

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, 1.2mg 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/m² 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. Patients with Grade 2 ALT and/or AST increases, should be followed with serial laboratory evaluations every one to two weeks after the observation of Grade 2 toxicity until resolved to establish whether a dose interruption or reduction is required.

For Grade 3 or 4 adverse reactions:

- 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 m²	Paediatric patients with body surface area less than 1.0 m²
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

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

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).

Transaminase elevations

ALT and AST increase were reported in patients receiving larotrectinib (see section 4.8). The majority of ALT and AST increases occurred in the first 3 months of treatment.

Liver function including ALT and AST assessments should be monitored before the first dose and monthly for the first 3 months of treatment, then periodically during treatment, with more frequent testing in patients who develop transaminase elevations. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, the VITRAKVI dose should be modified when resumed (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).

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 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 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 inducers on larotrectinib

Co-administration of VITRAKVI with strong or moderate CYP3A and P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, 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 rifampin (a strong CYP3A and P-gp inducer) 600 mg twice 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 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.

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 the 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 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 ($\geq 20\%$) of VITRAKVI in order of decreasing frequency were increased ALT (32%), fatigue (30%), constipation (29%), increased AST (27%), dizziness (26%), vomiting (23%), anaemia (23%), and nausea (22%).

The majority of adverse reactions were Grade 1 or 2. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (1%) ALT increased (1%) and AST increased ($<1\%$). The highest reported grade was Grade 3 for adverse reactions anaemia, weight increased, fatigue, dizziness, paraesthesia, muscular weakness, nausea, myalgia, gait disturbance, vomiting and leukocyte count decreased. All the reported Grade 3 adverse reactions occurred in less than 5% of patients, with the exception of anaemia (8%).

Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions, regardless of attribution occurred in 5% of patients (one case each of ALT increased, AST increased, bile duct adenocarcinoma, gait disturbance, intestinal perforation, jaundice, malignant neoplasm progression, neutrophil count decreased, small intestinal obstruction, spinal cord compression, and viral infection). 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 196 patients with TRK fusion-positive cancer in one of three on-going clinical trials, Studies 1, 2 (“NAVIGATE”), and 3 (“SCOUT”). The safety population, characteristics were comprised of patients with a median age of 37.5 years (range: 0.1, 84) with 37% of patients being paediatric patients. Median time on treatment for the overall safety population (n=196) was 9.3 months (range: 0.10, 51.6).

The adverse drug reactions reported in patients (n=196) treated with VITRAKVI are shown in Table 2 and Table 3.

The adverse drug reactions are classified according to the System Organ Class.

Frequency groups are defined by the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 2: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (overall safety population n=196)

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		Anaemia Neutrophil count decreased (Neutropenia) ^a
	Uncommon		Leukocyte count decreased (Leukopenia)
Nervous system disorders	Very common	Dizziness	
	Common	Gait disturbance Paraesthesia	Dizziness Paraesthesia
	Uncommon		Gait disturbance
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting	
	Common	Dysgeusia ^b	
	Uncommon		Nausea Vomiting
Musculoskeletal and connective tissue disorders	Very common	Myalgia	
	Common	Muscular weakness	Myalgia Muscular weakness
General disorders and administration site conditions	Very common	Fatigue	
	Common		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)

^a Grade 4 reactions were reported

^b ADR dysgeusia includes the preferred terms “dysgeusia” and “taste disorder”

Table 3: Adverse drug reactions reported in TRK fusion-positive paediatric cancer patients treated with VITRAKVI at recommended dose (n=73); all Grades

System organ class	Frequency	Infants and toddlers (n=29) ^a	Children (n=30) ^b	Adolescents (n=14) ^c	Paediatric patients (n=73)
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)
Nervous system disorders	Very common			Dizziness	
	Common		Dizziness Paraesthesia Gait disturbance	Paraesthesia	Dizziness Paraesthesia Gait disturbance
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting	Nausea Constipation Vomiting	Nausea Vomiting	Nausea Constipation Vomiting
	Common		Dysgeusia	Constipation	Dysgeusia
Musculoskeletal and connective tissue disorders					
	Common		Myalgia Muscular weakness	Myalgia 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 Blood alkaline phosphatase increased	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		Weight increased (Abnormal weight gain)	Weight increased (Abnormal weight gain)	

^a Infant/toddlers (28 days to 23 months): two Grade 4 Neutrophil count decreased (Neutropenia) reactions reported. Grade 3 reactions included seven cases of Neutrophil count decreased (Neutropenia), three cases of Anaemia, three cases of Weight increased (Abnormal weight gain), and one case each of ALT increased and Vomiting.

^b Children (2 to 11 years): no Grade 4 reactions were reported. Three reported Grade 3 cases of Neutrophil count decreased (Neutropenia), and one case each of Paraesthesia and Myalgia

^c Adolescents (12 to <18 years): no Grades 3 and 4 reactions were reported.

Description of selected adverse reactions

Neurologic reactions

In the overall safety database (n= 196), the maximum grade neurologic reaction observed was Grade 3 which was observed in five (3%) patients and included dizziness (two patients, 1%), paraesthesia (two patients, 1%), and gait disturbance (one patient, <1%). The overall incidence was 26% for dizziness, 8% for paraesthesia and 4% for gait disturbance. Neurologic reactions leading to dose modification included dizziness (2%), paraesthesia (1%), and gait disturbance (<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).

Transaminase elevations

In the overall safety database (n=196), the maximum grade transaminase elevation observed was Grade 4 ALT increase in 2 patients (1%) and AST increase in 1 patient (<1%). Grade 3 ALT and AST increases in 4 (2%) and 2 (1%) of patients, respectively. Majority of Grade 3 elevations were transient appearing in the first or second month of treatment and resolving to Grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in 10 (5%) and 8 (4%) of patients, respectively, and Grade 1 ALT and AST increases were observed in 47 (24%) and 41 (21%) of patients, respectively. ALT and AST increases leading to dose modifications occurred in 10 (5%) patients and 8 (4%) patients, respectively (see section 4.4). No patient permanently discontinued the treatment due to Grade 3-4 ALT and AST increases.

Additional information on special populations

Paediatric patients

Of the 196 patients treated with VITRAKVI, 73 (37%) patients were from 28 days to 18 years of age. Of these 73 patients, 40% were 28 days to < 2 years (n=29), 41% were 2 years to < 12 years (n=30), and 19% were 12 years to < 18 years (n=14). The safety profile in the paediatric population (< 18 years) was consistent in types of reported adverse reactions to those observed in the adult population. The majority of adverse reactions were Grade 1 or 2 in severity (see Table 3) and were resolved without VITRAKVI dose modification or discontinuation. The adverse reactions of vomiting (38% versus 15% in adults), leucocyte count decrease (16% versus 11% in adults), neutrophil count decrease (27% versus 7% in adults), and blood alkaline phosphatase increased (12% versus 4% in adults) were more frequent in paediatric patients compared to adults.

Elderly

Of the 196 patients in the overall safety population who received VITRAKVI, 35 (18%) patients were 65 years or older and 10 (5%) 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 gait disturbance (11% versus 5% in all adults) was 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il>

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: L01XE53.

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 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-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 effect

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 4). The 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 164 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 2019. 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, 24 patients with primary CNS tumours and measurable disease at baseline were treated in Study 2 (“NAVIGATE”) and in Study 3 (“SCOUT”). All 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 upon the molecular test methods: next generation sequencing (NGS) used in 166 patients, reverse transcription-polymerase chain reaction (RT-PCR) used in 9 patients, fluorescence *in situ* hybridization (FISH) used in 12 patients, and Nanostring in 1 patient as routinely performed at certified laboratories.

Table 4: 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 <ul style="list-style-type: none"> Phase 1, open-label, dose escalation and expansion study; expansion phase required tumours with an <i>NTRK</i> gene fusion Adult patients (≥ 18 years) with advanced solid tumours with an <i>NTRK</i> 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 <ul style="list-style-type: none"> Phase 2 multinational, open label, tumour “basket” study Adult and paediatric patients ≥ 12 years with advanced solid tumours with an <i>NTRK</i> gene fusion 	100 mg twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution)	Thyroid (n=23) ^b Salivary gland (n=18) Soft tissue sarcoma (n=16) NSCLC (n=11) ^{b, c} Colorectal (n=8) Primary CNS (n=7) Melanoma (n=6) Breast, non-secretory (n=3) Breast, secretory (n=2) GIST (n=2) ^a Biliary (n=2) Pancreas (n=2) SCLC (n=1) ^{b, d} Appendix (n=1) Bone sarcoma (n=1) Hepatic ^e (n=1) Prostate (n=1)	105
Study 3 “SCOUT” NCT02637687 <ul style="list-style-type: none"> Phase 1/2 multinational, open-label, dose escalation and expansion study; Phase 2 expansion cohort required advanced solid tumours with an <i>NTRK</i> 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=32) Soft tissue sarcoma (n=18) Primary CNS (n=17) Bone sarcoma (n=1) Congenital mesoblastic nephroma (n=1) Melanoma (n=1)	70
Total number of patients (n)*			188

* consist of 164 patients with IRC tumour response assessment and 24 patients with primary CNS tumours (including astrocytoma, glioblastoma, glioma, glioneuronal tumours, neuronal and mixed neuronal-glial tumours, and primitive neuroectodermal tumour with investigator tumour response assessment)

^a GIST: gastrointestinal stromal tumour

^b brain metastases observed in 6 NSCLC, 4 thyroid, 2 melanoma, 1 SCLC patient and 1 breast (non-secretory) patient

^c NSCLC: non-small cell lung cancer

^d SCLC: small cell lung cancer

^e hepatocellular carcinoma

Baseline characteristics for the pooled 164 patients with solid tumours with an *NTRK* gene fusion were as follows: median age 42 years (range 0.1-84 years); 34% < 18 years of age, and 66% ≥ 18 years; 77% white and 49% male; and ECOG PS 0-1 (86%), 2 (12%), or 3 (2%). Ninety-four percent of patients had received prior treatment for their cancer, defined as surgery, radiotherapy, or systemic

therapy. Of these, 77% had received prior systemic therapy with a median of 1 prior systemic treatment regimen. Twenty-two percent of all patients had received no prior systemic therapy. Of those 164 patients the most common tumour types represented were soft tissue sarcoma (22%), infantile fibrosarcoma (20%), thyroid cancer (16%), salivary gland tumour (13%), and lung cancer (8%).

Baseline characteristics for the 24 patients with primary CNS tumours with an *NTRK* gene fusion assessed by investigator were as follows: median age 8 years (range 1.3-79 years); 20 patients < 18 years of age, and 4 patients ≥ 18 years, and 19 patients white and 11 patients male; and ECOG PS 0-1 (22 patients), or 2 (1 patient). All 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=164) and with post-hoc addition of primary CNS tumours (n=24) resulting in the pooled population (n=188), are presented in Table 5 and Table 6.

Table 5: Pooled efficacy results in solid tumours including and excluding primary CNS tumours

Efficacy parameter	Analysis in solid tumours excluding primary CNS tumours (n=164) ^a	Analysis in solid tumours including primary CNS tumours (n=188) ^{a, b}
Overall response rate (ORR) % (n) [95% CI]	73% (119) [65, 79]	66% (124) [59, 73]
Complete response (CR)	19% (31)	18% (33)
Pathological complete response ^c	5% (8)	4% (8)
Partial response (PR)	49% (80)	44% (83) ^d
Time to first response (median, months) [range]	1.84 [0.92, 14.55]	1.84 [0.92, 14.55]
Duration of response (median, months) [range] % with duration ≥ 12 months % with duration ≥ 24 months	NR [0.0+, 50.6+] 76% 67%	NR [0.0+, 50.6+] 74% 65%

NR: not reached

+ denotes ongoing

^a Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (93 patients).

^b Investigator assessment using either RANO or RECIST v1.1 criteria for primary CNS tumours (24 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

^d An additional 1% (2 patients with primary CNS tumours) had partial responses, pending confirmation.

Table 6: Overall response rate and duration of response by tumour type

Tumour type	Patients (n=188)	ORR		DOR		
		%	95% CI	months		Range (months)
				≥ 12	≥ 24	
Soft tissue sarcoma ^a	36	81%	64%, 92%	69%	69%	0.0, 50.6+
Infantile fibrosarcoma ^a	32	97%	84%, 100%	72%	63%	1.6+, 28.6+
Thyroid ^a	27	56%	35%, 75%	93%	58%	3.7+, 32.9
Primary CNS ^b	24	21%	7%, 42%	NR	NR	1.7+, 10.1+
Salivary gland ^a	21	86%	64%, 97%	94%	87%	1.9+, 44.7+
Lung ^a	13	77%	46%, 95%	62%	62%	3.7+, 36.8+

Colon ^a	8	38%	94%, 76%	50%	NR	5.4+, 20.7+
Melanoma ^a	7	43%	10%, 82%	50%	NR	1.9+, 23.2+
Breast ^{a, c}	5	60%	15%, 95%	NR	NR	5.6+, 9.2+
Gastrointestinal stromal tumour ^a	4	100%	40%, 100%	75%	38%	9.5, 31.1+
Bone sarcoma ^a	2	50%	1%, 99%	0%	0%	9.5
Cholangiocarcinoma ^a	2	SD, NE	NA	NA	NA	NA
Pancreas ^a	2	SD, SD	NA	NA	NA	NA
Congenital mesoblastic nephroma ^a	1	100%	3%, 100%	100%	NR	20.8+
Unknown primary cancer	1	100%	3%, 100%	0%	0%	7.4
Appendix ^a	1	SD	NA	NA	NA	NA
<u>Hepatic</u>	1	NE	NA	NA	NA	NA
Prostate	1	PD	NA	NA	NA	NA

DOR: duration of response

NA: not applicable due to small numbers or lack of response
NE: not evaluable

NR: not reached

PD: progressive disease

SD: stable disease

+ denotes ongoing response

^a independent review committee analysis by RECIST v1.1

^b patients with a primary CNS tumour were evaluated per investigator assessment using either RANO or RECIST v1.1 criteria

^c with 3 patients having non-secretory (1 complete, 1 partial responder and 1 progressive disease) and 2 patients having secretory breast cancer (1 partial and 1 stable disease)

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=109), the ORR was 63%. In the paediatric sub-population (n=55), the ORR was 91%.

In 165 patients with wide molecular characterisation before larotrectinib treatment, the ORR in 79 patients who had other genomic alterations in addition to *NTRK* gene fusion was 58%, and in 86 patients without other genomic alterations ORR was 74%.

Pooled primary analysis set

The pooled primary analysis set consisted of 164 patients and did not include primary CNS tumours. Median time on treatment before disease progression was 14.7 months (range: 0.10 to 51.6 months) based on July 2019 cut-off. Forty-four percent of patients had received VITRAKVI for 12 months or more and 21% had received VITRAKVI 24 months or more, with follow-up ongoing at the time of the analysis.

At the time of analysis, the median duration of response had not been reached, an estimated 76% [95% CI: 67, 85] of responses lasted 12 months or longer, and 67% [95% CI: 55, 78] of responses lasted 24 months or longer. Ninety percent (90%) [95% CI: 85, 95] of patients treated were alive one year after the start of therapy and 82% [95% CI: 75, 90] after two years with the median for overall survival not yet being reached. Median progression free survival was 33.4 months at the time of the analysis, with a progression free survival rate of 66% [95% CI: 58, 74] after 1 year and 58% [95% CI: 48, 67] after 2 years.

The median change in tumour size in the pooled primary analysis set was a decrease of 68%.

Patients with primary CNS tumours

At the time of data cut-off, of the 24 patients with primary CNS tumours confirmed response was observed in 5 patients (21%) with 2 of the 24 patients (8%) being complete responders and 3 patients (12.5%) being partial responders. In 2 additional patients (8%) a not yet confirmed partial response was observed. Further 15 patients (63%) had stable disease. Two patients (8%) had progressive disease. At the time of data cut-off, time on treatment ranged from 1.2 to 21.4 months and was ongoing in 15 out of 24 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 ($t_{1/2}$) 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 (\pm 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 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 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 (1 month to <3 months of age) at the recommended dose of 100 mg/m² 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-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-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 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
- Hydroxypropyl betadex
- Glycerol
- Sorbitol
- Sodium citrate dihydrate, granular
- Sodium phosphate
- Citric acid
- Glycerin, natural flavor
- Propylene glycol
- Citrus fruit flavour
- Potassium sorbate
- Methyl parahydroxybenzoate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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) 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 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 7.
- 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 7: 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 Israel Ltd., 36 Hacharash St., Hod Hasharon

8. MANUFACTURER

Bayer AG51368 Leverkusen, Germany.

9. MARKETING AUTHORISATION NUMBER

VITRAKVI 20 mg/mL oral solution

Revised in December 2020 according to MoH guidelines