]
Complete response (CR)	22% (66)	20% (71)
Pathological complete response[c]	7% (20)	5% (20)
Partial response (PR)	37% (112)	35% (128)
Time to first response (median, months) [range]	1.84 [0.89, 22.90]	1.84 [0.89, 49.87]
Duration of response (median, months) [range] % with duration ≥ 12 months % with duration ≥ 24 months % with duration ≥ 36 months % with duration ≥ 48 months	43.3 [0.0+, 84.7+] 80% 66% 57% 48%	43.3 [0.0+, 84.7+] 79% 65% 54% 47%

+ denotes ongoing
[a] Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (304 patients).
[b] Evaluated using either RANO or RECIST v1.1 criteria for primary CNS tumours (60 patients).
[c] A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumour cells and negative margins on post-surgical pathology evaluation. The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v.1.1.

Table 7: Overall response rate and duration of response by tumour type*

Tumour type	Patients (n=364)	ORR[a]		DOR			
		%	95% CI	months			Range (months)
				≥ 12	≥ 24	≥ 36	
Soft tissue sarcoma	72	68%	56%, 79%	80%	72%	60%	0.03+, 84.7+
Primary CNS	60	35%	23%, 48%	66%	50%	50%	2.8+, 70.9+
Infantile fibrosarcoma	49	94%	83%, 99%	83%	66%	60%	1.6+, 73.7+
Lung	32	69%	50%, 84%	75%	52%	45%	1.9+, 67.2+
Thyroid	31	65%	45%, 81%	85%	63%	47%	3.7, 83.9+
Salivary gland	27	85%	66%, 96%	91%	86%	76%	2.7, 81.1+
Colon	25	48%	28%, 69%	83%	62%	31%	3.9, 56.3+
Breast	16						
Non-secretory[c]	10	30%	7%, 65%	67%	0%	0%	7.4, 15.3
Secretory[b]	6	83%	36%, 100%	80%	80%	80%	11.1, 69.2+
Melanoma	11	45%	17%, 77%	50%	NR	NR	1.9+, 23.2+
Pancreas	7	14%	0%, 58%	0%	0%	0%	5.8, 5.8
Gastrointestinal stromal tumour	5	80%	28%, 99%	75%	38%	38%	9.5, 50.4+
Bone sarcoma	3	33%	1%, 91%	0%	0%	0%	9.5, 9.5
Congenital mesoblastic nephroma	2	100%	16%, 100%	100%	100%	50%	32.9, 44.5
Cervix	2	50%	1%, 99%	100%	NR	NR	18.7+, 18.7+
Unknown primary cancer	2	100%	16%, 100%	0	0	0	5.6, 7.4
External auditory canal	1	100%	3%, 100%	100%	100%	100%	45.1+, 45.1+
Lipofibromatosis	1	100%	3%, 100%	100%	NR	NR	17.7+, 17.7+

DOR: duration of response
NE: not evaluable
NR: not reached
* no data are available for the following tumour types: cholangiocarcinoma (n=4); gastric (n=3); prostate (n=2); appendix, hepatic, duodenal, oesophageal, rectal, testes, thymus, urothelial, uterus (n=1 each)
+ denotes ongoing response
[a] evaluated per independent review committee analysis by RECIST v1.1 for all tumour types except patients with a primary CNS tumour who were evaluated using either RANO or RECIST v1.1 criteria
[b] with 2 complete, 2 partial response
[c] with 1 complete, 2 partial response

Due to the rarity of TRK fusion-positive cancer, patients were studied across multiple tumour types with a limited number of patients in some tumour types, causing uncertainty in the ORR estimate per tumour type. The ORR in the total population may not reflect the expected response in a specific tumour type.

In the adult sub-population (n=222), the ORR was 51%. In the paediatric sub-population (n=142), the ORR was 74%.

In 257 patients with wide molecular characterisation before larotrectinib treatment, the ORR in 120 patients who had other genomic alterations in addition to *NTRK* gene fusion was 53%, and in 137 patients without other genomic alterations ORR was 68%.

Pooled primary analysis set

The pooled primary analysis set consisted of 304 patients and did not include primary CNS tumours. Median time on treatment before disease progression was 15.9 months (range: 0.1 to 99.4 months) based on July 2024 cut-off. Fifty-five percent of patients had received VITRAKVI for 12 months or more, 37% had received VITRAKVI 24 months or more, and 28% had received VITRAKVI 36 months or more. Follow-up was ongoing at the time of the analysis for 27% of patients.
At the time of analysis, the median duration of response is 43.3 months (range: 0.0+ to 84.7+), an estimated 80% [95% CI: 74, 86] of responses lasted 12 months or longer, 66% [95% CI: 59, 74] of responses lasted 24 months or longer, and 57% [95% CI: 49, 64] of responses lasted 36 months or longer. Eighty-three percent (83%) [95% CI: 79, 88] of patients treated were alive one year after the start of therapy, 73% [95% CI: 68, 78] after two years after the start of therapy, and 68% [95% CI: 63, 74] after three years with the median for overall survival not yet being reached. Median progression free survival was 28.0 months at the time of the analysis, with a progression free survival rate of 63% [95% CI: 57, 69] after 1 year, 54% [95% CI: 48, 60] after 2 years, and 44% [95% CI: 38, 50] after 3 years.
The median change in tumour size in the pooled primary analysis set was a decrease of 66%.

Patients with primary CNS tumours

At the time of data cut-off, of the 60 patients with primary CNS tumours confirmed response was observed in 21 patients (35%) with 5 of the 60 patients (8%) being complete responders and 16 patients (27%) being partial responders. Further 24 patients (40%) had stable disease. 13 patients (22%) had progressive disease. At the time of data cut-off, time on treatment ranged from 1.2 to 67.3 months and was ongoing in 20 out of 60 patients, with all of these patients receiving post-progression treatment.

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

In cancer patients given VITRAKVI capsules, peak plasma levels (C_{max}) of larotrectinib were achieved at approximately 1 hour after dosing. Half-life ($t_{½}$) is approximately 3 hours and steady state is reached within 8 days with a systemic accumulation of 1.6 fold. At the recommended dose of 100 mg taken twice daily, steady-state arithmetic mean (± standard deviation) C_{max} and daily AUC in adults were 914 ± 445 ng/mL and 5410 ± 3813 ng*h/mL, respectively. *In vitro* studies indicate that larotrectinib is not a substrate for either OATP1B1 or OATP1B3.

In vitro studies indicate that larotrectinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations and is unlikely to affect clearance of substrates of these CYPs.
In vitro studies indicate that larotrectinib does not inhibit the transporters BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B3, BSEP, MATE1 and MATE2-K at clinically relevant concentrations and is unlikely to affect clearance of substrates of these transporters.

Absorption

VITRAKVI is available as a capsule and oral solution formulation.
The mean absolute bioavailability of larotrectinib was 34% (range: 32% to 37%) following a single 100 mg oral dose. In healthy adult subjects, the AUC of larotrectinib in the oral solution formulation was similar to the capsule, with C_{max} 36% higher with the oral solution formulation.

Larotrectinib C_{max} was reduced by approximately 35% and there was no effect on AUC in healthy subjects administered VITRAKVI after a high-fat and high-calorie meal compared to the C_{max} and AUC after overnight fasting.

Effect of gastric pH-elevating agents on larotrectinib
Larotrectinib has pH-dependent solubility. *In vitro* studies show that in liquid volumes relevant to the gastrointestinal (GI) tract larotrectinib is fully soluble over entire pH range of the GI tract. Therefore, larotrectinib is unlikely to be affected by pH-modifying agents.

Distribution

The mean volume of distribution of larotrectinib in healthy adult subjects was 48 L following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose. Binding of larotrectinib to human plasma proteins *in vitro* was approximately 70% and was independent of drug concentration. The blood-to-plasma concentration ratio was approximately 0.9.

Biotransformation

Larotrectinib was metabolised predominantly by CYP3A4/5 *in vitro*. Following oral administration of a single 100 mg dose of radiolabelled larotrectinib to healthy adult subjects, unchanged larotrectinib (19%) and an O-glucuronide that is formed following loss of the hydroxypyrrolidine-urea moiety (26%) were the major circulating radioactive drug components.

Elimination

The half-life of larotrectinib in plasma of cancer patients given 100 mg twice daily of VITRAKVI was approximately 3 hours. Mean clearance (CL) of larotrectinib was approximately 34 L/h following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose of VITRAKVI.

Excretion

Following oral administration of 100 mg radiolabelled larotrectinib to healthy adult subjects, 58% of the administered radioactivity was recovered in faeces and 39% was recovered in urine and when an IV microtracer dose was given in conjunction with a 100 mg oral dose of larotrectinib, 35% of the administered radioactivity was recovered in faeces and 53% was recovered in urine. The fraction excreted as unchanged drug in urine was 29% following IV microtracer dose, indicating that direct renal excretion accounted for 29% of total clearance.

Linearity / non-linearity

The area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of larotrectinib after a single dose in healthy adult subjects were dose proportional up to 400 mg and slightly greater than proportional at doses of 600 to 900 mg.

Special populations

Paediatric patients
Based on population pharmacokinetic analyses, exposure (C_{max} and AUC) in paediatric patients at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID was higher than in adults (≥ 18 years of age) given the dose of 100 mg BID (see Table 8).
Data defining exposure in small children (1 month to < 2 years of age) at the recommended dose is limited (n=46).

Table 8: Exposure (C_{max} and AUC[a]) in patients grouped by age group at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID

Age group	n=438[b]	Fold difference compared to patients ≥ 18 years of age[c]	
		C_{max}	AUC[a]
1 to < 3 months	12	3.2	4.5
3 to < 6 months	4	3.0	3.2
6 to < 12 months	19	2.1	1.7
1 to < 2 years	11	1.6	1.1
2 to < 6 years	37	1.6	1.1
6 to < 12 years	38	1.3	1.2
12 to < 18 years	32	0.9	0.8
≥ 18 years	285	1.0	1.0

[a] area under the plasma concentration-time curve at steady-state
[b] number of patients from 23 September 2024 data cut-off
[c] fold difference is the ratio of stated age group to ≥18 years group. A fold-difference of 1 equates to no difference.

Elderly
There is no clinically meaningful difference in larotrectinib exposure in patients > 65 years compared to those in younger patients (< 65 years).

Patients with hepatic impairment
A pharmacokinetic study was conducted in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, and in healthy adult control subjects with normal hepatic function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib $AUC_{0\text{-}inf}$ was observed in subjects with mild, moderate and severe hepatic impairment of 1.3, 2 and 3.2-fold respectively versus those with normal hepatic function. C_{max} was observed to increase slightly by 1.1, 1.1 and 1.5-fold respectively.

Patients with renal impairment
A pharmacokinetic study was conducted in subjects with end stage renal disease requiring dialysis, and in healthy adult control subjects with normal renal function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib C_{max} and $AUC_{0\text{-}inf}$, of 1.25 and 1.46-fold respectively was observed in renally impaired subjects versus those with normal renal function.

Other special populations
Gender and race have no effect on the systemic exposure of larotrectinib based on population pharmacokinetic analysis.

5.3 Preclinical safety data

Systemic toxicity

Systemic toxicity was assessed in studies with daily oral administration up to 3 months in rats and monkeys. Dose limiting skin lesions were only seen in rats and were primarily responsible for mortality and morbidity. Skin lesions were not seen in monkeys.
Clinical signs of gastrointestinal toxicity were dose limiting in monkeys. In rats, severe toxicity (STD10) was observed at doses corresponding to 1- to 2-times the human AUC at the recommended clinical dose. No relevant systemic toxicity was observed in monkeys at doses which correspond to > 10-times the human AUC at the recommended clinical dose.

Embryotoxicity / Teratogenicity

Larotrectinib was not teratogenic and embryotoxic when dosed daily during the period of organogenesis to pregnant rats and rabbits at maternotoxic doses, i.e. corresponding to 32-times (rats) and 16-times (rabbits) the human AUC at the recommended clinical dose. Larotrectinib crosses the placenta in both species.

Reproduction toxicity

Fertility studies with larotrectinib have not been conducted. In 3-months toxicity studies, larotrectinib had no histological effect on the male reproductive organs in rats and monkeys at the highest tested doses corresponding to approximately 7-times (male rats) and 10-times (male monkeys) the human AUC at the recommended clinical dose. In addition, larotrectinib had no effect on spermatogenesis in rats.

In a 1-month repeat-dose study in rats, fewer corpora lutea, increased incidence of anestrus and decreased uterine weight with uterine atrophy were observed and these effects were reversible. No effects on female reproductive organs were seen in the 3-months toxicity studies in rats and monkeys at doses corresponding to approximately 3-times (female rats) and 17-times (female monkeys) the human AUC at the recommended clinical dose.
Larotrectinib was administered to juvenile rats from postnatal day (PND) 7 to 70. Pre-weaning mortality (before PND 21) was observed at the high dose level corresponding to 2.5- to 4-times the AUC at the recommended dose. Growth and nervous system effects were seen at 0.5- to 4-times the AUC at the recommended dose. Body weight gain was decreased in pre-weaning male and female pups, with a post-weaning increase in females at the end of exposure whereas reduced body weight gain was seen in males also post-weaning without recovery. The male growth reduction was associated with delayed puberty. Nervous system effects (i.e. altered hindlimb functionality and, likely, increases in eyelid closure) demonstrated partial recovery. A decrease in pregnancy rate was also reported despite normal mating at the high-dose level.

Genotoxicity and carcinogenicity

Carcinogenicity studies have not been performed with larotrectinib.
Larotrectinib was not mutagenic in bacterial reverse mutation (Ames) assays and in *in vitro* mammalian mutagenesis assays. Larotrectinib was negative in the *in vivo* mouse micronucleus test at the maximum tolerated dose of 500 mg/kg.

Safety pharmacology

The safety pharmacology of larotrectinib was evaluated in several *in vitro* and *in vivo* studies that assessed effects on the CV, CNS, respiratory, and GI systems in various species. Larotrectinib had no adverse effect on haemodynamic parameters and ECG intervals in telemetered monkeys at exposures (C_{max}) which are approximately 6-fold the human therapeutic exposures. Larotrectinib had no neurobehavioural findings in adult animals (rats, mice, cynomolgus monkeys) at exposure (C_{max}) at least 7-fold higher than the human exposure. Larotrectinib had no effect on respiratory function in rats; at exposures (C_{max}) at least 8-times the human therapeutic exposure. In rats, larotrectinib accelerated intestinal transit and increased gastric secretion and acidity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening: 30 days.
Store in a refrigerator (2 °C - 8 °C).

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber glass (type III) bottle with a child-resistant polypropylene (PP) screw cap with a polyethylene (PE) seal liner.

Each carton contains one bottle of 100 mL oral solution.

6.6 Special precautions for disposal and other handling

Instructions for use

Oral syringe

- Use a suitable oral syringe with CE marking and bottle adapter (28 mm diameter) if applicable.
  - For volumes less than 1 mL use a 1 mL oral syringe with 0.1 mL graduation.
  - For volumes of 1 mL and higher use a 5 mL oral syringe with 0.2 mL graduation.
- Open the bottle: press the bottle cap and turn it counter clockwise.
- Insert the bottle adapter into the bottle neck and ensure it is well fixed.
- Take the oral syringe and ensure that the plunger is fully depressed. Put the oral syringe in the adapter opening. Turn the bottle upside down.
- Fill the oral syringe with small amount of solution by pulling the plunger down, then push the plunger upwards to remove any bubbles.
- Pull the plunger down to the graduation mark equal to the quantity in mL as prescribed.
- Turn the bottle the right way up and remove the oral syringe from the bottle adapter.
- Slowly depress the plunger, directing the liquid towards the inside cheek to allow for natural swallowing.
- Close the bottle with the original bottle cap (leaving the adapter in place).

Nasogastric feeding tube

- Use a suitable nasogastric feeding tube. The outer diameter of the nasogastric feeding tube should be selected based on the patient characteristics. Typical tube diameter, tube lengths and derived prime volumes are presented in Table 9.
- The feeding should be stopped and the tube flushed with at least 10 mL water. NOTE: See exceptions regarding neonates and patients with fluid restrictions in the sub-point directly below.
- A suitable syringe should be used to administer VITRAKVI to the nasogastric feeding tube. The tube should be flushed again with at least 10 mL water to ensure VITRAKVI is delivered and to clear the tube.
  Neonates and children with fluid restrictions may require minimal flushing volume of 0.5 to 1 mL or flushing with air to deliver VITRAKVI.
- Restart the feeding.

Table 9: Recommended tube dimensions per age group

Patient	Tube diameter for standard feeds	Tube diameter for high density feeds	Tube length (cm)	Tube prime volume (mL)
Neonate	4-5 FR	6 FR	40-50	0.25-0.5
Children	6 FR	8 FR	50-80	0.7-1.4
Adult	8 FR	10 FR	80-120	1.4-4.2

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

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1385/003 – VITRAKVI 20 mg/mL oral solution

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2019
Date of latest renewal: 22 July 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 20 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral solution contains larotrectinib sulfate equivalent to 20 mg of larotrectinib.

Excipients with known effect:
Each mL of oral solution contains 2 mg sodium benzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Colourless to yellow or orange or red or brownish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Treatment with VITRAKVI should be initiated by physicians experienced in the administration of anticancer therapies.

The presence of an *NTRK* gene fusion in a tumour specimen should be confirmed by a validated test prior to initiation of treatment with VITRAKVI.

Posology

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.

Missed dose
If a dose is missed, the patient should not take two doses at the same time to make up for a missed dose. Patients should take the next dose at the next scheduled time. If the patient vomits after taking a dose, the patient should not take an additional dose to make up for vomiting.

Dose modification
For all grade 2 adverse reactions, continued dosing may be appropriate, though close monitoring to ensure no worsening of the toxicity is advised.

For all grade 3 or 4 adverse reactions not referring to liver function test abnormalities:
- VITRAKVI should be withheld until the adverse reaction resolves or improves to baseline or grade 1. Resume at the next dose modification if resolution occurs within 4 weeks.
- VITRAKVI should be permanently discontinued if an adverse reaction does not resolve within 4 weeks.

The recommended dose modifications for VITRAKVI for adverse reactions are provided in Table 1.

Table 1: Recommended dose modifications for VITRAKVI for adverse reactions

Dose modification	Adult and paediatric patients with body surface area of at least 1.0 m^2	Paediatric patients with body surface area less than 1.0 m^2
First	75 mg twice daily	75 mg/m^2 twice daily
Second	50 mg twice daily	50 mg/m^2 twice daily
Third	100 mg once daily	25 mg/m^2 twice daily[a]

[a] Paediatric patients on 25 mg/m^2 twice daily should remain on this dose even if body surface area becomes greater 1.0 m^2 during the treatment. Maximum dose should be 25 mg/m^2 twice daily at the third dose modification.

VITRAKVI should be permanently discontinued in patients who are unable to tolerate VITRAKVI after three dose modifications.

The recommended dose modifications in case of liver function tests abnormalities during treatment with VITRAKVI are provided in Table 2.

Table 2: Recommended dose modifications and management for VITRAKVI for liver function test abnormalities

Laboratory parameters	Recommended measures
Grade 2 ALT and/or AST (>3x ULN and ≤5x ULN)	- Conduct serial laboratory evaluations frequently after the observation of grade 2 toxicity, until resolved, to establish whether a dose interruption or reduction is required.
Grade 3 ALT and/or AST (>5x ULN and ≤20x ULN) or Grade 4 ALT and/or AST (>20x ULN), with bilirubin <2x ULN	- Withhold treatment until the adverse reaction resolves or improves to baseline. Monitor liver function frequently until resolution or return to baseline. Permanently discontinue treatment if an adverse reaction does not resolve. - Resume at the next dose modification if adverse reactions resolve. Treatment should only be resumed in patients where the benefit outweighs the risk. - Permanently discontinue treatment if a grade 4 ALT and/or AST elevation occurs after resuming treatment.
ALT and/or AST ≥3x ULN with bilirubin ≥2x ULN	- Withhold treatment and monitor liver function frequently until resolution or return to baseline. - Consider permanent treatment discontinuation. - Treatment should only be resumed in patients where the benefit outweighs the risk. - If resumed, start at the next lower dose. Monitor liver function frequently upon restart. - Permanently discontinue treatment if adverse reaction recurs after resuming treatment.

ALT Alanine aminotransferase
AST Aspartate aminotransferase
ULN upper limit of normal

Special populations

Elderly
No dose adjustment is recommended in elderly patients (see section 5.2).

Hepatic impairment
The starting dose of VITRAKVI should be reduced by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A) (see section 5.2).

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2).

Co-administration with strong CYP3A4 inhibitors
If co-administration with a strong CYP3A4 inhibitor is necessary, the VITRAKVI dose should be reduced by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, VITRAKVI should be resumed at the dose taken prior to initiating the CYP3A4 inhibitor (see section 4.5).

Method of administration

VITRAKVI is for oral use.

VITRAKVI is available as a capsule or oral solution with equivalent oral bioavailability and may be used interchangeably.

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.
- For doses below 1 mL a 1 mL oral syringe should be used. The calculated dose volume should be rounded to the nearest 0.1 mL.
- For doses of 1 mL and higher a 5 mL oral syringe should be used. The dose volume should be calculated to the nearest 0.2 mL.
- VITRAKVI should not be mixed with feeding formulas, if administered via nasogastric feeding tube. Mixing with the feeding formulas could lead to tube blockages.
- For instructions for use of oral syringes and feeding tubes see section 6.6.

The oral solution can be taken with or without food but should not be taken with grapefruit or grapefruit juice.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Efficacy across tumour types

The benefit of VITRAKVI has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit *NTRK* gene fusions. Favourable effects of VITRAKVI have been shown on the basis of overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genetic alterations (see section 5.1). For these reasons, VITRAKVI should only be used if there are no treatment options for which clinical benefit has been established, or where such treatment options have been exhausted (i.e., no satisfactory treatment options).

Neurologic reactions

Neurologic reactions including dizziness, gait disturbance and paraesthesia were reported in patients receiving larotrectinib (see section 4.8). For the majority of neurologic reactions, onset occurred within the first three months of treatment. Withholding, reducing, or discontinuing VITRAKVI dosing should be considered, depending on the severity and persistence of these symptoms (see section 4.2).

Hepatotoxicity

Abnormalities of liver function tests including increased ALT, AST, alkaline phosphatase (ALP) and bilirubin have been observed in patients receiving larotrectinib (see section 4.8). The majority of ALT and AST increases occurred within 3 months of starting treatment. Cases of hepatotoxicity with increases in ALT and/or AST of grade 2, 3 or 4 severity and increases in bilirubin ≥ 2x ULN have been reported.
In patients with hepatic transaminase elevations, withhold, modify dose or permanently discontinue VITRAKVI based on the severity (see section 4.2).
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 (see section 4.2).

Co-administration with CYP3A4/P-gp inducers

Avoid co-administration of strong or moderate CYP3A4/P-gp inducers with VITRAKVI due to a risk of decreased exposure (see section 4.5).

Contraception in female and male

Women of childbearing potential must use highly effective contraception while taking VITRAKVI and for at least one month after stopping treatment (see sections 4.5 and 4.6).
Males of reproductive potential with a non-pregnant woman partner of childbearing potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose (see section 4.6).

Important information about some of the ingredients

Sodium benzoate: this medicinal product contains 2 mg per 1 mL.
Sodium: this medicinal product contains less than 1 mmol sodium (23 mg) per 5 mL, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents on larotrectinib

Effect of CYP3A, P-gp and BCRP inhibitors on larotrectinib
Larotrectinib is a substrate of cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of VITRAKVI with strong or moderate CYP3A inhibitors, P-gp and BCRP inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole or grapefruit) may increase larotrectinib plasma concentrations (see section 4.2).
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with itraconazole (a strong CYP3A inhibitor and P-gp and BCRP inhibitor) 200 mg once daily for 7 days increased larotrectinib C_{max} and AUC by 2.8-fold and 4.3-fold, respectively.
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with a single dose of 600 mg rifampicin (a P-gp and BCRP inhibitor) increased larotrectinib C_{max} and AUC by 1.8-fold and 1.7-fold, respectively.

Effect of CYP3A and P-gp inducers on larotrectinib
Co-administration of VITRAKVI with strong or moderate CYP3A inducers and strong P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, or St. John's Wort) may decrease larotrectinib plasma concentrations and should be avoided (see section 4.4).
Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with rifampicin (a strong CYP3A and P-gp inducer) 600 mg once daily for 11 days decreased larotrectinib C_{max} and AUC by 71% and 81%, respectively. No clinical data is available on the effect of a moderate inducer, but a decrease in larotrectinib exposure is expected.

Effects of larotrectinib on other agents

Effect of larotrectinib on CYP3A substrates
Clinical data in healthy adult subjects indicate that co-administration of VITRAKVI (100 mg twice daily for 10 days) increased the C_{max} and AUC of oral midazolam 1.7-fold compared to midazolam alone, suggesting that larotrectinib is a weak inhibitor of CYP3A.
Exercise caution with concomitant use of CYP3A substrates with narrow therapeutic range (e.g. alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus) in patients taking VITRAKVI. If concomitant use of these CYP3A substrates with narrow therapeutic range is required in patients taking VITRAKVI, dose reductions of the CYP3A substrates may be required due to adverse reactions.

Effect of larotrectinib on CYP2B6 substrates
In vitro studies indicate that larotrectinib induces CYP2B6. Co-administration of larotrectinib with CYP2B6 substrates (e.g. bupropion, efavirenz) may decrease their exposure.

Effect of larotrectinib on other transporter substrates
In vitro studies indicate that larotrectinib is an inhibitor of OATP1B1. No clinical studies have been performed to investigate interactions with OATP1B1 substrates. Therefore, it cannot be excluded whether co-administration of larotrectinib with OATP1B1 substrates (e.g. valsartan, statins) may increase their exposure.

Effect of larotrectinib on substrates of PXR regulated enzymes
In vitro studies indicate that larotrectinib is a weak inducer of PXR regulated enzymes (e.g. CYP2C family and UGT). Co-administration of larotrectinib with CYP2C8, CYP2C9 or CYP2C19 substrates (e.g. repaglinide, warfarin, tolbutamide or omeprazole) may decrease their exposure.

Hormonal contraceptives
It is currently unknown whether larotrectinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should be advised to add a barrier method.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Based on the mechanism of action, foetal harm cannot be excluded when administering larotrectinib to a pregnant woman. Women of childbearing potential should have a pregnancy test prior to starting treatment with VITRAKVI.
Women of reproductive potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose. As it is currently unknown whether larotrectinib may reduce the effectiveness of systemically acting hormonal contraceptives, women using systemically acting hormonal contraceptives should be advised to add a barrier method.
Males of reproductive potential with a non-pregnant woman partner of childbearing potential should be advised to use highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose.

Pregnancy

There are no data from the use of larotrectinib in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of VITRAKVI during pregnancy.

Breast-feeding

It is unknown whether larotrectinib/metabolites are excreted in human milk.
A risk to newborns/infants cannot be excluded.
Breast-feeding should be discontinued during treatment with VITRAKVI and for 3 days following the final dose.

Fertility

There are no clinical data on the effect of larotrectinib on fertility. No relevant effects on fertility were observed in repeat-dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

VITRAKVI has a moderate influence on the ability to drive and use machines. Dizziness and fatigue have been reported in patients receiving larotrectinib, mostly grade 1 and 2 during the first 3 months of treatment. This may influence the ability to drive and use machines during this time period. Patients should be advised not to drive and use machines, until they are reasonably certain VITRAKVI therapy does not affect them adversely (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (≥ 20%) of VITRAKVI in order of decreasing frequency were increased ALT (36%), increased AST (33%), vomiting (30%), anaemia (28%), constipation (28%), diarrhoea (27%), nausea (24%), fatigue (23%), and dizziness (20%).
The majority of adverse reactions were grade 2 or 3. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (2%), ALT increased (1%), AST increased, leukocyte count decreased, platelet count decreased, muscular weakness and blood alkaline phosphatase increased (each in < 1%). The highest reported grade was grade 3 for adverse reactions anaemia (7%), weight increased (6%), diarrhoea (4%), gait disturbance and vomiting (each 1%), and fatigue, dizziness, paraesthesia, nausea, myalgia, and constipation (each in < 1%).
Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions occurred in 2% of patients (2 cases each of neutrophil count decreased, ALT increased, and AST increased, 1 case each of gait disturbance, and muscular weakness). The majority of adverse reactions leading to dose reduction occurred in the first three months of treatment.

Tabulated list of adverse reactions

The safety of VITRAKVI was evaluated in 361 patients with TRK fusion-positive cancer in one of three on-going clinical trials, Studies 1, 2 (“NAVIGATE”), and 3 (“SCOUT”) and post-marketing. The safety population characteristics were comprised of patients with a median age of 39.0 years (range: 0, 90) with 37% of patients being paediatric patients. Median time on treatment for the overall safety population (n=361) was 16.2 months (range: 0.1, 89.1).
The adverse drug reactions reported in patients (n=361) treated with VITRAKVI are shown in Table 3 and Table 4.

The adverse drug reactions are classified according to the System Organ Class.
Frequency groups are defined by the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), and not known (cannot be estimated from available data).
Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (overall safety population, n=361) and post-marketing

System organ class	Frequency	All grades	Grades 3 and 4
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	
	Common	Platelet count decreased (Thrombocytopenia)	Anaemia Neutrophil count decreased (Neutropenia)[a] Leukocyte count decreased (Leukopenia)[a]
	Uncommon		Platelet count decreased (Thrombocytopenia)[a, b]
Nervous system disorders	Very common	Dizziness	
	Common	Gait disturbance Paraesthesia	Gait disturbance
	Uncommon		Dizziness Paraesthesia
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting Diarrhoea	
	Common	Dysgeusia[c]	Diarrhoea Vomiting
	Uncommon		Nausea Constipation
Hepatobiliary disorders	Not known	Liver injury[d]	
Musculoskeletal and connective tissue disorders	Very common	Myalgia	
	Common	Muscular weakness	
	Uncommon		Myalgia Muscular weakness[a, b]
General disorders and administration site conditions	Very common	Fatigue	
	Uncommon		Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain)	
	Common	Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased[a] Aspartate aminotransferase (AST) increased[a] Weight increased (Abnormal weight gain)
	Uncommon		Blood alkaline phosphatase increased[a, b]

[a] grade 4 reactions were reported

[b] each grade frequency was less than <1%

[c] ADR dysgeusia includes the preferred terms “dysgeusia” and “taste disorder”

[d] includes cases with ALT/AST ≥3x ULN and bilirubin ≥2x ULN

Table 4: Adverse drug reactions reported in TRK fusion-positive paediatric cancer patients treated with VITRAKVI at recommended dose (n=135); all grades

System organ class	Frequency	Infants and toddlers (n=43)[a]	Children (n=67)[b]	Adolescents (n=25)[c]	Paediatric patients (n=135)
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) Platelet count decreased (Thrombocytopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia) Platelet count decreased (Thrombocytopenia)
	Common		Platelet count decreased (Thrombocytopenia)	Platelet count decreased (Thrombocytopenia)	
Nervous system disorders	Very common			Dizziness	
	Common	Dizziness	Dizziness Paraesthesia Gait disturbance	Paraesthesia Gait disturbance	Dizziness Paraesthesia Gait disturbance
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea	Nausea Constipation Vomiting Diarrhoea
	Common		Dysgeusia		Dysgeusia
Musculoskeletal and connective tissue disorders	Very common		Myalgia	Myalgia	Myalgia
	Common	Muscular weakness	Muscular weakness	Muscular weakness	Muscular weakness
General disorders and administration site conditions	Very common	Fatigue	Fatigue	Fatigue	Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased

[a] Infant/toddlers (28 days to 23 months): 5 grade 4 Neutrophil count decreased (Neutropenia) reactions and 2 Blood alkaline phosphatase increased reported. Grade 3 reactions included 11 cases of Neutrophil count decreased (Neutropenia), 4 cases of ALT increased, 3 cases each of Anaemia, Diarrhoea, and Weight increased (Abnormal weight gain), and 2 cases each of Blood alkaline phosphatase increased, and Vomiting and 1 case of AST increased.

[b] Children (2 to 11 years): 1 grade 4 Leukocytes count decreased reported. 9 reported grade 3 cases of Neutrophil count decreased (Neutropenia), 4 cases of Weight increased (Abnormal weight gain), 2 cases each of ALT increased, Anaemia, Diarrhoea, and Vomiting and 1 case each of AST increased, Gait disturbance, Paraesthesia and Myalgia.

[c] Adolescents (12 to <18 years): no grade 4 reactions were reported. Grade 3 reactions were reported in 1 case each of ALT increased, AST increased, Fatigue, Gait disturbance, and Muscular weakness.

Description of selected adverse reactions

Neurologic reactions
In the overall safety database (n=361), the maximum grade neurologic adverse reaction observed was grade 3 or 4 which was observed in 10 (3%) patients and included gait disturbance (4 patients, 1%), dizziness (3 patients, <1%), and paraesthesia (3 patients, <1%). The overall incidence was 20% for dizziness, 7% for paraesthesia and 5% for gait disturbance. Neurologic reactions leading to dose modification or interruptions included dizziness (1%), gait disturbance (<1%), and paraesthesia (<1%). One patient permanently discontinued the treatment due to grade 3 gait disturbance. In all cases except of one, patients with evidence of anti-tumour activity who required a dose reduction were able to continue dosing at a reduced dose and/or schedule (see section 4.4).

Hepatotoxicity
Abnormalities of liver function tests including ALT, AST, ALP and bilirubin have been observed in patients treated with VITRAKVI.
In the overall safety database (n=361), the maximum grade transaminase elevation observed was grade 4 ALT increase in 7 patients (2%) and AST increase in 4 patients (1%). Grade 3 ALT and AST increases in 26 (7%) and 22 (6%) of patients, respectively. Majority of grade 3 elevations were transient appearing in the first three months of treatment and resolving to grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in 37 (10%) and 33 (9%) of patients, respectively, and grade 1 ALT and AST increases were observed in 173 (48%) and 177 (49%) of patients, respectively. ALT and AST increases leading to dose modifications or interruptions occurred in 25 (7%) patients and 21 (6%) patients, respectively (see section 4.4). Two patients permanently discontinued the treatment with 1 patient due to grade 3 ALT and grade 3 AST increases.
Cases of hepatotoxicity with increases in ALT and/or AST of grade 2, 3 or 4 severity and increases in bilirubin ≥ 2x ULN have been reported. In some cases, the dose of VITRAKVI was withheld and restarted at a reduced dose, while in other cases treatment was permanently discontinued (see section 4.4).

Additional information on special populations

Paediatric patients
Of the 361 patients treated with VITRAKVI, 135 (37%) patients were from birth to < 18 years of age (n=13 from birth to < 3 months, n=4 ≥ 3 months to < 6 months, n=17 ≥ 6 months to < 12 months, n=9 ≥ 12 months to < 2 years, n=30 ≥ 2 years to < 6 years, n=37 ≥ 6 years to < 12 years, n=25 ≥ 12 years to < 18 years). The majority of adverse reactions were grade 1 or 2 in severity and were resolved without VITRAKVI dose modification or discontinuation. Adverse reactions of grade 3 or 4 in severity were generally observed more frequently in patients < 6 years of age. They were reported in 77% of patients from birth to < 3 months and in 47% of patients ≥ 3 months to < 6 years. Decreased neutrophil count has been reported to have led to study drug discontinuation, dose modification and dose interruption.

Elderly
Of the 361 patients in the overall safety population who received VITRAKVI, 69 (19%) patients were 65 years or older and 22 (6%) patients were 75 years or older. The safety profile in elderly patients (≥ 65 years) is consistent with that seen in younger patients. The adverse reaction dizziness (30% versus 28% in all adults), anaemia (36% versus 28% in all adults), diarrhoea (25% versus 23% in all adults), muscular weakness (13% versus 11% in all adults), platelet count decreased (12% versus 6% in all adults), gait disturbance (9% versus 5% in all adults), and dysgeusia (9% versus 6% in all adults) were more frequent in patients of 65 years or older.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited experience of overdose with VITRAKVI. Symptoms of overdose are not established. In the event of overdose, physicians should follow general supportive measures and treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, protein kinase inhibitors, ATC code: L01EX12.

Mechanism of action

Larotrectinib is an adenosine triphosphate (ATP)-competitive and selective tropomyosin receptor kinase (TRK) inhibitor that 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.

Acquired resistance mutations after progression on TRK inhibitors have been observed. Larotrectinib had minimal activity in cell lines with point mutations in the TRKA kinase domain, including the clinically identified acquired resistance mutation, G595R. Point mutations in the TRKC kinase domain with clinically identified acquired resistance to larotrectinib include G623R, G696A, and F617L.

The molecular causes for primary resistance to larotrectinib are not known. It is therefore not known if the presence of a concomitant oncogenic driver in addition to an *NTRK* gene fusion affects the efficacy of TRK inhibition. The measured impact of any concomitant genomic alterations on larotrectinib efficacy is provided below (see clinical efficacy).

Pharmacodynamic effects

Cardiac electrophysiology
In 36 healthy adult subjects receiving single doses ranging from 100 mg to 900 mg, VITRAKVI did not prolong the QT interval to any clinically relevant extent.
The 200 mg dose corresponds to a peak exposure (C_{max}) similar to that observed with larotrectinib 100 mg BID at steady state. A shortening of QTcF was observed with VITRAKVI dosing, with a maximum mean effect observed between 3 and 24 hours after C_{max}, with a geometric mean decrease in QTcF from baseline of -13.2 msec (range -10 to -15.6 msec). Clinical relevance of this finding has not been established.

Clinical efficacy

Overview of studies
The efficacy and safety of VITRAKVI were studied in three multicentre, open-label, single-arm clinical studies in adult and paediatric cancer patients (Table 5). Two studies are still ongoing. Patients with and without documented *NTRK* gene fusion were allowed to participate in Study 1 and Study 3 ("SCOUT"). Patients enrolled to Study 2 ("NAVIGATE") were required to have TRK fusion-positive cancer. The pooled primary analysis set of efficacy includes 364 patients with TRK fusion-positive cancer enrolled across the three studies that had measurable disease assessed by RECIST v1.1, a non-CNS primary tumour and received at least one dose of larotrectinib as of July 2024. These patients were required to have received prior standard therapy appropriate for their tumour type and stage of disease or who, in the opinion of the investigator, would have had to undergo radical surgery (such as limb amputation, facial resection, or paralysis causing procedure), or were unlikely to tolerate, or derive clinically meaningful benefit from available standard of care therapies in the advanced disease setting. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC). In addition, 60 patients with primary CNS tumours and measurable disease at baseline were treated in Study 2 ("NAVIGATE") and in Study 3 ("SCOUT"). Fifty-seven of the 60 primary CNS tumour patients had received prior cancer treatment (surgery, radiotherapy and/or previous systemic therapy). Tumour responses were assessed by the investigator using RANO or RECIST v1.1 criteria.

Identification of *NTRK* gene fusions relied on tissue samples for the molecular test methods: next generation sequencing (NGS) used in 327 patients, polymerase chain reaction (PCR) used in 14 patients, fluorescence *in situ* hybridization (FISH) used in 18 patients, and other testing methods (Sequencing, Nanostring, Sanger sequencing, or Chromosome Microarray) used in 5 patients.

Table 5: Clinical studies contributing to the efficacy analyses in solid and primary CNS tumours

Study name, design and patient population	Dose and formulation	Tumour types included in efficacy analysis	n
Study 1 NCT02122913 • Phase 1, open-label, dose escalation and expansion study; expansion phase required tumours with an *NTRK* gene fusion • Adult patients (≥ 18 years) with advanced solid tumours with an *NTRK* gene fusion	Doses up to 200 mg once or twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Thyroid (n=4) Salivary gland (n=3) GIST (n=2)[a] Soft tissue sarcoma (n=2) NSCLC (n=1)[b, c] Unknown primary cancer (n=1)	13
Study 2 "NAVIGATE" NCT02576431 • Phase 2 multinational, open label, tumour "basket" study • Adult and paediatric patients ≥ 12 years with advanced solid tumours with an *NTRK* gene fusion	100 mg twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	NSCLC (n=29)[b, c] Soft tissue sarcoma (n=28) Thyroid (n=26)[b] Colon (n=25) Salivary gland (n=24) Primary CNS (n=19) Melanoma (n=10)[b] Breast, non-secretory (n=10)[b] Pancreas (n=7) Breast, secretory (n=5) Cholangiocarcinoma (n=4) GIST (n=3)[a] Gastric (n=3) Prostate (n=2) Appendix, Atypical carcinoid lung cancer, Bone sarcoma, Cervix, Hepatic[e], Duodenal, External auditory canal[b], Oesophageal, SCLC[b, d], Rectal, Testes[b], Thymus, Unknown primary cancer, Urothelial, Uterus (n=1 each)	210
Study 3 "SCOUT" NCT02637687 • Phase 1/2 multinational, open-label, dose escalation and expansion study; Phase 2 expansion cohort required advanced solid tumours with an *NTRK* gene fusion, including locally advanced infantile fibrosarcoma • Paediatric patients from birth to 21 years with advanced cancer or with primary CNS tumours	Doses up to 100 mg/m^2 twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Infantile fibrosarcoma (n=49) Soft tissue sarcoma (n=42)[b] Primary CNS (n=41) Congenital mesoblastic nephroma (n=2) Bone sarcoma (n=2) Breast secretory, Cervix, Lipofibromatosis, Melanoma, Thyroid (n=1 each)	141
Total number of patients (n)[*]			364

[*] consist of 304 patients with IRC tumour response assessment and 60 patients with primary CNS tumours (including astrocytoma, ganglioglioma, glioblastoma, glioma, glioneuronal tumours, neuronal and mixed neuronal-glial tumours, oligodendroglioma, and primitive neuro-ectodermal tumour, not specified) with investigator tumour response assessment

[a] GIST: gastrointestinal stromal tumour

[b] brain metastases were observed in some patients in the following tumour types: lung (NSCLC, SCLC), thyroid, melanoma, breast (non-secretory), external auditory canal, soft tissue sarcoma and testes

[c] NSCLC: non-small cell lung cancer
[d] SCLC: small cell lung cancer
[e] hepatocellular carcinoma

Baseline characteristics for the pooled 304 patients with solid tumours with an *NTRK* gene fusion were as follows: median age 44.5 years (range 0-90 years); 33% < 18 years of age, and 67% ≥ 18 years; 55% white and 47% male; and ECOG PS 0-1 (88%), 2 (10%), or 3 (2%). Ninety-one percent of patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. Of these, 72% had received prior systemic therapy with a median of 1 prior systemic treatment regimen. Twenty-eight percent of all patients had received no prior systemic therapy. Of those 304 patients the most common tumour types represented were soft tissue sarcoma (24%), infantile fibrosarcoma (16%), lung cancer (11%), thyroid cancer (10%), salivary gland tumour (9%) and colon cancer (8%).
Baseline characteristics for the 60 patients with primary CNS tumours with an *NTRK* gene fusion assessed by investigator were as follows: median age 9.1 years (range 0-79 years); 43 patients < 18 years of age, and 17 patients ≥ 18 years, and 39 patients white and 28 patients male; and ECOG PS 0-1 (52 patients), or 2 (5 patients). Fifty-seven (95%) patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic therapy. There was a median of 1 prior systemic treatment regimen received.

Efficacy results
The pooled efficacy results for overall response rate, duration of response and time to first response, in the primary analysis population (n=304) and with post-hoc addition of primary CNS tumours (n=60) resulting in the pooled population (n=364), are presented in Table 6 and Table 7.

Table 6: Pooled efficacy results in solid tumours including and excluding primary CNS tumours

Efficacy parameter	**Analysis in solid tumours excluding primary CNS tumours (n=304)**[a]	**Analysis in solid tumours including primary CNS tumours (n=364)**[a, b]
Overall response rate (ORR) % (n) [95% CI]	65% (198) [59, 70]	60% (219) [55, 65]
Complete response (CR)	22% (66)	20% (71)
Pathological complete response[c]	7% (20)	5% (20)
Partial response (PR)	37% (112)	35% (128)
Time to first response (median, months) [range]	1.84 [0.89, 22.90]	1.84 [0.89, 49.87]
Duration of response (median, months) [range] % with duration ≥ 12 months % with duration ≥ 24 months % with duration ≥ 36 months % with duration ≥ 48 months	43.3 [0.0+, 84.7+] 80% 66% 57% 48%	43.3 [0.0+, 84.7+] 79% 65% 54% 47%

+ denotes ongoing
[a] Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (304 patients).
[b] Evaluated using either RANO or RECIST v1.1 criteria for primary CNS tumours (60 patients).
[c] A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumour cells and negative margins on post-surgical pathology evaluation. The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v.1.1.

Table 7: Overall response rate and duration of response by tumour type*

Tumour type	Patients (n=364)	ORR[a]		DOR			
		%	95% CI	months			Range (months)
				≥ 12	≥ 24	≥ 36	
Soft tissue sarcoma	72	68%	56%, 79%	80%	72%	60%	0.03+, 84.7+
Primary CNS	60	35%	23%, 48%	66%	50%	50%	2.8+, 70.9+
Infantile fibrosarcoma	49	94%	83%, 99%	83%	66%	60%	1.6+, 73.7+
Lung	32	69%	50%, 84%	75%	52%	45%	1.9+, 67.2+
Thyroid	31	65%	45%, 81%	85%	63%	47%	3.7, 83.9+
Salivary gland	27	85%	66%, 96%	91%	86%	76%	2.7, 81.1+
Colon	25	48%	28%, 69%	83%	62%	31%	3.9, 56.3+
Breast	16						
Non-secretory[c]	10	30%	7%, 65%	67%	0%	0%	7.4, 15.3
Secretory[b]	6	83%	36%, 100%	80%	80%	80%	11.1, 69.2+
Melanoma	11	45%	17%, 77%	50%	NR	NR	1.9+, 23.2+
Pancreas	7	14%	0%, 58%	0%	0%	0%	5.8, 5.8
Gastrointestinal stromal tumour	5	80%	28%, 99%	75%	38%	38%	9.5, 50.4+
Bone sarcoma	3	33%	1%, 91%	0%	0%	0%	9.5, 9.5
Congenital mesoblastic nephroma	2	100%	16%, 100%	100%	100%	50%	32.9, 44.5
Cervix	2	50%	1%, 99%	100%	NR	NR	18.7+, 18.7+
Unknown primary cancer	2	100%	16%, 100%	0	0	0	5.6, 7.4
External auditory canal	1	100%	3%, 100%	100%	100%	100%	45.1+, 45.1+
Lipofibromatosis	1	100%	3%, 100%	100%	NR	NR	17.7+, 17.7+

DOR: duration of response
NE: not evaluable
NR: not reached
* no data are available for the following tumour types: cholangiocarcinoma (n=4); gastric (n=3); prostate (n=2); appendix, hepatic, duodenal, oesophageal, rectal, testes, thymus, urothelial, uterus (n=1 each)
+ denotes ongoing response
[a] evaluated per independent review committee analysis by RECIST v1.1 for all tumour types except patients with a primary CNS tumour who were evaluated using either RANO or RECIST v1.1 criteria
[b] with 2 complete, 2 partial response
[c] with 1 complete, 2 partial response

Due to the rarity of TRK fusion-positive cancer, patients were studied across multiple tumour types with a limited number of patients in some tumour types, causing uncertainty in the ORR estimate per tumour type. The ORR in the total population may not reflect the expected response in a specific tumour type.

In the adult sub-population (n=222), the ORR was 51%. In the paediatric sub-population (n=142), the ORR was 74%.

In 257 patients with wide molecular characterisation before larotrectinib treatment, the ORR in 120 patients who had other genomic alterations in addition to *NTRK* gene fusion was 53%, and in 137 patients without other genomic alterations ORR was 68%.

Pooled primary analysis set

The pooled primary analysis set consisted of 304 patients and did not include primary CNS tumours. Median time on treatment before disease progression was 15.9 months (range: 0.1 to 99.4 months) based on July 2024 cut-off. Fifty-five percent of patients had received VITRAKVI for 12 months or more, 37% had received VITRAKVI 24 months or more, and 28% had received VITRAKVI 36 months or more. Follow-up was ongoing at the time of the analysis for 27% of patients.
At the time of analysis, the median duration of response is 43.3 months (range: 0.0+ to 84.7+), an estimated 80% [95% CI: 74, 86] of responses lasted 12 months or longer, 66% [95% CI: 59, 74] of responses lasted 24 months or longer, and 57% [95% CI: 49, 64] of responses lasted 36 months or longer. Eighty-three percent (83%) [95% CI: 79, 88] of patients treated were alive one year after the start of therapy, 73% [95% CI: 68, 78] after two years after the start of therapy, and 68% [95% CI: 63, 74] after three years with the median for overall survival not yet being reached. Median progression free survival was 28.0 months at the time of the analysis, with a progression free survival rate of 63% [95% CI: 57, 69] after 1 year, 54% [95% CI: 48, 60] after 2 years, and 44% [95% CI: 38, 50] after 3 years.
The median change in tumour size in the pooled primary analysis set was a decrease of 66%.

Patients with primary CNS tumours

At the time of data cut-off, of the 60 patients with primary CNS tumours confirmed response was observed in 21 patients (35%) with 5 of the 60 patients (8%) being complete responders and 16 patients (27%) being partial responders. Further 24 patients (40%) had stable disease. 13 patients (22%) had progressive disease. At the time of data cut-off, time on treatment ranged from 1.2 to 67.3 months and was ongoing in 20 out of 60 patients, with all of these patients receiving post-progression treatment.

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

In cancer patients given VITRAKVI capsules, peak plasma levels (C_{max}) of larotrectinib were achieved at approximately 1 hour after dosing. Half-life ($t_{½}$) is approximately 3 hours and steady state is reached within 8 days with a systemic accumulation of 1.6 fold. At the recommended dose of 100 mg taken twice daily, steady-state arithmetic mean (± standard deviation) C_{max} and daily AUC in adults were 914 ± 445 ng/mL and 5410 ± 3813 ng*h/mL, respectively. *In vitro* studies indicate that larotrectinib is not a substrate for either OATP1B1 or OATP1B3.

In vitro studies indicate that larotrectinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations and is unlikely to affect clearance of substrates of these CYPs.
In vitro studies indicate that larotrectinib does not inhibit the transporters BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B3, BSEP, MATE1 and MATE2-K at clinically relevant concentrations and is unlikely to affect clearance of substrates of these transporters.

Absorption

VITRAKVI is available as a capsule and oral solution formulation.
The mean absolute bioavailability of larotrectinib was 34% (range: 32% to 37%) following a single 100 mg oral dose. In healthy adult subjects, the AUC of larotrectinib in the oral solution formulation was similar to the capsule, with C_{max} 36% higher with the oral solution formulation.

Larotrectinib C_{max} was reduced by approximately 35% and there was no effect on AUC in healthy subjects administered VITRAKVI after a high-fat and high-calorie meal compared to the C_{max} and AUC after overnight fasting.

Effect of gastric pH-elevating agents on larotrectinib
Larotrectinib has pH-dependent solubility. *In vitro* studies show that in liquid volumes relevant to the gastrointestinal (GI) tract larotrectinib is fully soluble over entire pH range of the GI tract. Therefore, larotrectinib is unlikely to be affected by pH-modifying agents.

Distribution

The mean volume of distribution of larotrectinib in healthy adult subjects was 48 L following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose. Binding of larotrectinib to human plasma proteins *in vitro* was approximately 70% and was independent of drug concentration. The blood-to-plasma concentration ratio was approximately 0.9.

Biotransformation

Larotrectinib was metabolised predominantly by CYP3A4/5 *in vitro*. Following oral administration of a single 100 mg dose of radiolabelled larotrectinib to healthy adult subjects, unchanged larotrectinib (19%) and an O-glucuronide that is formed following loss of the hydroxypyrrolidine-urea moiety (26%) were the major circulating radioactive drug components.

Elimination

The half-life of larotrectinib in plasma of cancer patients given 100 mg twice daily of VITRAKVI was approximately 3 hours. Mean clearance (CL) of larotrectinib was approximately 34 L/h following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose of VITRAKVI.

Excretion

Following oral administration of 100 mg radiolabelled larotrectinib to healthy adult subjects, 58% of the administered radioactivity was recovered in faeces and 39% was recovered in urine and when an IV microtracer dose was given in conjunction with a 100 mg oral dose of larotrectinib, 35% of the administered radioactivity was recovered in faeces and 53% was recovered in urine. The fraction excreted as unchanged drug in urine was 29% following IV microtracer dose, indicating that direct renal excretion accounted for 29% of total clearance.

Linearity / non-linearity

The area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of larotrectinib after a single dose in healthy adult subjects were dose proportional up to 400 mg and slightly greater than proportional at doses of 600 to 900 mg.

Special populations

Paediatric patients
Based on population pharmacokinetic analyses, exposure (C_{max} and AUC) in paediatric patients at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID was higher than in adults (≥ 18 years of age) given the dose of 100 mg BID (see Table 8).
Data defining exposure in small children (1 month to < 2 years of age) at the recommended dose is limited (n=46).

Table 8: Exposure (C_{max} and AUC[a]) in patients grouped by age group at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID

Age group	n=438[b]	Fold difference compared to patients ≥ 18 years of age[c]	
		C_{max}	AUC[a]
1 to < 3 months	12	3.2	4.5
3 to < 6 months	4	3.0	3.2
6 to < 12 months	19	2.1	1.7
1 to < 2 years	11	1.6	1.1
2 to < 6 years	37	1.6	1.1
6 to < 12 years	38	1.3	1.2
12 to < 18 years	32	0.9	0.8
≥ 18 years	285	1.0	1.0

[a] area under the plasma concentration-time curve at steady-state
[b] number of patients from 23 September 2024 data cut-off
[c] fold difference is the ratio of stated age group to ≥18 years group. A fold-difference of 1 equates to no difference.

Elderly
There is no clinically meaningful difference in larotrectinib exposure in patients > 65 years compared to those in younger patients (< 65 years).

Patients with hepatic impairment
A pharmacokinetic study was conducted in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, and in healthy adult control subjects with normal hepatic function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib $AUC_{0\text{-}inf}$ was observed in subjects with mild, moderate and severe hepatic impairment of 1.3, 2 and 3.2-fold respectively versus those with normal hepatic function. C_{max} was observed to increase slightly by 1.1, 1.1 and 1.5-fold respectively.

Patients with renal impairment
A pharmacokinetic study was conducted in subjects with end stage renal disease requiring dialysis, and in healthy adult control subjects with normal renal function matched for age, body mass index and sex. All subjects received a single 100 mg dose of larotrectinib. An increase in larotrectinib C_{max} and $AUC_{0\text{-}inf}$, of 1.25 and 1.46-fold respectively was observed in renally impaired subjects versus those with normal renal function.

Other special populations
Gender and race have no effect on the systemic exposure of larotrectinib based on population pharmacokinetic analysis.

5.3 Preclinical safety data

Systemic toxicity

Systemic toxicity was assessed in studies with daily oral administration up to 3 months in rats and monkeys. Dose limiting skin lesions were only seen in rats and were primarily responsible for mortality and morbidity. Skin lesions were not seen in monkeys.
Clinical signs of gastrointestinal toxicity were dose limiting in monkeys. In rats, severe toxicity (STD10) was observed at doses corresponding to 1- to 2-times the human AUC at the recommended clinical dose. No relevant systemic toxicity was observed in monkeys at doses which correspond to > 10-times the human AUC at the recommended clinical dose.

Embryotoxicity / Teratogenicity

Larotrectinib was not teratogenic and embryotoxic when dosed daily during the period of organogenesis to pregnant rats and rabbits at maternotoxic doses, i.e. corresponding to 32-times (rats) and 16-times (rabbits) the human AUC at the recommended clinical dose. Larotrectinib crosses the placenta in both species.

Reproduction toxicity

Fertility studies with larotrectinib have not been conducted. In 3-months toxicity studies, larotrectinib had no histological effect on the male reproductive organs in rats and monkeys at the highest tested doses corresponding to approximately 7-times (male rats) and 10-times (male monkeys) the human AUC at the recommended clinical dose. In addition, larotrectinib had no effect on spermatogenesis in rats.

In a 1-month repeat-dose study in rats, fewer corpora lutea, increased incidence of anestrus and decreased uterine weight with uterine atrophy were observed and these effects were reversible. No effects on female reproductive organs were seen in the 3-months toxicity studies in rats and monkeys at doses corresponding to approximately 3-times (female rats) and 17-times (female monkeys) the human AUC at the recommended clinical dose.
Larotrectinib was administered to juvenile rats from postnatal day (PND) 7 to 70. Pre-weaning mortality (before PND 21) was observed at the high dose level corresponding to 2.5- to 4-times the AUC at the recommended dose. Growth and nervous system effects were seen at 0.5- to 4-times the AUC at the recommended dose. Body weight gain was decreased in pre-weaning male and female pups, with a post-weaning increase in females at the end of exposure whereas reduced body weight gain was seen in males also post-weaning without recovery. The male growth reduction was associated with delayed puberty. Nervous system effects (i.e. altered hindlimb functionality and, likely, increases in eyelid closure) demonstrated partial recovery. A decrease in pregnancy rate was also reported despite normal mating at the high-dose level.

Genotoxicity and carcinogenicity

Carcinogenicity studies have not been performed with larotrectinib.
Larotrectinib was not mutagenic in bacterial reverse mutation (Ames) assays and in *in vitro* mammalian mutagenesis assays. Larotrectinib was negative in the *in vivo* mouse micronucleus test at the maximum tolerated dose of 500 mg/kg.

Safety pharmacology

The safety pharmacology of larotrectinib was evaluated in several *in vitro* and *in vivo* studies that assessed effects on the CV, CNS, respiratory, and GI systems in various species. Larotrectinib had no adverse effect on haemodynamic parameters and ECG intervals in telemetered monkeys at exposures (C_{max}) which are approximately 6-fold the human therapeutic exposures. Larotrectinib had no neurobehavioural findings in adult animals (rats, mice, cynomolgus monkeys) at exposure (C_{max}) at least 7-fold higher than the human exposure. Larotrectinib had no effect on respiratory function in rats; at exposures (C_{max}) at least 8-times the human therapeutic exposure. In rats, larotrectinib accelerated intestinal transit and increased gastric secretion and acidity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water
Hydroxypropylbetadex 0.69
Sucralose (E 955)
Sodium citrate (E 331)
Sodium benzoate (E 211)
Strawberry flavour
Citric acid (E 330)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening: 10 days.
Store in a refrigerator (2 °C - 8 °C).

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber glass (type III) bottle with a child-resistant polypropylene (PP) screw cap.

Each carton contains two bottles containing 50 mL oral solution each.

6.6 Special precautions for disposal and other handling

Instructions for use

Oral syringe

- Use a suitable oral syringe with CE marking and bottle adapter (28 mm diameter) if applicable.
  - For volumes less than 1 mL use a 1 mL oral syringe with 0.1 mL graduation.
  - For volumes of 1 mL and higher use a 5 mL oral syringe with 0.2 mL graduation.
- Open the bottle: press the bottle cap and turn it counter clockwise.
- Insert the bottle adapter into the bottle neck and ensure it is well fixed.
- Take the oral syringe and ensure that the plunger is fully depressed. Put the oral syringe in the adapter opening. Turn the bottle upside down.
- Fill the oral syringe with small amount of solution by pulling the plunger down, then push the plunger upwards to remove any bubbles.
- Pull the plunger down to the graduation mark equal to the quantity in mL as prescribed.
- Turn the bottle the right way up and remove the oral syringe from the bottle adapter.
- Slowly depress the plunger, directing the liquid towards the inside cheek to allow for natural swallowing.
- Close the bottle with the original bottle cap (leaving the adapter in place).

Nasogastric feeding tube

- Use a suitable nasogastric feeding tube. The outer diameter of the nasogastric feeding tube should be selected based on the patient characteristics. Typical tube diameter, tube lengths and derived prime volumes are presented in Table 9.
- The feeding should be stopped and the tube flushed with at least 10 mL water. NOTE: See exceptions regarding neonates and patients with fluid restrictions in the sub-point directly below.
- A suitable syringe should be used to administer VITRAKVI to the nasogastric feeding tube. The tube should be flushed again with at least 10 mL water to ensure VITRAKVI is delivered and to clear the tube.
  Neonates and children with fluid restrictions may require minimal flushing volume of 0.5 to 1 mL or flushing with air to deliver VITRAKVI.
- Restart the feeding.

Table 9: Recommended tube dimensions per age group

Patient	Tube diameter for standard feeds	Tube diameter for high density feeds	Tube length (cm)	Tube prime volume (mL)
Neonate	4-5 FR	6 FR	40-50	0.25-0.5
Children	6 FR	8 FR	50-80	0.7-1.4
Adult	8 FR	10 FR	80-120	1.4-4.2

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

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1385/004 – VITRAKVI 20 mg/mL oral solution

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2019
Date of latest renewal: 22 July 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further investigate the long-term toxicity and developmental effects of larotrectinib in paediatric patients, with particular focus on neurodevelopment including cognitive function, the MAH should submit the final report of study LOXO-TRK-15003 (SCOUT) including 5 year follow up data.	31 March 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 25 mg hard capsules
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains larotrectinib sulfate, equivalent to 25 mg of larotrectinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Swallow whole.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VITRAKVI 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 25 mg hard capsules
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains larotrectinib sulfate, equivalent to 25 mg of larotrectinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 100 mg hard capsules
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains larotrectinib sulfate, equivalent to 100 mg of larotrectinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Swallow whole.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VITRAKVI 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 100 mg hard capsules
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains larotrectinib sulfate, equivalent to 100 mg of larotrectinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 20 mg/mL oral solution
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral solution contains larotrectinib sulfate, equivalent to 20 mg of larotrectinib.

3. LIST OF EXCIPIENTS

Contains: sucrose, E 420, E 1520, E 218. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

100 mL oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 30 days of opening.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VITRAKVI 20 mg/mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 20 mg/mL oral solution
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral solution contains larotrectinib sulfate, equivalent to 20 mg of larotrectinib.

3. LIST OF EXCIPIENTS

Contains: sucrose, E 420, E 1520, E 218. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

100 mL oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 30 days of opening.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 20 mg/mL oral solution
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral solution contains larotrectinib sulfate, equivalent to 20 mg of larotrectinib.

3. LIST OF EXCIPIENTS

Contains: E 211. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

2 × 50 mL oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 10 days of opening.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VITRAKVI 20 mg/mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 20 mg/mL oral solution
larotrectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral solution contains larotrectinib sulfate, equivalent to 20 mg of larotrectinib.

3. LIST OF EXCIPIENTS

Contains: E 211. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

50 mL oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 10 days of opening.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/19/1385/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

VITRAKVI 25 mg hard capsules
VITRAKVI 100 mg hard capsules
larotrectinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace “you” with “your child” throughout.

What is in this leaflet:

1. What VITRAKVI is and what it is used for

What VITRAKVI is used for
VITRAKVI contains the active substance larotrectinib.

It is used in adults, adolescents and children to treat solid tumours (cancer) in various parts of the body that are caused by a change in the NTRK gene (neurotrophic tyrosine receptor kinase).
VITRAKVI is only used when
- these cancers are advanced or have spread to other parts of the body or if a surgery to remove the cancer is likely to cause severe complications **and**
- there are no satisfactory treatment options.

Before you are given VITRAKVI, your doctor will do a test to check if you have the change in the NTRK gene.

How VITRAKVI works
In patients whose cancer is due to an altered NTRK gene, the change in the gene causes the body to make an abnormal protein called TRK fusion protein, which can lead to uncontrolled cell growth and cancer. VITRAKVI blocks the action of TRK fusion proteins and so may slow or stop the growth of the cancer. It may also help to shrink the cancer.

If you have any questions on how VITRAKVI works or why it has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take VITRAKVI

Do not take VITRAKVI if
- you are allergic to larotrectinib or any of the other ingredients of this medicine (listed in section 6).

Tests and checks
VITRAKVI can increase the amount of the liver enzymes ALT and AST and bilirubin in your blood. Your doctor will do blood tests before and during treatment to check the level of ALT, AST and bilirubin and check how well your liver is working.

Other medicines and VITRAKVI
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This is because some medicines may affect the way VITRAKVI works or VITRAKVI may affect how other medicines work.
In particular, tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- medicines used to treat fungal or bacterial infections called itraconazole, voriconazole, clarithromycin, telithromycin, troleandomycin
- a medicine used to treat Cushing's syndrome called ketoconazole
- medicines used to treat HIV infection called atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, rifabutin, efavirenz
- a medicine used to treat depression called nefazodone
- medicines used to treat epilepsy called phenytoin, carbamazepine, phenobarbital
- a herbal medicine used to treat depression called St. John's wort
- a medicine used to treat tuberculosis called rifampicin
- a medicine used for strong pain relief called alfentanil
- medicines used to prevent organ rejection after an organ transplant called ciclosporin, sirolimus, tacrolimus
- a medicine used to treat an abnormal heart rhythm called quinidine
- medicines used to treat migraines called dihydroergotamine, ergotamine
- a medicine used to treat long-term pain called fentanyl
- a medicine used to control involuntary movements or sounds called pimozide
- a medicine to help you stop smoking called bupropion
- medicines to reduce blood sugar levels called repaglinide, tolbutamide
- a medicine that prevents blood clots called warfarin
- a medicine used to reduce the amount of acid produced in the stomach called omeprazole
- a medicine used to help control high blood pressure called valsartan
- a group of medicines used to help lower cholesterol called statins
- hormonal medicines used for contraception, see section "contraception – for men and women" below.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Taking VITRAKVI with food and drink
Do not eat grapefruit or drink grapefruit juice while taking VITRAKVI. This is because it may increase the amount of VITRAKVI in your body.

Pregnancy and breast-feeding
Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
You should not use VITRAKVI during pregnancy since the effect of VITRAKVI on the unborn is not known.

Breast-feeding
Do not breast-feed while taking this medicine and for 3 days after the last dose. This is because it is not known if VITRAKVI passes into breast milk.

Contraception – for men and women
You should avoid getting pregnant while taking this medicine.
If you are able to become pregnant, your doctor should do a pregnancy test before you start treatment.
You must use effective methods of contraception while taking VITRAKVI and for at least 1 month after the last dose, if

- you are able to become pregnant. If you use hormonal contraceptives, you should also use a barrier method, such as a condom.
- you have sex with a woman able to become pregnant.

Ask your doctor about the best method of contraception for you.

Driving, cycling and using machines
VITRAKVI may make you feel dizzy or tired. If this happens, do not drive, cycle or use any tools or machines.

3. How to take VITRAKVI

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
Adults (from 18 years)

- The recommended dose of VITRAKVI is 100 mg (1 capsule of 100 mg or 4 capsules of 25 mg), two times a day.
- Your doctor will review your dose and change it as needed.

Children and adolescents

- Your child's doctor will work out the right dose for your child based on their height and weight.
- The maximum recommended dose is 100 mg (1 capsule of 100 mg or 4 capsules of 25 mg), two times a day.
- Your child's doctor will review the dose and change it as needed.

An oral solution of VITRAKVI is available for patients who cannot swallow the capsules.

How to take this medicine

- VITRAKVI can be taken with or without food.
- Do not eat grapefruit or drink grapefruit juice while taking this medicine.
- Swallow the VITRAKVI capsules whole with a glass of water. Do not open, chew or crush the capsule as it has a very bitter taste.

If you take more VITRAKVI than you should
Talk to your doctor, pharmacist or nurse or go to a hospital straight away. Take the medicine pack and this leaflet with you.

If you miss a dose of VITRAKVI
Do not take a double dose to make up for a forgotten dose or if you vomit after taking this medicine. Take your next dose at the usual time.

If you stop taking VITRAKVI
Do not stop taking this medicine without talking to your doctor first. It is important to take VITRAKVI for as long as your doctor tells you.
If you are not able to take the medicine as your doctor prescribed talk to your doctor straight away.
If you have further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You should **immediately contact your doctor** if you experience any of the following **serious side effects:**
- feeling dizzy (very common side effect, may affect more than 1 in 10 people), tingling, feeling numb, or a burning feeling in your hands and feet, difficulty walking normally (common side effect, may affect up to 1 in 10 people). This could be symptoms of **nervous system problems.**

Your doctor may decide to lower the dose, or pause or stop the treatment.

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:
Very common (may affect more than 1 in 10 people):
- you may look pale and feel your heart pumping, which could be symptoms of low red blood cells (anaemia)
- flu like symptoms including fever, which could be symptoms of low white blood cells (neutropenia, leukopenia)
- feeling or being sick (nausea or vomiting)
- diarrhoea
- constipation
- muscle pain (myalgia)
- feeling tired (fatigue)
- increased amount of liver enzymes in blood tests
- weight increase.

Common (may affect up to 1 in 10 people):
- you may bruise or bleed more easily, which could be symptoms of reduced number of platelets (thrombocytopenia)
- change in how things taste (dysgeusia)
- muscle weakness
- increased amount of “alkaline phosphatase” in blood tests (very common in children).

Not known (not known how often they occur)
- you may experience a combination of tiredness, upper right stomach pain, loss of appetite, nausea or vomiting, yellowing of your skin or eyes, bruising or bleeding more easily, and dark urine. These could be symptoms of liver problems.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VITRAKVI

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and the bottle label after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not use this medicine if you notice that capsules look damaged.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What VITRAKVI contains
The active substance is larotrectinib.
Each VITRAKVI 25 mg capsule contains 25 mg of larotrectinib (as sulfate).
Each VITRAKVI 100 mg capsule contains 100 mg of larotrectinib (as sulfate).

The other ingredients are:
Capsule shell:
- Gelatin
- Titanium dioxide (E 171)

Printing ink:
- Shellac, bleached dewaxed
- Indigo carmine aluminium lake (E 132)
- Titanium dioxide (E 171)
- Propylene glycol (E 1520)
- Dimeticone 1000

What VITRAKVI looks like and the contents of the bottle
- VITRAKVI 25 mg is supplied as white opaque hard gelatine capsule, (18 mm long x 6 mm wide), with blue printing of BAYER-cross and “25 mg” on the body of the capsule
- VITRAKVI 100 mg is supplied as white opaque hard gelatine capsule, (22 mm long x 7 mm wide), with blue printing of BAYER-cross and “100 mg” on the body of the capsule

Each carton contains 1 child-resistant plastic bottle containing 56 hard gelatine capsules.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: Information for the patient

VITRAKVI 20 mg/mL oral solution
larotrectinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace "you" with "your child" throughout.

What is in this leaflet:

1. What VITRAKVI is and what it is used for

What VITRAKVI is used for
VITRAKVI contains the active substance larotrectinib.

It is used in adults, adolescents and children to treat solid tumours (cancer) in various parts of the body that are caused by a change in the NTRK gene (neurotrophic tyrosine receptor kinase).
VITRAKVI is only used when
- these cancers are advanced or have spread to other parts of the body or if a surgery to remove the cancer is likely to cause severe complications **and**
- there are no satisfactory treatment options.

Before you are given VITRAKVI, your doctor will do a test to check if you have the change in the NTRK gene.

How VITRAKVI works
In patients whose cancer is due to an altered NTRK gene, the change in the gene causes the body to make an abnormal protein called TRK fusion protein, which can lead to uncontrolled cell growth and cancer. VITRAKVI blocks the action of TRK fusion proteins and so may slow or stop the growth of the cancer. It may also help to shrink the cancer.

If you have any questions on how VITRAKVI works or why it has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take VITRAKVI

Do not take VITRAKVI if
- you are allergic to larotrectinib or any of the other ingredients of this medicine (listed in section 6).

Tests and checks
VITRAKVI can increase the amount of the liver enzymes ALT and AST and bilirubin in your blood. Your doctor will do blood tests before and during treatment to check the level of ALT, AST and bilirubin and check how well your liver is working.

Other medicines and VITRAKVI
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This is because some medicines may affect the way VITRAKVI works or VITRAKVI may affect how other medicines work.
In particular, tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- medicines used to treat fungal or bacterial infections called itraconazole, voriconazole, clarithromycin, telithromycin, troleandomycin
- a medicine used to treat Cushing's syndrome called ketoconazole
- medicines used to treat HIV infection called atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, rifabutin, efavirenz
- a medicine used to treat depression called nefazodone
- medicines used to treat epilepsy called phenytoin, carbamazepine, phenobarbital
- a herbal medicine used to treat depression called St. John's wort
- a medicine used to treat tuberculosis called rifampicin
- a medicine used for strong pain relief called alfentanil
- medicines used to prevent organ rejection after an organ transplant called ciclosporin, sirolimus, tacrolimus
- a medicine used to treat an abnormal heart rhythm called quinidine
- medicines used to treat migraines called dihydroergotamine, ergotamine
- a medicine used to treat long-term pain called fentanyl
- a medicine used to control involuntary movements or sounds called pimozide
- a medicine to help you stop smoking called bupropion
- medicines to reduce blood sugar levels called repaglinide, tolbutamide
- a medicine that prevents blood clots called warfarin
- a medicine used to reduce the amount of acid produced in the stomach called omeprazole
- a medicine used to help control high blood pressure called valsartan
- a group of medicines used to help lower cholesterol called statins
- hormonal medicines used for contraception, see section "contraception – for men and women" below.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Taking VITRAKVI with food and drink
Do not eat grapefruit or drink grapefruit juice while taking VITRAKVI. This is because it may increase the amount of VITRAKVI in your body.

Pregnancy and breast-feeding
Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
You should not use VITRAKVI during pregnancy since the effect of VITRAKVI on the unborn is not known.

Breast-feeding
Do not breast-feed while taking this medicine and for 3 days after the last dose. This is because it is not known if VITRAKVI passes into breast milk.

Contraception – for men and women
You should avoid getting pregnant while taking this medicine.
If you are able to become pregnant, your doctor should do a pregnancy test before you start treatment.
You must use effective methods of contraception while taking VITRAKVI and for at least 1 month after the last dose, if
- you are able to become pregnant. If you use hormonal contraceptives, you should also use a barrier method, such as a condom.
- you have sex with a woman able to become pregnant.

Ask your doctor about the best method of contraception for you.

Driving, cycling and using machines
VITRAKVI may make you feel dizzy or tired. If this happens, do not drive, cycle or use any tools or machines.

VITRAKVI contains:
- **sucrose**: it may be harmful to the teeth. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
- 22 mg **sorbitol** in 1 mL. Sorbitol is a source of fructose. If your doctor has told you that you or your child have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you or your child take or receive this medicine.
- less than 1 mmol (or 23 mg) of **sodium** per 5 mL, that is to say essentially 'sodium free'.
- 1.2 mg **propylene glycol** in 1 mL. If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.
- **parahydroxybenzoate**: it may cause allergic reactions (possibly delayed).

3. How to take VITRAKVI

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
Adults (from 18 years)
- The recommended dose of VITRAKVI is 100 mg (5 mL), two times a day.
- Your doctor will review your dose and change it as needed.

Children and adolescents
- Your child's doctor will work out the right dose for your child based on their height and weight.
- The maximum recommended dose is 100 mg (5 mL), two times a day.
- Your child's doctor will review the dose and change it as needed.

How to take this medicine
- VITRAKVI can be taken with or without food.
- Do not eat grapefruit or drink grapefruit juice while taking this medicine.
- Along with this medicine you need a bottle adapter (28 mm diameter) and a syringe that can be used to give medicines by mouth. Use a 1 mL syringe with 0.1 mL marks for doses less than 1 mL. Use a 5 mL syringe with 0.2 mL marks for doses of 1 mL or more.
  - Press the bottle cap and turn it anti-clockwise to open the bottle.
  - Put the bottle adapter into the bottle neck and make sure it is well fixed.
  - Push the plunger fully into the syringe and then put the syringe in the adapter opening. Turn the bottle upside down.
  - Fill the syringe with a small amount of solution by pulling the plunger down, then push the plunger upwards to remove any large bubbles that are in the syringe.
  - Pull the plunger down to the mark equal to the dose in mL prescribed by your doctor.
  - Turn the bottle the right way up and take the syringe out of the adapter.
  - Put the syringe in the mouth, pointing towards the inside of the cheek – this will help you swallow the medicine naturally. Slowly press the plunger in.
  - Put the bottle cap on and tightly close the bottle - leave the adapter in the bottle.

  If necessary, VITRAKVI may be administered via a nasogastric feeding tube. For details how to do so, please ask your doctor, pharmacist or nurse.

If you take more VITRAKVI than you should
Talk to your doctor, pharmacist or nurse or go to a hospital straight away. Take the medicine pack and this leaflet with you.

If you miss a dose of VITRAKVI
Do not take a double dose to make up for a forgotten dose or if you vomit after taking this medicine. Take your next dose at the usual time.

If you stop taking VITRAKVI
Do not stop taking this medicine without talking to your doctor first. It is important to take VITRAKVI for as long as your doctor tells you.
If you are not able to take the medicine as your doctor prescribed talk to your doctor straight away.
If you have further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You should **immediately contact your doctor** if you experience any of the following **serious side effects:**
- feeling dizzy (very common side effect, may affect more than 1 in 10 people), tingling, feeling numb, or a burning feeling in your hands and feet, difficulty walking normally (common side effect, may affect up to 1 in 10 people). This could be symptoms of **nervous system problems.**

Your doctor may decide to lower the dose, or pause or stop the treatment.

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:
Very common (may affect more than 1 in 10 people):
- you may look pale and feel your heart pumping, which could be symptoms of low red blood cells (anaemia)
- flu like symptoms including fever, which could be symptoms of low white blood cells (neutropenia, leukopenia)
- feeling or being sick (nausea or vomiting)
- diarrhoea
- constipation
- muscle pain (myalgia)
- feeling tired (fatigue)
- increased amount of liver enzymes in blood tests
- weight increase.

Common (may affect up to 1 in 10 people):
- you may bruise or bleed more easily, which could be symptoms of reduced number of platelets (thrombocytopenia)
- change in how things taste (dysgeusia)
- muscle weakness
- increased amount of "alkaline phosphatase" in blood tests (very common in children).

Not known (not known how often they occur)
- you may experience a combination of tiredness, upper right stomach pain, loss of appetite, nausea or vomiting, yellowing of your skin or eyes, bruising or bleeding more easily, and dark urine. These could be symptoms of liver problems.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VITRAKVI

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and the bottle label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C - 8 °C).
- Do not freeze.
- Once the bottle is open, you must use your medicine within 30 days of opening.
- Do not take the medicine if the bottle or bottle screw cap looks damaged or looks like it has leaked.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What VITRAKVI contains
The active substance is larotrectinib.
Each mL of oral solution contains 20 mg of larotrectinib (as sulfate).

The other ingredients are:
- 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

See “VITRAKVI contains” in section 2 for more information.

What VITRAKVI looks like and the contents of the bottle
VITRAKVI is a clear yellow to orange oral solution.

Each carton contains 1 child-resistant glass bottle containing 100 mL oral solution.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: Information for the patient

VITRAKVI 20 mg/mL oral solution
larotrectinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace "you" with "your child" throughout.

What is in this leaflet:

1. What VITRAKVI is and what it is used for

What VITRAKVI is used for
VITRAKVI contains the active substance larotrectinib.

It is used in adults, adolescents and children to treat solid tumours (cancer) in various parts of the body that are caused by a change in the NTRK gene (neurotrophic tyrosine receptor kinase).
VITRAKVI is only used when
- these cancers are advanced or have spread to other parts of the body or if a surgery to remove the cancer is likely to cause severe complications **and**
- there are no satisfactory treatment options.

Before you are given VITRAKVI, your doctor will do a test to check if you have the change in the NTRK gene.

How VITRAKVI works
In patients whose cancer is due to an altered NTRK gene, the change in the gene causes the body to make an abnormal protein called TRK fusion protein, which can lead to uncontrolled cell growth and cancer. VITRAKVI blocks the action of TRK fusion proteins and so may slow or stop the growth of the cancer. It may also help to shrink the cancer.

If you have any questions on how VITRAKVI works or why it has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take VITRAKVI

Do not take VITRAKVI if
- you are allergic to larotrectinib or any of the other ingredients of this medicine (listed in section 6).

Tests and checks
VITRAKVI can increase the amount of the liver enzymes ALT and AST and bilirubin in your blood. Your doctor will do blood tests before and during treatment to check the level of ALT, AST and bilirubin and check how well your liver is working.

Other medicines and VITRAKVI
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This is because some medicines may affect the way VITRAKVI works or VITRAKVI may affect how other medicines work.
In particular, tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- medicines used to treat fungal or bacterial infections called itraconazole, voriconazole, clarithromycin, telithromycin, troleandomycin
- a medicine used to treat Cushing's syndrome called ketoconazole
- medicines used to treat HIV infection called atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, rifabutin, efavirenz
- a medicine used to treat depression called nefazodone
- medicines used to treat epilepsy called phenytoin, carbamazepine, phenobarbital
- a herbal medicine used to treat depression called St. John's wort
- a medicine used to treat tuberculosis called rifampicin
- a medicine used for strong pain relief called alfentanil
- medicines used to prevent organ rejection after an organ transplant called ciclosporin, sirolimus, tacrolimus
- a medicine used to treat an abnormal heart rhythm called quinidine
- medicines used to treat migraines called dihydroergotamine, ergotamine
- a medicine used to treat long-term pain called fentanyl
- a medicine used to control involuntary movements or sounds called pimozide
- a medicine to help you stop smoking called bupropion
- medicines to reduce blood sugar levels called repaglinide, tolbutamide
- a medicine that prevents blood clots called warfarin
- a medicine used to reduce the amount of acid produced in the stomach called omeprazole
- a medicine used to help control high blood pressure called valsartan
- a group of medicines used to help lower cholesterol called statins
- hormonal medicines used for contraception, see section "contraception – for men and women" below.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Taking VITRAKVI with food and drink
Do not eat grapefruit or drink grapefruit juice while taking VITRAKVI. This is because it may increase the amount of VITRAKVI in your body.

Pregnancy and breast-feeding
Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
You should not use VITRAKVI during pregnancy since the effect of VITRAKVI on the unborn is not known.

Breast-feeding
Do not breast-feed while taking this medicine and for 3 days after the last dose. This is because it is not known if VITRAKVI passes into breast milk.

Contraception – for men and women
You should avoid getting pregnant while taking this medicine.
If you are able to become pregnant, your doctor should do a pregnancy test before you start treatment.
You must use effective methods of contraception while taking VITRAKVI and for at least 1 month after the last dose, if
- you are able to become pregnant. If you use hormonal contraceptives, you should also use a barrier method, such as a condom.
- you have sex with a woman able to become pregnant.

Ask your doctor about the best method of contraception for you.

Driving, cycling and using machines
VITRAKVI may make you feel dizzy or tired. If this happens, do not drive, cycle or use any tools or machines.

VITRAKVI contains:
- 2 mg **sodium benzoate** in 1 mL.
- less than 1 mmol (or 23 mg) of **sodium** per 5 mL, that is to say essentially 'sodium free'.

3. How to take VITRAKVI

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
Adults (from 18 years)
- The recommended dose of VITRAKVI is 100 mg (5 mL), two times a day.
- Your doctor will review your dose and change it as needed.

Children and adolescents
- Your child's doctor will work out the right dose for your child based on their height and weight.
- The maximum recommended dose is 100 mg (5 mL), two times a day.
- Your child's doctor will review the dose and change it as needed.

How to take this medicine
- VITRAKVI can be taken with or without food.
- Do not eat grapefruit or drink grapefruit juice while taking this medicine.
- Along with this medicine you need a bottle adapter (28 mm diameter) and a syringe that can be used to give medicines by mouth. Use a 1 mL syringe with 0.1 mL marks for doses less than 1 mL. Use a 5 mL syringe with 0.2 mL marks for doses of 1 mL or more.
  - Press the bottle cap and turn it anti-clockwise to open the bottle.
  - Put the bottle adapter into the bottle neck and make sure it is well fixed.
  - Push the plunger fully into the syringe and then put the syringe in the adapter opening. Turn the bottle upside down.
  - Fill the syringe with a small amount of solution by pulling the plunger down, then push the plunger upwards to remove any large bubbles that are in the syringe.
  - Pull the plunger down to the mark equal to the dose in mL prescribed by your doctor.
  - Turn the bottle the right way up and take the syringe out of the adapter.
  - Put the syringe in the mouth, pointing towards the inside of the cheek – this will help you swallow the medicine naturally. Slowly press the plunger in.
  - Put the bottle cap on and tightly close the bottle - leave the adapter in the bottle.

  If necessary, VITRAKVI may be administered via a nasogastric feeding tube. For details how to do so, please ask your doctor, pharmacist or nurse.

If you take more VITRAKVI than you should
Talk to your doctor, pharmacist or nurse or go to a hospital straight away. Take the medicine pack and this leaflet with you.

If you miss a dose of VITRAKVI
Do not take a double dose to make up for a forgotten dose or if you vomit after taking this medicine. Take your next dose at the usual time.

If you stop taking VITRAKVI
Do not stop taking this medicine without talking to your doctor first. It is important to take VITRAKVI for as long as your doctor tells you.
If you are not able to take the medicine as your doctor prescribed talk to your doctor straight away.
If you have further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You should **immediately contact your doctor** if you experience any of the following **serious side effects:**
- feeling dizzy (very common side effect, may affect more than 1 in 10 people), tingling, feeling numb, or a burning feeling in your hands and feet, difficulty walking normally (common side effect, may affect up to 1 in 10 people). This could be symptoms of **nervous system problems.**

Your doctor may decide to lower the dose, or pause or stop the treatment.

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:
Very common (may affect more than 1 in 10 people):
- you may look pale and feel your heart pumping, which could be symptoms of low red blood cells (anaemia)
- flu like symptoms including fever, which could be symptoms of low white blood cells (neutropenia, leukopenia)
- feeling or being sick (nausea or vomiting)
- diarrhoea
- constipation
- muscle pain (myalgia)
- feeling tired (fatigue)
- increased amount of liver enzymes in blood tests
- weight increase.

Common (may affect up to 1 in 10 people):
- you may bruise or bleed more easily, which could be symptoms of reduced number of platelets (thrombocytopenia)
- change in how things taste (dysgeusia)
- muscle weakness
- increased amount of “alkaline phosphatase” in blood tests (very common in children).

Not known (not known how often they occur)
- you may experience a combination of tiredness, upper right stomach pain, loss of appetite, nausea or vomiting, yellowing of your skin or eyes, bruising or bleeding more easily, and dark urine. These could be symptoms of liver problems.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VITRAKVI

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and the bottle label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C - 8 °C).
- Do not freeze.
- Once the bottle is open, you must use your medicine within 10 days of opening.
- Do not take the medicine if the bottle or bottle screw cap looks damaged or looks like it has leaked.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What VITRAKVI contains
The active substance is larotrectinib.
Each mL of oral solution contains 20 mg of larotrectinib (as sulfate).

The other ingredients are:
- Purified water
- Hydroxypropylbetadex 0.69
- Sucralose (E 955)
- Sodium citrate (E 331)
- Sodium benzoate (E 211)
- Strawberry flavour
- Citric acid (E 330)

See “VITRAKVI contains” in section 2 for more information.

What VITRAKVI looks like and the contents of the bottle
VITRAKVI is a colourless to yellow or orange or red or brownish oral solution.

Each carton contains 2 child-resistant glass bottles containing 50 mL oral solution each.

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Germany

Manufacturer
Bayer AG
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51368 Leverkusen
Germany

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.