Summary Report of Benefit-Risk Assessment

VITRAKVI HARD CAPSULE 25MG AND 100MG
VITRAKVI ORAL SOLUTION 20MG/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Larotrectinib
Product Registrant	Bayer (South East Asia) Pte Ltd
Product Registration Number	SIN15991P, SIN15992P, SIN15993P
Application Route	Abridged evaluation
Date of Approval	17 August 2020

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A INTRODUCTION

Vitrakvi is approved for the treatment of adult and paediatric patients with solid tumours that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

The approval is subject to the submission of the final pooled analysis and final study reports of ongoing clinical studies to confirm the efficacy and safety of larotrectinib

The active substance, larotrectinib, is an oral tyrosine kinase inhibitor that binds to and inhibits TRK family of proteins inclusive of TRKA, TRKB and TRKC that are encoded by NTRK1, NTRK2 and NTRK3 genes respectively, and inhibits the proliferation of tumour cells.

Vitrakvi is available in the following presentations:

A) Capsules containing 25 mg and 100 mg of larotrectinib. Other ingredients are present in the capsule shell (gelatin, titanium dioxide) and printing ink (shellac, FD&C blue # 2 aluminium lake, titanium dioxide, propylene glycol, ammonia solution, and dimethicone).

B) Oral solution containing 20 mg/mL of larotrectinib. Other ingredients present in the oral solution are purified water, hydroxypropyl betadex, sodium citrate, Ora-Sweet® (purified water, sucrose, glycerol, sorbitol, citric acid, sodium dihydrogen phosphate, flavouring and preservative agents methylparahydroxybenzoate and potassium sorbate), natural masking type flavour (glycerol, natural flavour ingredients), natural bitterness masking type flavour (glycerol, natural flavour ingredients), bitterness masking flavour (propylene glycol, natural flavour) and FONATECH® taste modifier flavour (propylene glycol, glycerol, natural flavour).

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, larotrectinib, is manufactured at [redacted] The drug products, Vitrakvi capsules and oral solution, are manufactured at Penn Pharmaceutical Services Ltd., Tredegar, UK.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented are adequate to support the approved storage condition and re-test period. [redacted] The drug substance is approved for storage at store at or below 30ºC with a re-test period of 36 months.

Drug product: *Vitrakvi Hard Capsule 25mg and 100mg*
The capsule is filled directly with the drug substance without any formulation with other excipients. The process is considered to be a standard process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted are adequate to support the approved shelf-life of 24 months when stored at or below 30 ºC. The container closure system is a High density polyethylene (HDPE)-bottles with a child-resistant polypropylene (PP) cap with a polyethylene (PE) heat seal layer.

Drug product: *Vitrakvi Oral Solution 20mg/mL*
All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted are adequate to support the approved shelf-life of 24 months when stored between 2°C to 8°C. The in-use period after opening is 30 days and is supported by appropriate data. The container closure system is amber glass (type III) bottle with a child-resistant polypropylene (PP) cap with a polyethylene (PE) seal liner.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of larotrectinib in the treatment of solid tumours with NTRK gene fusion was based primarily on the pooled efficacy analysis of three ongoing studies: Study LOXO-TRK-14001, Study LOXO-TRK-15003 and Study LOXO-TRK-15002.

Study LOXO-TRK-14001 was a Phase I, multicentre, open-label, single-arm, dose-escalation and dose-expansion study in adult patients (≥18 years of age) with locally advanced or

metastatic solid tumours with or without NTRK gene fusion that had progressed or was non-responsive to available therapies, were unfit for standard chemotherapy or for which no standard or available curative therapy exists. Dose escalation proceeded through 6 planned dose levels or until the maximum tolerated dose (MTD) was reached. As of the data cut-off date (19 February 2018), a total of 61 patients had undergone treatment in the dose escalation phase and the results demonstrated that larotrectinib 100mg twice daily (BID) provided sustained inhibition of TRK targets without dose-limiting toxicity. Patients in the dose-expansion and efficacy phase were thus administered larotrectinib 100 mg BID based on a 28-day treatment cycle until disease progression or unacceptable toxicity. In addition, 9 patients were enrolled and treated with at least 1 dose of study drug in the expansion phase, hence a total of 70 patients have been dosed. Of these, 8 patients had solid tumours with NTRK gene fusions (100 mg BID: 6; 150 mg BID: 2).

Study LOXO-TRK-15003 was a Phase I/II, multicentre, open-label, single-arm, dose-finding and efficacy study in paediatric patients aged 1 month to 21 years with an advanced solid tumour or a primary CNS tumour. The study was conducted in 2 phases – Phase 1 was a dose-escalation and dose-expansion study to identify the optimal dose of larotrectinib and define its safety profile, while Phase 2 was an efficacy study of larotrectinib specifically involving patients with tumours bearing NTRK fusions (infantile fibrosarcoma (IFS), other extracranial solid tumours, primary CNS tumours).

As of the data cut-off date (19 February 2018), the dose-escalation study in Phase 1 was completed with 24 patients. No dose-limiting toxicities (DLT) were reported from Cohort 1 (larotrectinib 9.6 to 55.0 mg/m^2; n=4) and Cohort 2 (larotrectinib 17.3 to 120mg/m^2; n=11), while 1 out of 9 patients in Cohort 3 (larotrectinib 100 mg/m^2 BID, maximum of 100 mg BID) experienced DLT. The recommended larotrectinib dose for paediatric patients was then set at 100mg/m^2 BID (with a maximum of 100 mg BID), based on the totality of safety, pharmacokinetic and efficacy information from this study and across the entire larotrectinib program. In addition, there were 5 patients in the dose-expansion study in Phase 1 and 14 patients in Phase 2 who received larotrectinib 100mg/m^2 BID based on a 28-day treatment cycle until disease progression or unacceptable toxicity. In total, 43 patients including 34 patients who had solid tumours with NTRK gene fusion had been treated.

Study LOXO-TRK-15002 was a Phase II, multicentre, open-label, basket study in adult and adolescent patients ≥12 years of age with advanced solid tumour harboring NTRK1, NTRK2 or NTRK3 gene fusion. Patients included in this study must have received prior standard therapy appropriate for their tumour type and stage of disease or would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy in the opinion of the investigator. Patients were administered larotrectinib 100 mg twice daily based on 28-day treatment cycle until disease progression or unacceptable toxicity. The study comprised eight cohorts of patients with the following tumour histologies: non-small cell lung cancer, thyroid tumour, sarcoma, colon cancer, salivary gland tumour, biliary tumour, primary CNS tumour and all other solid tumours. As of the data cut-off date (19 February 2018), 63 patients who had solid tumours harboring NTRK gene fusion were enrolled and treated.

The interim pooled primary analysis set (PAS) comprised data from the first 55 paediatric and adult patients enrolled in the three clinical studies who had non-CNS primary tumour with documented NTRK gene fusion and had received more than one doses of larotrectinib and the data cut-off date was 17 July 2017. There were subsequently two extensions to the original PAS as additional subjects were enrolled and the second extended PAS (ePAS2). At the data cut-off on 30 July 2018, the dataset comprised 93 patients based on which patients with only primary CNS tumours were reviewed in a separate supplemental analysis set (SAS3).

The primary efficacy endpoint of the pooled analysis was overall response rate (ORR) determined by an independent review committee (IRC). The key secondary efficacy endpoints included time to response, time on treatment, duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

The ePAS2 population had median age of 41 years (range: 0.1 to 78 years old), with infants/toddlers and children forming 13% and 14% of the population respectively. The most common tumour types represented were soft tissue sarcoma (23%), salivary gland tumour (18%), IFS (14%), thyroid tumour (11%), lung and melanoma cancer (8% for each), and colon cancer (6%). There were less than 10% of patients with breast tumour, pancreas tumour, and gastrointestinal tumour in total. The proportion of patients with solid tumours harbouring NTRK1, NTRK2 and NTRK3 gene fusion were 44%, 3% and 48%, respectively. Most patients (97%) had received prior cancer-related treatment, which included surgery (84%), radiotherapy (48%) or systemic therapy (77%), with a median of 1 prior systemic treatment regimen; 21% of all patients had received no prior systemic therapy.

The primary CNS tumour population (SAS3) was represented by 9 patients with an age range of 2 to 79 years. Of these, 6 (66%) were children and adolescents, 4 (44%) had stage III/IV tumours at initial diagnosis and 4 (44%) had locally advanced disease at study enrolment. The proportion of patients with NTRK1, NTRK2 and NTRK3 gene fusion were 11%, 78% and 11%, respectively. All 9 of these patients had received prior systemic cancer treatment, with a median of 1 prior systemic treatment regimen, while 5 (56%) patients had received surgery and 5 (56%) patients had undergone radiotherapy.

Treatment with larotrectinib achieved an ORR of 72% (95% CI 62%, 81%) in the ePAS2 population. Of the 67 patients who responded to treatment, 15 (16%) had a complete response, while 51 (55%) had a partial response. 75% of responders had responses which lasted 12 months or longer, while the median time to first response was 1.81 months. The robustness of these results was supported by the consistency in results from PAS, ePAS and ePAS2. The ORR was 68% in adults and 82% in paediatrics in the ePAS2 population.

In terms of PFS, the disease progression rate was 37% and the median PFS was 27.4 months, while the PFS rates at 6 months and 12 months were 77% and 64%, respectively. The OS data were immature – 14 deaths (15%) were reported and the median duration of OS was not evaluable. The proportion of patients alive at 12 months was 88% (95% CI 81%, 95%).

Summary of key efficacy results from pooled analysis (cut-off date 30 July 2018)

Efficacy parameter	**ePAS2 (n=93)[a]**	**SAS3 (n=9)[b]**
Primary endpoint		
Overall response rate (ORR), n	67	1
Confirmed ORR (%)	72	11
95% CI	62, 81	0, 48
Key secondary endpoints		
Best response, n (%)		
Complete response (CR)	15 (16)	0
Surgical complete response[c]	1 (1)	0
Partial response (PR)	51 (55)	1 (11)
Stable disease (SD)	14 (15)	7 (78)
Progressive disease (PD)	9 (10)	0
Not evaluable	3 (3)	1 (11)
Time to first response (months), n	67	1

Median	1.81	1.81
Range	0.95, 14.55	0.95, 14.55
Duration of response (months), n	67	1
Median	NE	NE
Range	1.6+, 38.7+	2.0+, 2.0+
% of patients with duration ≥6 months	88	NE
% of patients with duration ≥12 months	75	NE
Progression-free survival (PFS) (months)		
Median	27.4	6.3
Range	0.03+, 39.7+	2.8, NE
PFS at 6 months (%)	77	71
PFS at 12 months (%)	64	NE
Overall survival (OS)		
OS events, n (%)	14 (15)	0
Median (months)	NE	NE
Alive at 12 months, % (95% CI)	88 (81, 95)	NE

NE: not evaluable;
+ 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 (9 patients)
c Paediatric patient (6 months old at enrolment) with locally advanced unresectable infantile fibrosarcoma with complete surgical response)

In the 9 patients with primary CNS tumours treated with larotrectinib (SAS3), the investigator-assessed ORR was 11%, with stable disease in 7 patients (78%), and 1 (11%) patient had partial response. The time on treatment ranged from 0.03 to 9.2 months. The disease control rate (DCR) (defined as complete response, partial response and stable disease for at least 16 weeks' duration) in this population was 67% (95% CI 30%, 93%).

In the updated analysis based on the later cut-off date of 15 July 2019, there were 24 evaluable patients with primary CNS tumours, the investigator-assessed ORR was 21% and the DCR was 62.5% (95%CI 4%, 81%). Complete response was achieved in 2 (8%) patients, partial response in 3 (13%) patients and stable disease in 15 (63%) patients. Of the 5 patients who achieved a response, 3 patients (60%) were still in response and 2 patients (40%) had progressed. The median duration of response was 4.9 months (range 1.7-10.1 months) and the median time to first response was 1.81 months. The median PFS was 11 months (95% CI 5.4, NE) with a median follow-up of 5.6 months. These results thus provided preliminary evidence of clinical efficacy in patients with primary CNS tumours harbouring NTRK gene fusion who had progressed on prior treatments and had no better alternative treatment options, although additional data are required to confirm the treatment benefit.

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

Further subgroup analyses were performed by tumour type, ORR consistent with the range that observed in the overall population was seen in several tumour types, in particular in patients with soft tissue sarcoma, infantile fibrosarcoma, salivary gland, thyroid, and lung tumours. Patients with melanoma and colon cancer had lower but considerably good response rates (ORR 43% and 33%, respectively). Stable disease was reached in one patient each with cholangiocarcinoma, appendix tumour, and pancreatic tumour, while the one patient with breast tumour had disease progression. For these tumour types, the data is limited due to the very small sample size, a firm conclusion on the efficacy of larotrectinib could not be drawn.

Overall response rate and duration of response by tumour type

Tumour type	Patients (n=102)	ORR % (95% CI)	Duration of response	
			Rate (%) DOR ≥12 months	Range (months)
Soft tissue sarcoma[a]	21	81 (58, 95)	78%	1.9+, 38.7+
Salivary gland[a]	17	88 (64, 99)	91%	3.7+, 33.7+
Infantile fibrosarcoma[a]	13	92 (64, 100)	60%	1.6+, 17.3+
Thyroid[a]	10	70 (35, 93)	86%	3.7, 29.8+
Primary CNS[b]	9	11 (0, 48)	NR	2.0+
Lung[a]	7	71 (29, 96)	75%	7.4+, 25.8+
Melanoma[a]	7	43 (10, 82)	50%	1.9+, 23.2+
Colon[a]	6	33 (4, 78)	NR	5.6, 9.2+
Gastrointestinal stromal tumour[a]	4	100 (40, 100)	67%	7.4+, 20.0+
Bone sarcoma[a]	2	50 (1, 99)	0%	9.5
Cholangiocarcinoma[a]	2	SD, NE	NA	NA
Congenital mesoblastic nephroma[a]	1	100 (3, 100)	NR	9.8+
Appendix[a]	1	SD	NA	NA
Breast[a,c]	1	PD	NA	NA
Pancreas[a]	1	SD	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] non-secretory

Overall, the robust ORR and durable response observed in the interim results of the pooled analysis provided preliminary evidence supporting the efficacy of larotrectinib for the intended population of patients with solid tumours harbouring NTRK gene fusion who had progressed on prior treatments or had no satisfactory alternative treatment options. In view of the limited number of patients in some tumour types, the ORR in the overall population may not be generalisable to specific tumours. Longer follow-up in more patients with various tumour types would be required to confirm the clinical benefit of larotrectinib.

D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of larotrectinib comprised a total of 208 patients with or without NTRK gene fusion solid tumours from the three studies based on a data cut-off date 30 July 2018. Of these, 137 patients (66%) had NTRK fusion cancers and there were 56 paediatric patients. In addition, 88 patients (42.3%) were treated for 6 months or more and 53 patients (25.5%) were treated for at least 1 year; the mean time on treatment was 7.9 months.

Overview of safety profile (n=208)

	Overall safety analysis set, n (%)
Any treatment-emergent adverse event (TEAE) TEAE related to larotrectinib	203 (98%) 167 (80%)
Grade 3 or 4 TEAE Grade 3 or 4 TEAE related to larotrectinib	103 (50%) 27 (13%)
TEAE leading to discontinuation TEAE leading to discontinuation related to larotrectinib	23 (11%) 5 (2%)
Serious TEAE Serious TEAE related to larotrectinib	70 (34%) 12 (6%)
Fatal TEAE Fatal TEAE related to larotrectinib	12 (6%) 0

Nearly all the patients experienced at least one treatment-emergent adverse event (TEAE). The most common TEAEs were fatigue (36%), dizziness (29%), nausea (28%), constipation (27%), cough, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased, anaemia (all 26%) and vomiting (24%). The most common treatment-related AEs were ALT increased (22%), dizziness (21%), AST increased (20%), fatigue (18%) and nausea (15%). The majority of the treatment-related TEAEs were Grade 1 (36%) or Grade 2 (32%) in severity. There were 25 patients (12%) who experienced a Grade 3 treatment-related AEs and 2 patients (1%) who experienced a Grade 4 treatment-related TEAE (ALT increased and neutrophil count decreased). No patient experienced a Grade 5 treatment-related TEAE. The most common (≥3%) Grade 3 treatment-related TEAEs were AST increased (2%) and anemia (2%).

Around one-third of the treated patients (34%) experienced at least one serious adverse event (SAE) during larotrectinib treatment. The most common SAEs were disease progression (4%), pyrexia (3%), diarrhoea, sepsis (2% each), abdominal pain, cellulitis, dehydration and vomiting (1% each). The incidence of treatment-related SAEs was 6%, including one case each of diarrhoea, vomiting, muscular weakness, myalgia, delirium, enterocutaneous fistula, ejection fraction decrease and haematuria.

TEAEs leading to larotrectinib discontinuation occurred in 23 patients (11%) and those attributed to larotrectinib occurred in 5 of these patients (2%). No patterns were apparent in these TEAEs as few TEAEs occurred in more than 1 patient each. There were 12 patients (6%) who experienced TEAEs with a fatal outcome within 30 days of receiving larotrectinib, all of which were attributed to either disease progression or to a complication of the primary malignancy, none were attributed to larotrectinib.

Among the 208 patients who received larotrectinib, 47 (22%) patients were ≥65 years of age. The incidence of treatment-related TEAEs was similar between the overall adult population and those 65 years and older (82% and 83%, respectively). The most common treatment-related TEAEs in patients ≥65 years of age were dizziness (30%), fatigue (28%), ALT increased (15%), nausea (15%), AST increased (15%) and constipation (17%).

In paediatric patients younger than 18 years old, TEAEs were reported for 54 (96%) patients, and treatment-related TEAEs were reported for 42 patients (75%). The most common treatment-related TEAEs in paediatrics were ALT increased (36%), AST increased (32%), leukocyte count decreased (20%), neutrophil count decreased (20%), anaemia (16%), nausea (14%), fatigue (13%), constipation (13%) and vomiting (11%). Across paediatric subgroups, common TEAEs tended to occur at a moderately higher incidence in the infants/toddlers age group, and these were related to vomiting, diarrhoea and pyrexia.

The notable safety concerns with larotrectinib were liver transaminase elevation, neurologic TEAEs, neutropenia and anaemia, all of which have been described in the approved package insert. Most of these TEAEs were Grade 1 severity and occurred within the first or second month of larotrectinib treatment. Notably, the incidence rate of ALT and AST increased was higher in paediatric patients compared to adult patients, 43% compared to 20%, respectively, for ALT increased, and 39% compared to 27%, respectively, for AST increased.

Overall, larotrectinib presented an acceptable safety profile for the intended population, given that these patients who only have, if at all, limited or toxic systemic therapies or treatment disfiguring and/or burdensome surgery available. The long-term safety and developmental effect of larotrectinib in paediatric patients have not been fully characterised. Appropriate

warnings and precautions have been put in place in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

There is currently no approved targeted treatment for patients with solid tumours harbouring NTRK gene fusion. Patients who had progressed after standard treatments with surgical resection, radiotherapy, and/or chemotherapy have few or no treatment options. Ongoing salvage treatment with existing alternatives is not beneficial for most patients due to known toxicities of available treatments or co-morbidities of the patient which predicted for a deterioration in quality of life with ongoing therapy. There is thus an unmet medical need for patients with NTRK gene fusion solid tumours.

Larotrectinib had been shown to achieve high ORR of 72% and durable PFS of 27.4 months in patients with rare NTRK gene fusion solid tumours who had progressed on prior treatments or had no satisfactory alternative treatment options. These results suggested a clinically meaningful benefit in patients, in particular, given the rarity and severity of the diseases. However, the evidence in several tumour types such as cholangiocarcinoma, appendix tumour, breast tumour and pancreatic tumour is very limited due to the extremely small number of patients with these tumours in the clinical studies. There was also preliminary evidence of larotrectinib treatment benefit in patients with primary CNS tumours based on an ORR of 21% and DCR of 62.5% in the updated analysis.

The safety profile of larotrectinib was considered acceptable relative to the benefits for patients who have no or limited satisfactory alternative treatment. The notable safety concerns with larotrectinib were transaminase elevation, neurologic events, neutropenia and anaemia, which have been adequately addressed in the local package insert via the provision of relevant warnings and precautions, and/or dose adjustment recommendations in the event of toxicity.

Overall, the preliminary benefit-risk profile of larotrectinib was considered favourable. Longer follow-up in more patients with various tumour types are required to confirm the clinical benefit of larotrectinib for the proposed tumour agnostic indication.

F CONCLUSION

Based on the review of quality, interim safety and efficacy data, the preliminary benefit-risk balance of Vitrakvi was deemed favourable for the treatment of patients with solid tumours that have a NTRK gene fusion, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory alternative treatments or that have progressed following treatment. Considering that long-term safety and developmental effect of Vitrakvi in paediatric patients have not been fully characterised and the data in specific tumours was limited, approval of the product registration was granted on 17 August 2020, subject to the submission of the final pooled analysis and final study reports of ongoing clinical studies to confirm the efficacy and safety of larotrectinib.

APPROVED PACKAGE INSERT AT REGISTRATION

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 capsule contains larotrectinib sulfate, equivalent to 25 mg of larotrectinib

Vitrakvi 100 mg capsules

Each 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

100 mL clear yellow to orange liquid solution

4. CLINICAL PARTICULARS

4.1 Indication(s)

Vitrakvi is indicated for the treatment of adult and pediatric patients with solid tumors that:

• have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation,

• are metastatic or where surgical resection is likely to result in severe morbidity, and

• have no satisfactory alternative treatments or that have progressed following treatment.

4.2 Dosage 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 Method of administration

For oral use

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

Capsule

The patient should be advised to swallow the capsule whole with a large amount of water. The capsule should not be opened, chewed or crushed.

Oral solution

Administer the oral solution by mouth or enterally by naso- or gastric- feeding tube with a dosing syringe.

4.2.2 Dosage regimen

Adults

The recommended dose of Vitrakvi in adults is 100 mg taken orally, twice daily until the patient is no longer clinically benefiting from therapy 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 (1 month to 18 years) is 100 mg/m^2 taken orally, twice daily with a maximum of 100 mg per dose until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Administer Vitrakvi with or without food.

If the patient vomits after taking a dose, the patient should not take an additional dose to make up for vomiting. 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.

4.2.3 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:

- Withhold VITRAKVI until adverse reaction resolves or improves to baseline or Grade 1.
  Resume at the next dosage modification if resolution occurs within 4 weeks.
- Permanently discontinue VITRAKVI 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 Dosage 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

Permanently discontinue VITRAKVI in patients who are unable to tolerate VITRAKVI after three dose modifications.

4.2.4 Co-administration with Strong CYP3A4 Inhibitors and Inducers

Co-administration with Strong CYP3A4 Inhibitors
Avoid coadministration of strong CYP3A4 inhibitors with VITRAKVI, including grapefruit or grapefruit juice. 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 "Interaction with other medicinal products and other forms of interaction").

Co-administration with Strong CYP3A4 Inducers

Avoid coadministration of strong CYP3A4 inducers with VITRAKVI. If coadministration of a strong CYP3A4 inducer cannot be avoided, double the VITRAKVI dose. After the inducer has been discontinued for 3 to 5 elimination half-lives, resume the VITRAKVI dose taken prior to initiating the CYP3A4 inducer (see "Interaction with other medicinal products and other forms of interaction").

4.2.4 Additional information on special populations

4.2.4.1 Patients with hepatic impairment

Reduce the starting dose of VITRAKVI by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment *(see section 'Pharmacokinetic properties')*. No dose adjustment is required in patients with mild (Child-Pugh A) hepatic impairment.

4.2.4.2 Patients with renal impairment

Clinical data from a pharmacokinetic study indicate that larotrectinib exposure was increased 1.46-fold in patients with end-stage renal disease. No dose adjustment is required for patients with renal impairment.

4.2.4.3 Geriatric patients

Clinical data indicate that age has no effect on the systemic exposure of larotrectinib *(see section 'Pharmacokinetic properties')*. No dose adjustment is necessary in elderly patients.

4.3 Contraindications

None

4.4 Special warnings and precautions for use

4.4.1 Neurologic Reactions

Neurologic reactions including dizziness, gait disturbance and paraesthesia were reported in patients receiving larotrectinib *(see section 'Undesirable effects')*. For the majority of neurologic reactions, onset occurred within the first three months of treatment.

Caution patients about driving and using machines, until they are reasonably certain Vitrakvi therapy does not affect them adversely. Withholding, reducing, or discontinuing Vitrakvi dosing should be considered, depending on the severity and persistence of these symptoms *(see section 'Dosage and method of administration ', and section 'Effects on ability to drive or use machines')*.

4.4.2 Transaminase Elevations

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

Monitor for liver function including ALT and AST assessments, 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. Withholding, reducing, or discontinuing Vitrakvi dosing should be considered, depending on the severity and persistence of the transaminase elevation *(see section 'Dosage and method of administration ')*.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of other agents on larotrectinib

Larotrectinib is a substrate of cytochrome P450 (CYP) 3A4, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of Vitrakvi with strong 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.

Co-administration of Vitrakvi with strong CYP3A4 and P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, or St. John's Wort) may decrease larotrectinib plasma concentrations.

4.5.1.1 Effect of CYP3A4, P-gp and BCRP Inhibitors on larotrectinib

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

4.5.1.2 Effect of CYP3A4 and P-gp Inducer on larotrectinib

Clinical data in healthy adult subjects indicate that co-administration of a single 100 mg Vitrakvi dose with rifampin (a strong CYP3A4 and P-gp inducer) 600 mg twice daily for 11 days decreased larotrectinib C_{max} and AUC by 81% and 71%, respectively.

4.5.1.3 Effect of other transporter inibitors on larotrectinib

In vitro, larotrectinib is not a substrate for the transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, or OATP1B3.

4.5.1.4 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.

4.5.2 Effects of larotrectinib on other agents

4.5.2.1 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.

4.5.2.2 Effect of larotrectinib on other CYP and transporter substrates

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 induces CYP2B6, but does not induce CYP1A2.
In vitro studies indicate that larotrectinib does not inhibit the transporters BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, MATE1 and MATE2-K at clinically relevant concentrations and is unlikely to affect clearance of substrates of these transporters.

4.6 Fertility, pregnancy and lactation

4.6.1 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.

4.6.2 Lactation

There are no data on the presence of larotrectinib in human milk, the effects of larotrectinib on the breastfed child, or the effects of larotrectinib on milk production. Because of the unknown risk of larotrectinib in nursing infants, advise a nursing woman to discontinue breastfeeding during treatment with larotrectinib and for 3 days (6 plasma half-lives of larotrectinib and its metabolites) following the final dose.

4.6.3 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 '*Preclinical safety data'*).

4.6.4 Women of childbearing potential / Contraception

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. Females of childbearing potential should have a pregnancy test prior to starting treatment with Vitrakvi.

Advise female patients of reproductive potential 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.

For males of reproductive potential with a non-pregnant female 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.

4.7 Effects on ability to drive or use machines

Neurologic reactions have been reported in patients receiving larotrectinib which may influence the ability to drive and use machines. Caution patients about driving and using machines, until they are reasonably certain Vitrakvi therapy does not affect them adversely *(see section 'Special warnings and precautions for use')*.

4.8 Undesirable effects

4.8.1 Summary of the safety profile

The safety of VITRAKVI was evaluated in 125 patients with TRK fusion-positive cancer in one of three clinical trials, Studies 1, 2 ("NAVIGATE"), and 3 ("SCOUT"). Median time on treatment for the overall safety population was 7.4 months (range: 0.03 to 40.7). The safety population characteristics were comprised of patients with a median age of 45 years (range: 0.1, 80) with 30% of patients being paediatric patients. The most common adverse drug reactions (≥ 20%) of VITRAKVI in order of decreasing frequency were fatigue (32%), increased ALT (31%), dizziness (30%), increased AST (29%), constipation (29%), nausea (26%), anaemia (24%), and vomiting (20%).

The majority of adverse reactions were Grade 1 or 2. Grade 4 was the highest reported grade for adverse reactions neutrophil count decreased (1.6%) and ALT increased (< 1%). The highest reported grade was Grade 3 for adverse reactions anaemia, weight increased, fatigue, increased AST, dizziness, paraesthesia, nausea, myalgia, and leukocyte count decreased. All the reported Grade 3 adverse reactions occurred in less than 5% of patients, with the exception of anaemia (7%).

Permanent discontinuation of VITRAKVI for treatment emergent adverse reactions, regardless of attribution occurred in 3% of patients (one case each of ALT increase, AST increase, intestinal perforation, jaundice, small intestinal obstruction). The majority of adverse reactions leading to dose reduction occurred in the first three months of treatment.

4.8.2 Tabulated list of adverse reactions

The adverse drug reactions reported in patients 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 (≥ 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 2: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (n=125)

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] Leukocyte count decreased (Leukopenia)
Nervous system disorders	Very common	Dizziness Paraesthesia	
	Common	Gait disturbance	Dizziness Paraesthesia
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting	
	Common	Dysgeusia	Nausea
Musculoskeletal and connective tissue disorders	Very common	Myalgia Muscular weakness	
	Common		Myalgia
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 Weight increased (Abnormal weight gain)

[a] Grade 4 reactions were reported

Table 3: Adverse drug reactions reported in TRK fusion-positive paediatric cancer patients treated with VITRAKVI at recommnded dose (n=37); all Grades

System organ class	Frequency	Infants and toddlers (n=14)[a]	Children (n=15)[b]	Adolescents (n=8)[c]	Paediatric patients (n=37)
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 Paraesthesia	
	Common		Paraesthesia Gait disturbance		Dizziness Paraesthesia Gait disturbance
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting	Nausea Constipation Vomiting	Nausea Vomiting	Nausea Constipation Vomiting
	Common		Dysgeusia		Dysgeusia
Musculoskeletal and connective tissue disorders	Very common			Myalgia Muscular weakness	
	Common		Myalgia		Myalgia Muscular weakness
General disorders and administration site conditions	Very common	Fatigue	Fatigue		Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain)	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 Weight increased (Abnormal weight gain) Blood alkaline phosphatase increased
	Common	Blood alkaline phosphatase increased			

[a] Infant/toddlers (28 days to 23 months): one Grade 4 Neutrophil count decreased (Neutropenia) reaction reported. Grade 3 reactions included two cases Neutrophil count decreased (Neutropenia) and one case of anaemia.

[b] Children (2 to 11 years): no Grade 4 reactions were reported. One reported Grade 3 case each of Neutrophil count decreased (Neutropenia), Paraesthesia, Myalgia, Weight increased (Abnormal weight gain).
[c] Adolescents (12 to <18 years): no Grades 3 and 4 reactions were reported.

4.8.3 Description of selected adverse reactions

4.8.3.1 Neurologic Reactions

In the overall safety database (n=125), the maximum grade neurologic reaction observed was Grade 3 which was observed in three (2%) patients and included dizziness (one patient, <1%) and paraesthesia (two patients, 1.6%). The overall incidence was 30% for dizziness, 10% for paraesthesia and 3% for gait disturbance. Neurologic reactions leading to dose modification included dizziness (2%). None of these adverse reactions led to treatment discontinuation. In all cases, 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 'Special warnings and precautions for use')

4.8.3.2 Transaminase Elevations

In the overall safety database (n=125), the maximum grade transaminase elevation observed was Grade 4 ALT increase in 1 patient (<1%). Grade 3 ALT and AST increases in 3 (2%) and 2 (2%) patients, respectively. Majority of Grade 3 elevations were transient appearing in first or second month of treatment and resolving to Grade 1 by months 3-4. Grade 2 ALT and AST increases were observed in 9 (7%) and 6 (5%) of patients, respectively, and Grade 1 ALT and AST increases were observed in 26 (21%) and 28 (22%) of patients, respectively.
ALT and AST increases leading to dose modifications occurred in 7 (6%) patients and 6 (5%) patients, respectively (see section 'Special warnings and precautions for use'). No patient permanently discontinued the treatment due to Grade 3-4 ALT and AST increases.

4.8.4 Additional information on special populations

4.8.4.1 Pediatric patients

Of 125 patients treated with VITRAKVI, 37 (30%) patients were from 28 days to 18 years of age. Of these 37 patients, 38% were 28 days to < 2 years (n=14), 41% were 2 years to < 12 years (n=15), and 22% were 12 years to < 18 years (n=8). 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 (35% versus 14% in adults), leucocyte count decrease (22% versus 9% in adults), neutrophil count decrease (30% versus 7% in adults), blood alkaline phosphatase increased (14% versus 2% in adults) and transaminase elevations (ALT 41% versus 27% in adults and AST 35% versus 26% in adults) were more frequent in paediatric patients compared to adults.

4.8.4.2 Elderly

Of 125 patients in the overall safety population who received VITRAKVI, 28 (22%) patients were 65 years or older and 8 (6%) patients were 75 years or older. The safety profile in elderly patients (≥ 65 years) is consistent with that seen in younger patients (< 65 years). The adverse reactions gait disturbance (17% versus 3% in under 65 years), and blood alkaline phosphatase increased (4% versus 2% in under 65 years) were more frequent in patients of 65 years or older.

4.9 Overdose

There is no known antidote for Vitrakvi. The treatment of overdose with Vitrakvi should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and Immunomodulating Agents, Antineoplastic agents, other antineoplastic agents

ATC Code: L01XF01

5.1.1 Mechanism of action

Larotrectinib is an orally-bioavailable, adenosine triphosphate (ATP)-competitive, potent and highly 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-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.

Larotrectinib demonstrated potent inhibition of TRK proteins and inhibition of proliferation of tumor cells in a concentration-dependent manner. In TRK fusion-driven mouse xenograft models larotrectinib treatment induced a significant reduction of tumor growth.

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).

5.1.2 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.

5.1.3 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 were ongoing at the time of approval.
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 93 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. 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, 9 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 98 patients, reverse transcription-polymerase chain reaction (RT-PCR) used in 1 patient and fluorescence *in situ* hybridization (FISH) used in 6 patients 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 • 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)	Salivary gland (n=3) GIST (n=2)[a] NSCLC (n=1)[c] Soft tissue sarcoma (n=1) Thyroid (n=1)	8
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)	Salivary gland (n=14) Thyroid (n=9)[b] Soft tissue sarcoma (n=9) Colorectal (n=6) Melanoma (n=6) NSCLC (n=5)[b, c] Primary CNS (n=4) GIST (n=2)[a] Biliary (n=2) SCLC (n=1)[b, d] Appendix (n=1) Breast (n=1) Bone sarcoma (n=1) Pancreas (n=1)	62
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=13) Soft tissue sarcoma (n=11) Primary CNS (n=5) Bone sarcoma (n=1) Congenital mesoblastic nephroma (n=1) Melanoma (n=1)	32
Total number of patients (n)*			102

* consist of 93 patients with IRC tumour response assessment and 9 patients with primary CNS tumours (including glioma, glioblastoma and astrocytoma) with investigator tumour response assessment

[a] GIST: gastrointestinal stromal tumour
[b] brain metastases observed in one thyroid, one NSCLC, and one SCLC patient
[c] NSCLC: non-small cell lung cancer
[d] SCLC: small cell lung cancer

Baseline characteristics for the pooled 93 patients with solid tumours with an *NTRK* gene fusion were as follows: median age 41 years (range 0.1-78 years); 30% < 18 years of age, and 70% ≥ 18 years; 70% white and 53% male; and ECOG PS 0-1 (89%), or 2 (11%). Ninety-seven 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-three percent of all patients had received no prior systemic therapy. The most common tumour types represented were soft tissue sarcoma (23%), salivary gland tumour (18%), infantile fibrosarcoma (14%), thyroid cancer (11%), lung and melanoma cancer (8% for each), and colon cancer (6%).
Baseline characteristics for the 9 patients with primary CNS tumours with an *NTRK* gene fusion assessed by investigator were as follows: median age 12 years (range 2-79 years); 6 patients < 18 years of age, and 3 patients ≥ 18 years, and 8 patients white and 5 patients male; and ECOG PS 0-1 (8 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=93) and with post-hoc addition of primary CNS tumours (n=9) resulting in the pooled population (n=102), 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=93)**[a]	**Analysis in solid tumours including primary CNS tumours (n=102)**[a, b]
Overall response rate (ORR) % (n) [95% CI]	72% (67) [62, 81]	67% (68) [57, 76]
Complete response (CR)	16% (15)	15% (15)
Surgical complete response[c]	1% (1)	1% (1)
Partial response (PR)	55% (51)	51% (52)
Time to first response (median, months) [range]	1.81 [0.95, 14.55]	1.81 [0.95, 14.55]
Duration of response (median, months) [range] % with duration ≥ 6 months % with duration ≥ 12 months	NR [1.6+, 38.7+] 88% 75%	NR [1.6+, 38.7+] 88% 75%

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 (9 patients).
[c] Paediatric patient (6 months old at enrolment) with locally advanced unresectable infantile fibrosarcoma with complete surgical response.

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

Tumour type	Patients (n=102)	ORR		DOR	
		%	95% CI	≥ 12 months	Range (months)
Soft tissue sarcoma[a]	21	81%	58%, 95%	78%	1.9+, 38.7+
Salivary gland[a]	17	88%	64%, 99%	91%	3.7+, 33.7+
Infantile fibrosarcoma[a]	13	92%	64%, 100%	60%	1.6+, 17.3+
Thyroid[a]	10	70%	35%, 93%	86%	3.7, 29.8+
Primary CNS[b]	9	11%	0%, 48%	NR	2.0+
Lung[a]	7	71%	29%, 96%	75%	7.4+, 25.8+
Melanoma[a]	7	43%	10%, 82%	50%	1.9+, 23.2+
Colon[a]	6	33%	4%, 78%	NR	5.6, 9.2+
Gastrointestinal stromal tumour[a]	4	100%	40%, 100%	67%	7.4+, 20.0+
Bone sarcoma[a]	2	50%	1%, 99%	0%	9.5
Cholangiocarcinoma[a]	2	SD, NE	NA	NA	NA
Congenital mesoblastic nephroma[a]	1	100%	3%, 100%	NR	9.8+
Appendix[a]	1	SD	NA	NA	NA
Breast[a, c]	1	PD	NA	NA	NA
Pancreas[a]	1	SD	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] non-secretory

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=65), the ORR was 68%. In the paediatric sub-population (n=28), the ORR was 82%.

In 85 patients with wide molecular characterisation before larotrectinib treatment, the ORR in 48 patients who had other genomic alterations in addition to *NTRK* gene fusion was 58%, and in 37 patients without other genomic alterations ORR was 84%.

Pooled primary analysis set

The pooled primary analysis set consisted of 93 patients and did not include primary CNS tumours. Median time on treatment was 12.1 months (range: 0.66 to 40.7 months) based on July 2018 cut-off. Fifty-two percent of patients had received VITRAKVI for 12 months or more and 30% had received VITRAKVI 18 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, 75% patients had responses which were ongoing with an estimated 88% of responses lasting 6 months or longer and 75% of responses lasting 12 months or longer. Eighty-eight percent (88%) [95% CI: 81, 95] of patients treated were alive one year after the start of therapy. Median progression free survival had not been reached at the time of analysis.
The median change in tumour size in the pooled primary analysis set was a decrease of 66%.

Patients with primary CNS tumours

At the time of data cut-off, 8 of 9 enrolled patients with primary CNS tumours were evaluable for response by investigator assessment. A partial response was observed in 1 patient. At the time of data cut-off, time on treatment ranged from 2.8 to 9.2 months and was ongoing in 6 out of 9 patients

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 [2.99 ± 1.52] steady-state (arithmetic mean (± standard deviation)) 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.

5.2.1 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.

5.2.2 Distribution

The mean volume of distribution (V_{ss}) of larotrectinib in healthy adult subjects was 48 L following intravenous administration of an IV microtracer in conjunction with a 100 mg oral dose, indicating moderate distribution into tissues from the plasma. 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.

5.2.3 Metabolism / 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.

5.2.4 Elimination / Excretion

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.

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.

5.2.5 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.

5.2.6 Additional information on special populations

5.2.6.1 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).

5.2.6.2 Geriatric patients

AUC in patients >65 years or >80 years were similar to those in younger patients (<65 years).

5.2.6.3 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.

5.2.6.4 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.

5.2.6.5 Gender, Race, Body Weight

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

5.3.1 Systemic toxicity

Systemic toxicity was assessed in studies with daily oral administration up to 13-weeks 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. The following additional relevant findings were observed in both species: increased body weight and food consumption; an adaptive response in the liver secondary to induction of drug metabolizing enzymes; elevated serum liver enzymes (ALT and/or AST); histopathological changes in lymphoid tissues without corresponding changes in white blood cell counts; in rats, pancreatic changes; minor, reversible changes on red blood cell parameters; and increased heart weights without histopathological correlate were reported. 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.

5.3.2 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.

5.3.3 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.

5.3.4 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.

5.3.5 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 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

Ora-Sweet®: purified water, sucrose, glycerol, sorbitol, citric acid, sodium dihydrogen phosphate, flavoring and preservative agents methylparahydroxybenzoate and potassium sorbate

Natural Masking Type Flavor: glycerol, natural flavor ingredients

Natural Bitterness Masking Type Flavor: glycerol, natural flavor ingredients

Bitterness Masking Flavor: propylene glycol, natural flavor

FONATECH® Taste Modifier Flavor: propylene glycol, glycerol, natural flavor

6.2 Shelf life

Capsules

24 months

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 with a polyethylene (PE) seal liner.

Each carton contains one bottle of 100 mL oral solution.

7 Product Owner

Bayer AG

Kaiser-Wilhelm-Allee 1, 51373 Leverkusen, Germany

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