Taiwan Food and Drug Administration

Assessment Report

Trade Name：
維泰凱膠囊 25 毫克 (Vitrakvi 25 mg capsule)
維泰凱膠囊 100 毫克 (Vitrakvi 100 mg capsule)
維泰凱口服溶液 20 毫克/毫升 (Vitrakvi 20 mg/ml oral solution)

Active Ingredient：Larotrectinib

License Number：衛部藥輸字第 027747/027748/027746 號

Applicant：台灣拜耳股份有限公司

Approval Date：109.1.15

Indication：
適用於有 NTRK 基因融合的實質腫瘤之成人和兒童病人，並應符合以下三項條件:

一、 具NTRK基因融合且無已知的後天阻抗性突變(acquired resistance mutation)
二、 為轉移性實體腫瘤，或手術切除極可能造成嚴重病症(severe morbidity)
三、 沒有合適的替代治療選項，或於治療後發生疾病惡化。

1. **Background Information**

Trade Name	維泰凱膠囊 25 毫克 (Vitrakvi 25 mg capsule) 維泰凱膠囊 100 毫克 (Vitrakvi 100 mg capsule) 維泰凱口服溶液 20 毫克/毫升 (Vitrakvi 20 mg/ml oral solution)
Active Ingredient(s)	Larotrectinib
Applicant	台灣拜耳股份有限公司
Dosage Form & Strengths	capsule 25 mg, 100 mg oral solution 20 mg/ml
Indication	適用於有 NTRK 基因融合的實質腫瘤之成人和兒童病人，並應符合以下三項條件: 一、 具NTRK基因融合且無已知的後天阻抗性突變(acquired resistance mutation) 二、 為轉移性實體腫瘤，或手術切除極可能造成嚴重病症(severe morbidity) 三、 沒有合適的替代治療選項，或於治療後發生疾病惡化。 本適應症係依據腫瘤反應率及反應持續時間獲得加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。 VITRAKVI is a kinase inhibitor 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. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
Posology	**1. 病人選擇** 依據腫瘤檢體中發現具NTRK基因融合，而選擇接受VITRAKVI治療的病人。在開始使用VITRAKVI之前，

應先由適當的檢測方式確定腫瘤檢體具有NTRK基因融合（例如次世代定序NGS）。

2. 建議劑量

體表面積至少有1.0平方公尺之成年與兒童病人的建議劑量

VITRAKVI的建議劑量是口服100 mg，每天兩次，搭配或不搭配食物皆可，直至疾病惡化或直至出現不可接受的毒性。

體表面積不到1.0平方公尺之兒童病人的建議劑量

VITRAKVI的建議劑量是口服100 mg/m^2，每天兩次，搭配或不搭配食物皆可，直至疾病惡化或直至出現不可接受的毒性。

3. 針對不良反應的劑量調整

針對第3或4級不良反應：

- 暫時停用VITRAKVI，直到不良反應緩解或改善至基期狀態或第1級。
  如果緩解發生在4週內，請在下一次劑量調整時重新開始用藥。
- 如果不良反應未在4週內緩解，請永久停用VITRAKVI。

發生不良反應時，建議 VITRAKVI 劑量調整如表 1。

表1 發生不良反應時，建議VITRAKVI劑量調整

劑量調整	**體表面積至少有1.0平方公尺的成年與兒童病人**	**體表面積不到1.0平方公尺的兒童病人**
第一次	75 mg每天口服兩次	75 mg/m^2每天口服兩次
第二次	50 mg每天口服兩次	50 mg/m^2每天口服兩次
第三次	100 mg每天口服一次	25 mg/m^2每天口服兩次

針對經過三次劑量調整後仍無法耐受VITRAKVI的病人，請永久停用VITRAKVI。

4. 併用強效CYP3A4抑制劑的劑量調整

避免併用強效CYP3A4抑制劑與VITRAKVI。如果無法避免與強效CYP3A4抑制劑併用，需調降VITRAKVI劑

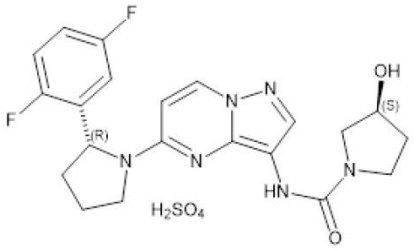
	量50%。在停用抑制劑3到5個清除半衰期後，請以CYP3A4抑制劑前使用的VITRAKVI劑量重新開始服用VITRAKVI。 **5. 併用強效CYP3A4誘導劑的劑量調整** 避免併用強效CYP3A4誘導劑與VITRAKVI。如果無法避免與強效CYP3A4誘導劑併用，需將VITRAKVI劑量調為兩倍。在停用誘導劑3到5個清除半衰期後，請以CYP3A4誘導劑前使用的VITRAKVI劑量重新開始服用VITRAKVI。 **6. 針對肝功能不全病人的劑量調整** 針對中度(Child-Pugh B)至重度(Child-Pugh C)肝損傷病人，調降VITRAKVI起始劑量50%。 **7. 給藥方式** 可使用VITRAKVI膠囊或口服溶液。 請勿在下一個排定劑量的6小時內補服遺漏的劑量。 如果在使用一劑VITRAKVI後發生嘔吐，請在排定時間服用下一劑藥物。 <u>膠囊</u> 需配水吞服完整膠囊。請勿咀嚼或弄碎膠囊。 <u>口服溶液</u> • 請冷藏保存含有VITRAKVI口服溶液的玻璃瓶。首次打開藥瓶的30天後剩餘未用的所有VITRAKVI口服溶液需丟棄。 • 在準備口服劑量給藥前，請先參閱使用說明。
Pharmacological Category **ATC Code**	L01XE53

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The chemical name of larotrectinib sulfate is (3*S*)-*N*-{5-[(2*R*)-2-(2,5-difluorophenyl)-1-pyrrolidinyl]pyrazolo[1,5-a]pyrimidin-3-yl}-3-hydroxy-1-pyrrolidinecarboxamide sulfate. The molecular formula for larotrectinib sulfate is $C_{21}H_{24}F_2N_6O_6S$ and the molecular weight is 526.51 g/mol. It has the following structure:



Larotrectinib sulfate is a chiral, non-hygroscopic, off-white to yellow to pinkish yellow solid. The solubility of larotrectinib sulfate is pH dependent. The chemical structure of larotrectinib sulfate is elucidated by IR, UV/VIS, ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, 2D-NMR spectroscopy, elementary analysis, mass spectrometry, and X-ray crystallography.

The specification for drug substance includes tests for appearance, identity, assay, impurities, residue on ignition, water content, residual solvents, and particle size.

2.1.2 Drug product (oral solution)

Vitrakvi 20 mg/mL oral solution consists of 100 mL solution of a 20 mg/mL larotrectinib (24.6 mg/mL larotrectinib sulfate) solution filled in 100 mL amber glass bottle and capped with child resistant closure. The specifications for the excipients are adequate.

Adequate release and shelf-life specifications have been presented for the Vitrakvi 20 mg/mL oral solution. Analytical methods were adequately described and well validated. Stability studies of drug product under long term condition (2℃-8℃) and accelerated condition (25℃/60% RH) have been carried out.

2.1.3 Drug product (capsule)

Vitrakvi 25 mg hard capsules is provided in a white opaque hard gelatin size “2” capsule printed with Bayer cross and the strength (25 mg) in blue ink. Vitrakvi 100 mg hard capsules is provided in a white opaque hard gelatin size “0” capsule printed with Bayer cross and the strength (100 mg) in blue ink.

The manufacturing process contains common steps for hard capsules to obtain drug product. The drug product specifications include appropriate tests for hard capsule dosage form. The analytical methods were adequately described and appropriately validated.

The container closure system for drug product is a standard high density polyethylene (HDPE) bottle with a child resistant polypropylene (PP) plastic closure. Stability studies of drug product under long term condition (25℃/60% RH) and accelerated condition (40℃/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Larotrectinib is a rationally designed, highly selective, and potent inhibitor of the tropomyosin receptor kinases (TRK), human tropomyosin receptor kinase A (TRKA), human tropomyosin receptor kinase B (TRKB), and human tropomyosin receptor kinase C (TRKC). In biochemical assays, larotrectinib inhibited the activity of all three wild-type Trk kinases at concentrations of between 5-11 nM (2.1-4.7 ng/mL). In transfected cells that overexpressed wild type Trk proteins or expressed either chimeric fusion proteins or the constitutively-active TrkAΔIg2 protein, larotrectinib inhibited proliferation at concentrations of between 6-25 nM (2.5-11.7 ng/mL). Peak plasma concentrations achieved in patients who received recommended clinical dose of 100 mg BID were ~914 ng/mL. In murine models harboring Trk-expressing tumors (constitutively active proteins due to chimeric gene fusions or deletion of the regulatory domain as well as overexpression of wild Trk), maximal anti-tumor activity in these models occurred at oral doses of 200 mg/kg, which corresponded to plasma concentrations of approximately 30 μg/mL and tumor concentrations of approximately 3 μg/mL and was associated with suppression of intratumoral pTrk, pAKT, and pERK.

In aspect of safety pharmacology, larotrectinib was a weak hERG inhibitor (IC50 of 147 μM), and there was no effect on ECG interval durations (including QT) or waveform morphologies in monkeys following administration of a single oral dose of 100 mg/kg. There were also no clear effects on respiratory endpoints in rats at an oral dose of 100 mg/kg. Larotrectinib appeared to increase GI motility in the rat following administration of a single oral dose of ≥10 mg/kg. This corresponded to an increase in gastric secretion at a dose of 100 mg/kg, but there was no evidence that larotrectinib irritated the gastric mucosa. There were no clear effects of larotrectinib on CNS function in a stand-alone single dose in vivo safety pharmacology study in rats at doses up to 100 mg/kg. However, behavioral observations suggestive of CNS effects did occur in longer-term rat toxicology studies, and neurotoxicity has been observed clinically as well.

2.2.2 Toxicological Studies

The sponsor evaluated the safety of larotrectinib in toxicology studies of up to 13 weeks duration in the rat and the monkey. Overt toxicity was only identified in the rat, and thus rat was regarded as the more sensitive species. In rat, dose limiting skin lesions were observed and were primarily responsible for mortality and morbidity in the 13-week repeat-dose study. Skin lesions were not reported in monkeys or humans. Other than the skin, there were no clear toxicological target organs identified.

Increased body weight was noted in all species and was considered as related to the

pharmacological activity as TRK inhibitor. Changes in brown fat were regarded as related to the hyperphagic obesity seen. In the 13-week monkey study, there was no evidence of significant target organ toxicity at doses of up to 100 mg/kg/day, and adverse clinical signs were limited to GI findings (emesis and discolored/liquid/ mucoid feces). Carcinogenicity studies were not conducted or required to support the use of larotrectinib in the proposed indication. Larotrectinib was negative in a standard battery of genotoxicity studies.

Although fertility studies with larotrectinib have not been conducted, larotrectinib affected neither the spermatogenesis in rats nor the histopathology of male reproductive tract in rats or monkeys. 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. Larotrectinib was not embroytoxic up to maternally toxic doses. Nonetheless, based on the mode of action of larotrectinib, the risk of fetal harm cannot be excluded when larotrectinib is administered to a pregnant woman, and pregnant women should be advised of the potential risk to a fetus.

In the juvenile rat study, the lowest dose (0.4/1.2 mg/kg/day), equivalent to 0.02-fold the recommended clinical exposure, was considered the NOAEL. At doses ≥4/12 mg/kg/day, increased mortality, neuronal effects, decreased growth and delay in sexual development were noted. At dose 15/45 mg/kg/day, CNS-related signs, skin lesions, and swollen abdomen (female) were noted. The observation that CNS findings in the juvenile animal study were more pronounced than those in older animals suggests that developing animals are at increased risk for neurological effects with larotrectinib.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The recommend dose is orally administered larotrectinib 100 mg twice daily for adult and 100 mg/m^2 twice daily with maximum of 100 mg BID for pediatric. Vitrakvi can be taken with or without food and recommended dose modifications for adverse reactions are appropriate.

The single-dose pharmacokinetics of larotrectinib is linear from 100 mg to 400 mg and slightly greater than proportional at doses of 600 mg to 900 mg in healthy volunteers. In adult patients who received Vitrakvi capsules 100 mg twice daily in Study LOXO-TRK-14001, peak plasma levels of larotrectinib were achieved at approximately 1 hour after dosing and steady-state was reached within 3 days. Mean steady-state larotrectinib (CV%) for C_{max} was 788 (81%) ng/mL and $AUC_{0\text{-}24hr}$ was 4351 (97%) ng•h/mL.

The mean absolute bioavailability of Vitrakvi capsules was 34% (range: 32% to 37%). In healthy subjects, the AUC of Vitrakvi oral solution was similar to that of the capsules and the C_{max} was 36% higher with the oral solution. The AUC of larotrectinib was similar and the C_{max} was reduced by 35% after oral administration of a single 100 mg capsule of Vitrakvi to healthy subjects taken with a high-fat meal compared to the C_{max} and AUC in the fasted state.

The mean (CV%) volume of distribution (V_{ss}) of larotrectinib is 48 (38%) L following intravenous administration of larotrectinib in healthy subjects. Larotrectinib is 70% bound to human plasma proteins *in vitro* and binding is independent of drug concentrations. The blood-to-plasma concentration ratio is 0.9. Larotrectinib is metabolized predominantly by CYP3A4. Following oral administration of a single [^{14}C]-radiolabeled 100 mg dose of larotrectinib to healthy subjects, 58% (5% unchanged) of the administered radioactivity was recovered in feces and 39% (20% unchanged) was recovered in urine. The mean (CV%) clearance (CL/F) of larotrectinib is 98 (44%) L/h and the half-life is 2.9 hours following oral administration of Vitrakvi in healthy subjects.

2.3.2 Interaction Studies

Larotrectinib is CYP3A4, P-gp and BCRP substrate. Avoid co-administration of Vitrakvi with a strong CYP3A4 inhibitor or a strong CYP3A4 inducer is recommended because they may alter larotrectinib exposure. If co-administration cannot to be avoided, the dose of Vitrakvi should be modified as recommended. Reduce the Vitrakvi dose by 50% when co-administrated with a strong CYP3A4 inhibitor. Double the Vitrakvi dose when co-administrated with a strong CYP3A4 inducer.

Coadministration of Vitrakvi with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions. Avoid co-administration of Vitrakvi with sensitive CYP3A4 substrates. If co-administration of these sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs.

2.3.3 Special Populations

Age did not affect significant the PK of larotrectinib based on the population PK analysis.

Following oral administration of a single 100 mg dose of Vitrakvi capsules in subjects with end-stage renal disease (e.g., subjects who required dialysis), the $AUC_{0\text{-inf}}$ of larotrectinib increased 1.5-fold and C_{max} increased 1.3-fold as compared to that in subjects with normal renal function. Therefore, no dose adjustment is recommended with renal impairment of any severity.

Following oral administration of a single 100 mg dose of Vitrakvi capsules, the $AUC_{0\text{-inf}}$ of

larotrectinib increased 1.3-fold in subjects with mild hepatic impairment, 2-fold in subjects with moderate hepatic impairment and 3.2-fold in subjects with severe hepatic impairment as compared to that in subjects with normal hepatic function. The C_{max} was similar in subjects with mild and moderate hepatic impairment and the C_{max} of larotrectinib increased 1.5-fold in subjects with severe hepatic impairment as compared to that in subjects with normal hepatic function. No dose adjustment is recommended for patient with mild hepatic impairment. Reduce the 50% starting dose of Vitrakvi in subjects with moderate and severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The efficacy of larotrectinib was evaluated in pediatric and adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label, single-arm clinical trials: Study LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. Adult patients received larotrectinib 100 mg orally twice daily and pediatric patients (18 years or younger) received larotrectinib 100 mg/m^2 up to a maximum dose of 100 mg orally twice daily until unacceptable toxicity or disease progression. Identification of positive NTRK gene fusion status was prospectively determined in local laboratories using next generation sequencing (NGS) or fluorescence in situ hybridization (FISH).

The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

The assessment of efficacy was based on the first 55 patients (primary analysis set, PAS) with solid tumors with an NTRK gene fusion enrolled across the three clinical trials. Baseline characteristics were: median age 45 years (range 4 months to 76 years); 22% <18 years of age, and 78% ≥18 years of age; 53% male; 67% White; 7% Hispanic/Latino, 4% Asian, 4% Black; and ECOG performance status 0-1 (93%) or 2 (7%). Eighty-two percent of patients had metastatic disease and 18% had locally advanced, unresectable disease. Ninety-eight percent of patients had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. Of these, 82% (n = 45) received prior systemic therapy with a median of two prior systemic regimens and 35% (n = 19) received three or more prior systemic regimens. The most common cancers were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%).

The overall response rate by IRC assessment for PAS was **75%** (95% CI: 64, 85). Efficacy results are presented in Table 1 and Table 2. A further 18 patients enrolled after the 55th PAS-evaluable patient but before the data cut-off of 19 FEB-2018 who met all PAS eligibility criteria and had central review of tumor response by the IRC were pooled to form ePAS (extended primary analysis set). A total of 73 adult and pediatric patients with the TRK fusion cancer comprised the ePAS. The response rate by IRC assessment were consistent with the first 55 patients enrolled (PAS) and 73 patients enrolled (ePAS). For ePAS, the ORR was **75%** (95% CI: 64, 85).

Table 1 Efficacy Results for Patients with Solid Tumors Harboring NTRK Gene Fusions in Pooled Analysis Sets

	PAS (N=55)
IRC Assessment	
Overall response rate (95%CI)	75% (61%, 85%)
Complete response	22%
Partial response	53%
Duration of response	N = 41
Range (months)	1.6+, 33.2+
% with duration ≥ 6 months	73%
% with duration ≥ 9 months	63%
% with duration ≥ 12 months	39%

Table 2 Efficacy Results by Tumor Type in Pooled Analysis Sets

Tumor Type	Patients (N=55)	ORR		DOR
		%	95% CI	Range (months)
Soft tissue sarcoma	11	91%	(59%, 100%)	3.6, 33.2+
Salivary gland	12	83%	(52%, 98%)	7.7, 27.9+
Infantile fibrosarcoma	7	100%	(59%, 100%)	1.4+, 10.2+
Thyroid	5	100%	(48%, 100%)	3.7, 27.0+
Lung	4	75%	(19%, 99%)	8.2, 20.3+
Melanoma	4	50%	NA	1.9, 17.5+*
Colon	4	25%	NA	5.6*
Gastrointestinal stromal tumor	3	100%	(29%, 100%)	9.5, 17.3
Cholangiocarcinoma	2	SD, NE	NA	NA
Appendix	1	SD	NA	NA

Breast	1	PD	NA	NA
Pancreas	1	SD	NA	NA

NA = not applicable due to small numbers or lack of response; CR = complete response; PR = partial response; NE = not evaluable; SD = stable disease; PD = progressive disease. + Denotes ongoing response. * Observed values at data cutoff, not a range.

2.4.2 Safety Results

The safety data showed exposure to larotrectinib in 176 patients, including 70 (40%) patients exposed for greater than 6 months and 35 (20%) patients exposed for greater than 1 year. Across these 176 patients, the median age was 51 years (range: 28 days to 82 years); 25% were 18 years or younger; 52% were male; and 72% were White, 11% were Hispanic/Latino, 8% were Black, and 3% were Asian. The most common tumors in order of decreasing frequency were soft tissue sarcoma (16%), salivary gland (11%), lung (10%), thyroid (9%), colon (8%), infantile fibrosarcoma (8%), primary central nervous system (CNS) (7%), or melanoma (5%). NTRK gene fusions were present in 60% of larotrectinib-treated patients. Most adults (80%) received larotrectinib 100 mg orally twice daily and 68% of pediatrics (18 years or younger) received larotrectinib 100 mg/m^2 twice daily up to a maximum dose of 100 mg twice daily. The dose ranged from 50 mg daily to 200 mg twice daily in adults and 9.6 mg/m2 twice daily to 120 mg/m2 twice daily in pediatrics.

The most common adverse reactions (≥ 20%) in order of decreasing frequency were fatigue, nausea, dizziness, vomiting, anemia, increased AST, cough, increased ALT, constipation, and diarrhea. The most common serious adverse reactions (≥ 2%) were pyrexia, diarrhea, sepsis, abdominal pain, dehydration, cellulitis, and vomiting. Grade 3 or 4 adverse reactions occurred in 51% of patients; adverse reactions leading to dose interruption or reduction occurred in 37% of patients and 13% permanently discontinued larotrectinib for adverse reactions. The most common adverse reactions (1-2% each) that resulted in discontinuation of larotrectinib were brain edema, intestinal perforation, pericardial effusion, pleural effusion, small intestinal obstruction, dehydration, fatigue, increased ALT, increased AST, enterocutaneous fistula, increased amylase, increased lipase, muscular weakness, abdominal pain, asthenia, decreased appetite, dyspnea, hyponatremia, jaundice, syncope, vomiting, acute myeloid leukemia, and nausea. The most common adverse reactions (≥ 3%) resulting in dose modification (interruption or reduction) were increased ALT (6%), increased AST (6%), and dizziness (3%). Most (82%) adverse reactions leading to dose modification occurred during the first three months of exposure.

Three AEs of special interest were defined prospectively, based on predictions from the TRK related neurobiology literature, the preclinical toxicology program, and from early clinical experience with larotrectinib. These were neurologic reactions, transaminase elevations, and

neutropenia.

Among the 176 patients who received larotrectinib, neurologic adverse reactions of any grade occurred in 53% of patients, including Grade 3 and Grade 4 neurologic adverse reactions in 6% and 0.6% of patients, respectively. The majority (65%) of neurologic adverse reactions occurred within the first three months of treatment (range: 1 day to 2.2 years). Grade 3 neurologic adverse reactions included delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). Grade 4 encephalopathy (0.6%) occurred in a single patient. Neurologic adverse reactions leading to dose modification included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%).

Among the 176 patients who received larotrectinib, increased transaminases of any grade occurred in 45%, including Grade 3 increased AST or ALT in 6% of patients. One patient (0.6%) experienced Grade 4 increased ALT. The median time to onset of increased AST was 2 months (range: 1 month to 2.6 years). The median time to onset of increased ALT was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients.

Based on the occurrence of neurologic reactions, a warning is proposed on the drug label. A warning is also proposed on the drug label to monitor liver function, and to consider reducing or discontinuing larotrectinib if ALT and/or AST elevations occur.

2.5 Bridging Study Evaluation

At the 100 mg single dose, the larotrectinib exposure in Asian target patients (N=4) was about 1.49-fold in non-Asian patients. At the 100 mg BID, the larotrectinib C_{max} and AUC_t in Asian target patients (N=3) was about 0.996-fold and 0.753-fold in non-Asian patients. The inter-subject variation of larotrectinib was about 40~60%.

Due to the limited Asian PK information provided, it was inconclusive to determine the ethnic difference from PK aspect. Considering (1) the difficulty to collect the target patients in reality and (2) the unmet medical need, it is recommended to waive pre-market bridging study request and a post-marketing study to collect additional East-Asian PK data is required.

Epidemiological studies on the prevalence of solid tumors harboring an NTRK gene fusion across ethnic populations are limited. In 3 early studies, few Asians (8 patients) were enrolled. Even though, the ORR is 75.0%, which is consistent with that for the overall population. No SAE is noted for Asians.

Overall, considering the characteristics of precision medicine of larotrectinib and based on available data, bridging study is waived. A post-marketing study to collect additional East-Asian PK data is required.

2.6 Conclusion

Overall, the submitted NDA package of larotrectinib for CMC, PT, PK and Clinical section were considered adequate and acceptable. The benefit/risk ratio is positive in 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.

The efficacy evidence primarily was based on surrogate endpoints, overall response rate and duration of response and an accelerated approval is recommended. The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post-market setting. A risk management plan (RMP) is not required to ensure that the benefits of the drug outweigh the risks.Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

3. Post-Marketing Requirements

Submit the following study report while available：

1. A non-interventional study entitled: "*ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib*", serves as the confirmatory trial.
   Note: This study is an international study and the sponsor (Bayer) agrees to enroll Taiwan population in the ON-TRK study.
2. A post-marketing study to collect additional East-Asian PK data is required.