An expanded access program to provide oral larotrectinib in patients with locally advanced or metastatic solid tumor harboring NTRK gene fusion

Objective for Larotrectinib EAP

To provide ethical access to larotrectinib for patients with locally advanced or metastatic cancer harboring *NTRK* gene fusion

Eligibility Criteria

Inclusion criteria

1. Written informed consent
2. Age ≥ 1 month
3. ECOG score of ≤3 or Lansky PS of ≥50 for patients <16 years old
4. Locally advanced or metastatic solid tumor
5. Tumor harboring *NTRK1*, *NTRK2* or *NTRK3* gene fusion confirmed by one of the local diagnostic testing methods: Fluorescence In-Situ Hybridization (FISH), Polymerase Chain Reaction (PCR) or Next-Generation Sequencing (NGS). De-identified pathology report with the confirmed NTRK gene fusion should be provided for Sponsor review as part of screening. Positive Immunohistochemistry (IHC) alone is not sufficient to be considered eligible.
6. Subjects must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the treating physician, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.
7. Patients unable to participate in any larotrectinib clinical trials with an inhibitor of tropmyosin-related kinases (TRK)
8. Adequate liver and renal function as assessed by the following laboratory requirements conducted within 7 days before starting larotrectinib treatment
    - Total bilirubin <2.5 × ULN, except in the setting of biliary obstruction. Subjects with a known history of Gilberts Disease and an isolated elevation of indirect bilirubin are eligible.

      For pediatric patients:
      Total bilirubin < 1.5 x ULN, except in the setting of biliary obstruction. Subjects with a known history of Gilbert Disease and an isolated elevation of indirect bilirubin are eligible.

    - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) <2.5 × upper limit of normal (ULN), or AST and ALT <5 × ULN if liver function abnormalities are due to underlying malignancy.

      For pediatric patients:
      Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) < 1.5 x ULN

- Serum creatinine <2.0 × ULN OR an estimated glomerular filtration rate ≥30 mL/minute using the Cockroft-Gault formula

$$\frac{(140\text{-age}) \times \text{body weight (kg)} \times 0.85 \text{ (if female)}}{\text{Serum creatinine (mg/dl)} \times 72}$$

with either result acceptable for enrollment.

Or, for pediatric patients

Estimated glomerular filtration rate ≥30 mL/minute/1.73 m2 based on local institutional practice for determination OR a serum creatinine at or below that based on age/gender as follows with either result acceptable for enrollment (Table Below):

Table Estimated glomerular filtration rate based on age and gender

Age	Maximum Serum Creatinine (mg/dL)		Maximum Serum Creatinine (µmol/L)	
	Male	Female	Male	Female
1 mth to <6 mths	0.4	0.4	35	35
6 mths to <1 year	0.5	0.5	44	44
1 to <2 years	0.6	0.6	53	53
2 to <6 years	0.8	0.8	71	71
6 to <10 years	1	1	88	88
10 to <13 years	1.2	1.2	106	106
13 to <16 years	1.5	1.4	132	124
≥16 years	1.7	1.4	150	124

9. Women of childbearing potential (WOCBP) and fertile men must agree to use adequate contraception when sexually active until at least 1 month after the last drug administration. The treating physician or a designated associate is requested to advise the patient how to achieve highly effective birth control.

Non-eligibility criteria

Patients who meet any of the following criteria are not allowed to receive Larotrectinib:

1. Investigational agent or anticancer therapy within 2 weeks prior to planned start of larotrectinib or 5 half-lives, whichever is shorter, and without recovery of clinically significant toxicities from that therapy.
2. Prior progression while receiving approved or investigational tyrosine kinase inhibitors targeting TRK. Subjects who received less than 28 days of treatment and discontinued because of intolerance or toxicity are eligible.
3. Symptomatic or unstable brain metastases. (Note: patients with asymptomatic brain metastases are eligible to participate). Patients with primary CNS tumors are eligible.
4. Active uncontrolled systemic bacterial, viral, or fungal infection, unstable cardiovascular disease or other systemic disease that would limit compliance with study procedures.
5. Inability to discontinue treatment with a strong CYP3A4 inhibitor or inducer prior to start of treatment initiation.
6. Pregnancy or lactation.

Dose Modifications for Adverse Reactions

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.

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.

Safety Reporting

What will be reported?

Bayer Pharmaceuticals and Clinigen will comply with pharmacovigilance legislation which includes the collection and reporting of all Adverse Events (SAEs/AEs) and other safety related information (OSRI) to all relevant regulatory authorities (where required). The prescribing Physician must follow all applicable national pharmacovigilance regulations and inform local competent authority(ies) of the Adverse Event and OSRI, where applicable.

How will safety be reported?

Details of the SAEs/AEs/OSRI must be submitted to CLINIGEN via its RWD Platform. Link of the Platform will be provided.

- All SAEs regardless of causality must be reported within one business day of awareness. A paper SAE form will be available through Clinigen's Medicine Access in the case the RWD platform is unavailable.
- All AEs regardless of causality must be reported in the Adverse Event page in the RWD Platform
- OSRI must be reported to country or local regulatory authorities where required

Optional Real-World Data Collection

What is Real World Data?

Real-World Data (RWD) can be considered as data routinely captured as part of standard clinical practice. Bayer would like to collect certain RWD from physicians for their patients receiving Larotrectinib as part of the Expanded Access Program (EAP). As part of the EAP, it is appropriate for manufacturers of the treatment to ask physicians to provide certain RWD that may be useful to understand the patient response to treatment if local regulations permit. The following data points will be collected:

Visit type	To be collected
Baseline Visit	• Demography • Medical/Cancer history: ECOG/Lansky score • Treatment history: prior anti-cancer treatment and concomitant medication • Tumour characteristics • NTRK gene fusion results • Prior to Larotrectinib 1st dose: vital signs, physical examination, lab assessment
Treatment Visit	• Vital signs • Brief physical examination/ECOG • Larotectinib dosing • Lab assessment • Adverse events • Concomitant medication
Larotrectinib Treatment Discontinuation/safety follow up (+ 30 days after last dose)	• Reason for discontinuation • Anti-cancer treatment post-larotrectinib • Adverse events • Concomitant medication

Long term follow-up Visit	• Adverse events • Concomitant medication • Survival status

Long term follow up visit ends when one of the following occurs:

- EAP in the respective country closes and larotrectinib transitions to commercially-available product
- Sponsor terminates EAP in all countries
  Patient withdraws from long term follow-up
- Death

When will patients be discontinued from larotrectinib treatment?

Patient can be discontinued from treatment for the following reasons:

- Patient's request at any time irrespective of reason
- Radiological disease progression
- Clinical progression
- Unacceptable adverse events, or change in underlying condition such that the patient can no longer tolerate therapy
- Physician's decision including patient non-compliant, need for other anticancer therapy or surgery or radiotherapy to the only site(s) of disease
- Pregnancy
- Transitioned to commercially-available product
- Sponsor termination of the protocol

Voluntary Tissue Sample Collection

Why are we collecting tissue samples?

Bayer would like to collect voluntary tissue samples to understand the degree of agreement between local labs and central labs for the NTRK- Fusion assessment. Any discrepancies found between the original test for eligibility and the voluntary testing will not affect the patient's treatment as the patient will already be receiving treatment.

How does it work?

Patients who opt-in for voluntary tissue collection will send samples directly to a designed central laboratory. Clinigen will provide with an instruction sheet with shipping details. Tissue samples will be returned to the patient and investigator after use.