1. NAME OF THE MEDICINAL PRODUCT

VITRAKVI 25 mg hard capsules

VITRAKVI 100 mg hard capsules

VITRAKVI 20 mg/ml oral solution

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 capsules

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

VITRAKVI 20 mg/ml oral solution

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

3. PHARMACEUTICAL FORM

VITRAKVI 25 mg hard capsules

White opaque hard gelatin capsule, size 2, with blue printing of "BAYER" cross and "25 mg" on body of capsule

VITRAKVI 100 mg hard capsules

White opaque hard gelatin capsule, size 0, with blue printing of "BAYER" cross and "100 mg" on body of capsule

VITRAKVI 20 mg/mL oral solution

2x50 mL colourless to yellow or orange or red or brownish solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indication(s)

VITRAKVI as monotherapy is indicated for the treatment of adult and pediatric patients with solid tumors

- that display a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation,

• 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

4.2 Posology and method of administration

Confirm the presence of an NTRK gene fusion in a tumor specimen prior to initiation of treatment with VITRAKVI.

4.2.1 Dosage regimen

Adults

The recommended dose of VITRAKVI in adults is 100 mg taken orally, twice daily until disease progression or until unacceptable toxicity occurs.

Pediatric

Dosing in pediatric patients is based on body surface area (BSA). The recommended dose of VITRAKVI in pediatric patients is 100 mg/m^2 taken orally, 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 dosage modification if resolution occurs within 4 weeks.
- VITRAKVI should be permanently discontinued if an adverse reaction does not resolve within 4 weeks.

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

Table 1 Recommended Dose Modifications for VITRAKVI for Adverse Reactions

Dosage Modification	Adult and Pediatric Patients with Body Surface Area of at Least 1.0 m^2	Pediatric Patients with Body Surface Area Less Than 1.0 m^2
First	75 mg orally twice daily	75 mg/m^2 orally twice daily
Second	50 mg orally twice daily	50 mg/m^2 orally twice daily
Third	100 mg orally once daily	25 mg/m^2 orally 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 than 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 necessary 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 *(*see section 5.2). No dose adjustment is required in patients with mild (Child-Pugh A) hepatic impairment (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 coadministration of a strong CYP3A4 inhibitor cannot be avoided, reduce the VITRAKVI dose by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the VITRAKVI 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.

Capsule
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.

Oral Solution
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.
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 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 adult patients.
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 child bearing 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).

Risk of jaundice in newborn babies due to sodium benzoate in Vitrakvi Oral Solution

Vitrakvi oral solution contains 2 mg sodium benzoate in each mL oral solution which is equivalent to 20 mg/m^2 per day. Sodium benzoate may increase jaundice in newborn babies (up to 4 weeks old). Increase in bilirubinaemia following bilirubin displacement from albumin by benzoic acid and benzoates may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

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 CYP3A4 inhibitors, P-gp and BCRP inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin,

troleandomycin, voriconazole, grapefruit or grapefruit juice) may increase larotrectinib plasma concentrations.

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 rifampin (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 Inducer on larotrectinib

Co-administration of VITRAKVI with strong or moderate CYP3A inducers and strong P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, or St. John's Wort) may decrease larotrectinib plasma concentrations and should be avoided.

Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg VITRAKVI dose with rifampin (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 CYP3A4 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 CYP3A4.

Exercise caution with concomitant use of CYP3A4 substrates with narrow therapeutic range (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus) in patients taking VITRAKVI. If concomitant use of these CYP3A4 substrates with narrow therapeutic range is required in patients taking VITRAKVI, dose modification of the CYP3A4 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Based on the mechanism of action and non-clinical data, there may be a risk of fetal harm 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 child-bearing potential, advise use of highly effective contraception during treatment with VITRAKVI and for at least one month after the final dose.

Pregnancy

There are no clinical data on the use of larotrectinib in pregnant women. In embryo-fetal development studies where pregnant rats and rabbits were dosed with larotrectinib during the period of organogenesis, malformations were observed at maternal exposures that were approximately 9- and 0.6- times, respectively, those observed at the clinical dose of 100 mg twice daily. VITRAKVI crosses the placenta in animals.

Based on its mechanism of action and non-clinical data, there may be risk of fetal harm when larotrectinib is administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Breast-feeding

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

Fertility

There are no clinical data on the effect of larotrectinib on fertility. Non-clinical fertility studies with larotrectinib have not been conducted; however, changes to the female reproductive organs in rats were observed in a repeated-dose toxicity study (see section 5.3).

4.7 Effects on ability to drive or 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 (33%), increased AST (31%), vomiting (28%), anaemia (27%), constipation (27%), diarrhoea (25%), nausea (23%), fatigue (22%), 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%) and ALT increased, AST increased, leucocyte 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 (4%), diarrhoea (3%), gait disturbance (1%), and fatigue, dizziness, paraesthesia, nausea, myalgia, and vomiting (each in < 1%).
Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions occurred in 2% of patients (2 cases of neutrophil count decreased, 1 case each of ALT increased, AST increased, gait disturbance, vomiting, muscular weakness, fatigue, and nausea). 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 335 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: 0.1, 90) with 37% of patients being paediatric patients. Median time on treatment for the overall safety population (n=335) was 14.5 months (range: 0.0, 75.2).

The adverse drug reactions reported in patients (n=335) 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=335) 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]
	Uncommon		Leukocyte count decreased (Leukopenia)[a, b] Platelet count decreased (Thrombocytopenia)[a]
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
	Uncommon		Vomiting Nausea
Hepatobiliary disorders	Not known	Liver injury[d]	Liver injury[a]
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=124); all grades

System organ class	Frequency	Infants and toddlers (n=42)[a]	Children (n=59)[b]	Adolescents (n=23)[c]	Paediatric patients (n=124)
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	
	Common		Muscular weakness	Muscular weakness	Myalgia 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)	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased

	Common		Blood alkaline phosphatase increased	Weight increased (Abnormal weight gain)	

[a] Infant/toddlers (28 days to 23 months): 5 grade 4 Neutrophil count decreased (Neutropenia) and 2 Blood alkaline phosphatase increased reaction reported. Grade 3 reactions included 12 cases of Neutrophil count decreased (Neutropenia), 3 cases each of anaemia, ALT increased, and Weight increased (Abnormal weight gain) and 2 cases each of Blood alkaline phosphatase increased, Diarrhoea, and Vomiting and 1 case of AST increased.

[b] Children (2 to 11 years): 1 grade 4 Leucocytes count decreased reported. 6 reported grade 3 cases of Neutrophil count decreased (Neutropenia), 2 cases each of Anaemia and Diarrhoea, and 1 case each of ALT increased, AST increased, Gait disturbance, Vomiting, Weight increased (Abnormal weight gain), 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 Fatigue, Gait disturbance, and Muscular weakness.

4.8.1 Description of selected adverse reactions

Neurologic Reactions

In the overall safety database (n=335), 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%) 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=335), the maximum grade transaminase elevation observed was grade 4 ALT increase in 6 patients (2%) and AST increase in 3 patients (1%). Grade 3 ALT and AST increases in 17 (5%) and 16 (5%) 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 34 (10%) and 32 (10%) of patients, respectively, and grade 1 ALT and AST increases were observed in 157 (47%) and 158 (47%) of patients, respectively.

ALT and AST increases leading to dose modifications or interruptions occurred in 13 (5%) patients and 12 (5%) patients, respectively (see section 4.4). One patient permanently discontinued the treatment due to grade 3-4 ALT and 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 adult patients. 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

Pediatric patients

Of the 335 patients treated with VITRAKVI, 124 (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=8 ≥ 12 months to < 2 years, n=27 ≥ 2 years to < 6 years, n=32 ≥ 6 years to < 12 years, n=23 ≥ 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 69% of patients from birth to < 3 months and in 48% 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 335 patients in the overall safety population who received VITRAKVI, 65 (19%) patients were 65 years or older and 20 (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 (32% versus 28% in all adults), anaemia (32% versus 25% in all adults), muscular weakness (14% versus 11% in all adults), and gait disturbance (8% versus 5% in all adults) were more frequent in patients of 65 years or older.

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

5.1.1 Mechanism of action

Larotrectinib is an adenosine triphosphate (ATP)-competitive and selective TRK kinase inhibitor that was rationally designed to avoid activity with off-target kinase. 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 IC50 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 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 and there was no relationship between exposure (C_{max}) and changes in the QT interval. The 200 mg dose corresponds to a peak exposure (Cmax) 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 Cmax, 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). The studies are 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 272 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 2022. 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, 41 patients with primary CNS tumours and measurable disease at baseline were treated in Study 2 ("NAVIGATE") and in Study 3 ("SCOUT"). Forty of the 41 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 276 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)	Soft tissue sarcoma (n=27) Thyroid (n=25)[b] NSCLC (n=24)[b, c] Salivary gland (n=22) Colon (n=18) Primary CNS (n=15) Melanoma (n=8)[b] Pancreas (n=6) Breast, non-secretory (n=6)[b] Breast, secretory (n=4) Cholangiocarcinoma (n=4) GIST (n=3)[a] Prostate (n=2) Appendix, Atypical carcinoid lung cancer, Bone sarcoma, Cervix ,Hepatic[e] , Duodenal, External auditory canal[b], Gastric, Oesophageal, SCLC [b, d], Rectal, Thymus, Unknown primary cancer, Urothelial, Uterus (n=1 each)	179

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 ≥ 1 month 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=39)[b] Primary CNS (n=26) Congenital mesoblastic nephroma (n=2) Bone sarcoma (n=2) Thyroid (n=1) Melanoma (n=1) Breast, secretory (n=1)	121
Total number of patients (n)[*]			313

[*] consist of 272 patients with IRC tumour response assessment and 41 patients with primary CNS tumours (including astrocytoma, ganglioglioma, glioblastoma, glioma, glioneuronal tumours, neuronal and mixed neuronal-glial tumours, 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, and soft tissue sarcoma

[c] NSCLC: non-small cell lung cancer

[d] SCLC: small cell lung cancer

[e] hepatocellular carcinoma

Baseline characteristics for the pooled 272 patients with solid tumours with an *NTRK* gene fusion were as follows: median age 41 years (range 0-90 years); 35% < 18 years of age, and 65% ≥ 18 years; 57% white and 49% male; and ECOG PS 0-1 (89%), 2 (9%), or 3 (2%). Ninety-two 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-six percent of all patients had received no prior systemic therapy. Of these 272 patients the most common tumour types represented were soft tissue sarcoma (25%), infantile fibrosarcoma (18%), thyroid cancer (11%), lung cancer (10%), and salivary gland tumour (9%).

Baseline characteristics for the 41 patients with primary CNS tumours with an *NTRK* gene fusion assessed by investigator were as follows: median age 11 years (range 1-79 years); 28 patients < 18 years of age, and 13 patients ≥ 18 years, and 28 patients white and 20 patients male; and ECOG PS 0-1 (36 patients), or 2 (4 patients). Forty (98%) 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=272) and with post-hoc addition of primary CNS tumours (n=41) resulting in the pooled population (n=313), 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=272)**[a]	**Analysis in solid tumours including primary CNS tumours (n=313)**[a, b]
Overall response rate (ORR) % (n) [95% CI]	67% (182) [61, 72]	61% (191) [55, 66]
Complete response (CR)	23% (62)	20% (63)
Pathological complete response[c]	5% (13)	4% (13)
Partial response (PR)	39% (107)	37% (115)
Time to first response (median, months) [range]	1.84 [0.89, 22.90]	1.84 [0.89, 22.90]
Duration of response (median, months) [range] % with duration ≥ 12 months % with duration ≥ 24 months % with duration ≥ 36 months	43.3 [0.0+, 65.4+] 80% 66% 54%	41.5 [0.0+, 65.4+] 79% 64% 52%

+ denotes ongoing

[a] Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (272 patients).

[b] Investigator assessment using either RANO or RECIST v1.1 criteria for primary CNS tumours (41 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=313)	ORR[a]		DOR			
		%	95% CI	months			Range (months)
				≥ 12	≥ 24	≥ 36	
Soft tissue sarcoma	68	68%	55%, 78%	84%	70%	49%	0.03+, 65.5
Infantile fibrosarcoma	49	92%	80%, 98%	80%	60%	53%	1.6+, 64.2+
Primary CNS	41	22%	11%, 38%	60%	50%	50%	3.5, 39.4+
Thyroid	30	63%	44%, 80%	89%	65%	54%	3.7+, 64.3+
Lung	27	74%	54%, 89%	72%	56%	42%	1.9+, 45.1+
Salivary gland	25	84%	64%, 95%	90%	86%	74%	7.4, 59.1+
Colon	18	50%	26%, 74%	86%	86%	43%	5.2, 39.4
Breast	11						
Non-secretory[c]	6	50%	12%, 88%	67%	67%	67%	7.4, 45.3+
Secretory[b]	5	80%	28%, 99%	75%	75%	NR	11.1+, 31.5
Melanoma	9	44%	14%, 79%	50%	NR	NR	1.9+, 23.2+
Pancreas	6	17%	0%, 64%	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%	100%	29.4+, 44.5

DOR: duration of response
NR: not reached
* no data are available for the following tumour types: cholangiocarcinoma (n=4); prostate, unknown primary cancer (n=2 each); appendix, cervix, hepatic, duodenal, external auditory canal, gastric, oesophageal, rectal, 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 per investigator assessment using either RANO or RECIST v1.1 criteria
[b] with 3 complete, 1 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=178), the ORR was 58%. In the paediatric sub-population (n=94), the ORR was 84%.

In 238 patients with wide molecular characterisation before larotrectinib treatment, the ORR in 128 patients who had other genomic alterations in addition to *NTRK* gene fusion was 52%, and in 110 patients without other genomic alterations ORR was 76%.

Pooled primary analysis set

The pooled primary analysis set consisted of 272 patients and did not include primary CNS tumours. Median time on treatment before disease progression was 19.6 months (range: 0.10 to 75.2 months) based on July 2022 cut-off. Fifty-seven percent of patients had received VITRAKVI for 12 months or more, 34% had received VITRAKVI 24 months or more, and 21% had received VITRAKVI 36 months or more, with follow-up ongoing at the time of the analysis.
At the time of analysis, the median duration of response is 43.3 months (range: 0.0+ to 65.4+) an estimated 80% [95% CI: 74, 86] of responses lasted 12 months or longer, 66% [95% CI: 58, 74] of responses lasted 24 months or longer, and 51% [95% CI: 42, 60] of responses lasted 36 months or longer. Eighty-six percent (86%) [95% CI: 82, 90] of patients treated were alive one year after the start of therapy, 77% [95% CI: 72, 82] after two years after the start of therapy, and 72% [95% CI: 66, 78] after three years with the median for overall survival not yet being reached. Median progression free survival was 30.8 months at the time of analysis, with a progression free survival rate of 65% [95% CI: 59, 71] after 1 year, 56% [95% CI: 49, 62] after 2 years, and 43% [95% CI: 36, 50] after 3 years.
The median change in tumour size in the pooled primary analysis set was a decrease of 79%.

Patients with primary CNS tumours

At the time of data cut-off, of the 41 patients with primary CNS tumours confirmed response was observed in 9 patients (22%) with 1 of the 41 patients (2%) being complete responders and 8 patients (20%) being partial responders. Further 20 patients (49%) had stable disease. Twelve patients (29%) had progressive disease. At the time of data cut-off, time on treatment ranged from 1.7 to 50.9 months and was ongoing in 13 out of 41 patients, with one of these patients receiving post-progression treatment.

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; C_{max} was 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 tract (GI) 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 metabolized predominantly by CYP3A4/5 *in vitro*. Following oral administration of a single 100 mg dose of radiolabeled 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 radiolabeled larotrectinib to healthy adult subjects, 58% of the administered radioactivity was recovered in feces 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 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

Pediatric patients

Based on population pharmacokinetic analyses exposure (C_{max} and AUC) in paediatric patients (1 month to <3 months of age) at the recommended dose of 100 mg/m^2 with a maximum of 100 mg BID was 3-fold higher than in adults (≥18 years of age) given the dose of 100 mg BID. At the recommended dose, the C_{max} in paediatric patients (≥3 months to <12 years of age) was higher than in adults, but the AUC was similar to that in adults. For paediatric patients older than 12 years of age, the recommended dose is likely to give similar C_{max} and AUC as observed in adults.

Data defining exposure in small children (1 month to <6 years of age) at the recommended dose is limited (n=33).

Elderly

There are limited data in elderly. PK data is available only in 2 patients over 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 did not appear to influence larotrectinib pharmacokinetics to a clinically significant extent. There was not enough data to investigate the potential influence of race on the systemic exposure of larotrectinib.

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 exposures 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.

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 (rat, mouse, dog, cynomolgus monkey). Larotrectinib had no adverse effects on hemodynamic parameters and ECG intervals in telemetered monkeys at exposures (C_{max}) which are approximately 6-fold the human therapeutic exposures. Larotrectinib had no neurobehavioral findings in rats and did not affect neuromuscular function in mice. In a juvenile toxicity study in rats, a low incidence of transient central nervous system-related signs including head flick and circling, increased escape time and number of errors in a maze swim test when the original path is reversed, skin lesions, and swollen abdomen (females) were observed at a dose corresponding to approximately 3-times (AUC) the human therapeutic exposure. Larotrectinib had no effects on respiratory function in rats; at exposures (C_{max}) at least 8-times the human therapeutic exposures. In rats, larotrectinib accelerated intestinal transit and increased gastric secretion and acidity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules

Gelatin (sourced from combine porcine and/or bovine origin)

Titanium dioxide

Printing ink - blue: Shellac, FD&C Blue # 2 aluminum lake, titanium dioxide, propylene glycol, ammonia solution, dimethicone

Oral solution

Purified water

Hydroxypropyl betadex

Sodium citrate

Sodium benzoate

Citric acid

Sucralose

Strawberry flavour

Maltodextrin

Triethyl citrate

Flavouring substances

Water

Propylene glycol

Flavouring preparations

6.2 Shelf life

Capsules

36 month

Oral solution

24 months.
Discard any unused VITRAKVI oral solution remaining after 30 days of first opening the first bottle.

6.3 Special precautions for storage

Capsules

Do not store above 30°C

Oral solution

Store solution refrigerated at 2° to 8° C. Do not freeze.

6.4 Nature and contents of container

Capsules

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

Each carton contains one bottle of 56 hard capsules.

Oral solution

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

Each carton contains two bottles of 50 mL oral solution.

7 Product Owner

Bayer AG

Kaiser-Wilhelm-Allee 1, 51373 Leverkusen, Germany

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