Post Authorization Safety Study (PASS) Information

Acronym/Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0, 04 SEP 2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	BAY2757556, TRK inhibitor, larotrectinib sulfate
Medicinal product	Larotrectinib, (25 mg capsule; 100 mg capsule; 20 mg/mL oral solution)
EU Product reference	Not yet available
EU Procedure number	EMEA/H/C/004919
US NDA number	NDA 210,861 (capsule; oral) NDA 211,710 (solution; oral)
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany
Research question and objectives	The purpose of this study is to describe, under real-world conditions, the safety and effectiveness of larotrectinib in patients with locally advanced or metastatic TRK fusion cancer for whom a decision to treat with larotrectinib has been made before enrollment. The primary objective of this study is to describe the safety of larotrectinib in adult and pediatric patients with locally advanced or metastatic TRK fusion cancer, including incidences of all treatment-emergent adverse events (TEAEs) in real-world practice conditions. The secondary objectives of this study are: • To describe the effectiveness of larotrectinib, including overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), progression-free survival

	(PFS), and overall survival (OS) by investigator-based assessment • To describe the patterns of larotrectinib treatment, including actual doses, duration of treatment (DOT), and other dosing parameters • To describe the effectiveness of larotrectinib in subgroups of patients, including but not limited to: by age, *NTRK* gene, *NTRK* gene partner, testing methodology, country/region, prior therapy (type and/or number of lines of therapy), and/or by other patient baseline characteristics • To describe long-term effects of larotrectinib on growth (height and weight), neurological outcomes, developmental milestones, and sexual development (Tanner scale) in the pediatric cohort Additional exploratory objectives include: • To describe the effectiveness of larotrectinib, including overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), progression-free survival (PFS) based on radiological assessments of tumor response as determined by an Blinded Independent Review Committee (BIRC) as applicable • To determine procedures avoided because of the use of larotrectinib (e.g. amputation or other disfiguring procedures) in infantile fibrosarcoma • To determine the number of patients who underwent surgery for a curative intent (excluding amputation) because of the use of larotrectinib • To describe systemic treatment prior to larotrectinib treatment, including doses, duration of treatment, best tumor response, and reasons for discontinuation, as appropriate
Countries of study	USA and countries in Europe/North/Latin America/Asia Pacific. The countries have not yet been identified. An updated list is available as a stand-alone document (listed in Annex 1).
Author	PPD, Bayer US LLC. 100 Bayer Boulevard, Whippany, 07981 NJ, USA

Marketing authorization holder

Marketing authorization holder(s)	Ex-USA: Bayer AG, 51368 Leverkusen, Germany USA: Oncology, Inc. Stamford, CT 06901, USA
MAH contact person	PPD, Global Regulatory Leader Bayer AG, 13353 Berlin, Germany:

The study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

Contents

2. List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical (Classification System)
BIRC	Blinded Independent Review Committee
BOR	Best Overall Response
CFR	Code of Federal Regulations
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria Adverse Event
DCR	Disease Control Rate
DMP	Data Management Plan
DOR	Duration of Response
DOT	Duration of Treatment
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
FISH	Fluorescent In Situ Hybridization
FPFV	First Patient First Visit
GI	Gastrointestinal
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
H&N	Head and Neck
HEOR	Health Economics and Outcomes Research
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board

IRC	Imaging Review Charter
IT	Information Technology
LCL	Lower Control Limit
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
N/A	Not Applicable
NCI	National Cancer Institute
NGS	Next-Generation Sequencing
NIS	Non-interventional Study
NNH	Number Needed to Harm
NTRK	Neurotrophic Tyrosine Kinase
ORR	Overall Response Rate
OS	Overall Survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Progressive Disease
PFS	Progression-Free Survival
PMCF study	Post Market Clinical Follow-up study
PR	Partial Response
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible for Pharmacovigilance
QRP	Quality Review Plan
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria In Solid Tumors
rt-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
STS	Soft Tissue Sarcoma
TEAE	Treatment Emergent Adverse Event
TTE	Time To Response
UCL	Upper Control Limit

3. Responsible parties

3.1 Study initiator and funder

Role: NIS Conduct Responsible
Name: PPD
E-mail: PPD

Role: Qualified Person responsible for Pharmacovigilance (QPPV)
Name: PPD

Role: MAH contact person (Regulatory Affairs)
Name: PPD

Role: NIS Safety Lead
Name: PPD

Role: NIS Medical Expert
Name: PPD

Role: NIS Statistician
Name: PPD

Role: NIS Data Manager
Name: PPD

Role: NIS Epidemiologist
Name: PPD

Role: NIS Health Economics and Outcomes Research (HEOR) responsible
Name: PPD

Role: Regulatory Affairs responsible
Name: PPD

Role: Real World Evidence (RWE) & Outcomes Data Generation (ODG) responsible
Name: PPD

Contact details of the responsible parties at Bayer AG are available upon request. Signatures of the responsible parties are collected in Annex 5: Signature pages.

3.2 Collaborators/Committees

Contact details on the coordinating and/or principal investigators, co-investigators and other site personnel for each country and site participating in the study are listed in a stand-alone document (see Annex 1) which is available upon request.

A Steering Committee of external experts will be asked to provide support for the development of the study protocol and CRF. The committee will also provide expertise and guidance regarding the study conduct, and the analysis, interpretation and publication of results. Information on the Steering Committee Members and the respective Charter are kept as stand-alone documents (see Annex 1) which are available upon request.

In addition to the local investigator-based assessment, radiological tumor assessments by a Blinded Independent Review Committee (BIRC) will be also described. Where available, copies of scans from radiological tumor assessments, typically in Digital Imaging and Communications in Medicine (DICOM) format, will be transmitted to and archived at a central imaging core laboratory for independent assessment. A BIRC will be instituted in order to describe the tumor response (per RECIST 1.1 or RANO as applicable) by independent review; an Imaging Review Charter (IRC) will describe the design and details of the independent review process(see Annex 1).

Administrative changes of responsible persons and/or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

4. Abstract

Acronym/Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0, 04 SEP 2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
Author	Marc Fellous, Bayer US LLC. 100 Bayer Boulevard, Whippany, 07981 NJ, USA
Rationale and background	TRK fusion cancer is rare but presents as a variety of solid tumors. Larotrectinib is a highly selective TRK inhibitor that, in a pooled analysis of patients in phase 1/2 clinical trials, demonstrated an effective and sustained response in the majority of patients with TRK fusion cancer. Because of the limited number of patients treated with larotrectinib, information relating to its safety profile in a broader population and over extended time periods is lacking. Therefore, there is a need for data in a larger patient population, and for real-world data on larotrectinib treatment. This study will describe the safety and effectiveness of larotrectinib under real-world treatment conditions and provide information about the management of patients with locally advanced or metastatic TRK fusion cancer in standard clinical practice.
Research question and objectives	The purpose of this study is to describe, under real-world conditions, the safety and effectiveness of larotrectinib in patients with locally advanced or metastatic TRK fusion cancer for whom a decision to treat with larotrectinib has been made before enrollment. The primary objective of this study is to describe the safety of larotrectinib in patients with locally advanced or metastatic TRK fusion cancer, including incidences of all treatment-emergent adverse events (TEAEs) in real-world practice conditions.

	The secondary objectives of this study are: • To describe the effectiveness of larotrectinib, including overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) by investigator-based assessment • To describe patterns of larotrectinib treatment, including actual doses, duration of treatment (DOT), and other dosing parameters • To describe the effectiveness of larotrectinib in subgroups of patients, including but not limited to: by age, *NTRK* gene, *NTRK* gene partner, testing methodology, country/region, prior therapy (type and/or number of lines of therapy), and/or by other patient baseline characteristics • To describe long-term effects of larotrectinib on growth (height and weight), neurological outcomes, developmental milestones, and sexual development (Tanner scale) in the pediatric cohort Additional exploratory objectives include: • To describe the effectiveness of larotrectinib, including overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), progression-free survival (PFS) based on radiological assessments of tumor response as determined by a Blinded Independent Review Committee (BIRC) as applicable • To determine procedures avoided because of the use of larotrectinib (e.g. amputation or other disfiguring procedure) in infantile fibrosarcoma • To determine the number of patients who underwent surgery for a curative intent (excluding amputation) because of the use of larotrectinib • To describe systemic treatment prior to larotrectinib treatment, including doses, DOT, best tumor response, and reasons for discontinuation, as appropriate
Study design	International, prospective, open-label, multicenter, multi-cohort, non-interventional study.

	Specific cohorts: gastrointestinal (GI), head and neck (H&N), lung, soft tissue sarcoma (STS), primary central nervous system (CNS), melanoma, pediatrics, and others. The recruitment period will be 36 months; the end of the study for all cohorts but the pediatric cohort will happen after the final patient has been in the study for at least 24 months, or is no longer under observation owing to being lost to follow-up, withdrawal, or death. For the pediatric cohort, each patient will be followed up for at least 60 months from larotrectinib initiation unless the patient is discontinued due to lost to follow-up, withdrawal, or death
Population	Adult and pediatric (from birth to 18 year old) patients with a locally advanced or metastatic solid tumor harboring an NTRK gene fusion (detected by NGS, FISH, rt-PCR or other genomic testing able to detect NTRK gene fusion) assessed locally for whom a decision to treat with larotrectinib has been made by the treating physician prior to or at the time of study enrollment.

Variables	Variables for the primary objective are TEAEs, including the frequency, severity according to CTCAE v.5, seriousness, causality of TEAEs, and action taken related to larotrectinib treatment. Data will be collected up to 30 days after last dose.
	
	Variables for the secondary and exploratory objectives are
	
	• Demographic data and baseline characteristics (including ECOG PS, Lansky performance status, or Karnofsky score and comorbidities)
	
	• Disease history (tumor type, date of diagnosis, TNM at diagnosis, prior treatment [surgery, radiotherapy, systemic therapy] and pathology report at initial diagnosis and after subsequent surgery as applicable)
	
	• Previous systemic therapy
	  o Initiation and termination dates
	  o Best tumor response to therapy
	  o Date of radiological progression on therapy
	
	• *NTRK* testing (date of the testing, testing method used, *NTRK* gene and gene partner involved in the gene fusion [when applicable], other genomic alterations) at baseline and subsequently as applicable

	• AEs /SAEs
	• Tumor assessments (at study enrollment and during larotrectinib treatment)
	• Larotrectinib use
	  o Initiation and termination dates
	  o Dosage and dose modification
	• Date of radiological and/or clinical progression on larotrectinib
	• Laboratory examination data
	• Date of death/last follow-up
	• Height, weight, neurological examination, developmental milestones, age at adrenarche if applicable (males), age at menarche if applicable (females), and sexual development using Tanner stages for the pediatric cohort only.
	• In patients with sarcoma, including infantile fibrosarcoma, whether an amputation was considered for the patient prior to treatment with larotrectinib
	• Surgery with curative intent while on larotrectinib (date and type of surgery)

Data sources	Treatment-related data are documented during visits that take place in routine practice. Historic data are based on medical records or on interviewing the patient or the patient's representative.
Study size	The study aim is to enroll and collect data from up to 300 patients, which will allow for the observation of at least 1 adverse event for even uncommon occurring events with a 95% probability. With 300 patients, if the observed incidence rate is between 1% and 10%, the width of a 95% confidence interval (CI) for the rate of AE will be approximately 2.69% to 7.12%. Patients will be allocated to one of the cohorts depending on their tumor type or age: gastrointestinal (GI), head and neck (H&N), lung, soft tissue sarcoma (STS), primary central nervous system (CNS), melanoma, pediatric, and 'other'.
Data analysis	Statistical analyses will be of an explorative and descriptive nature. The study is not aimed to test pre-defined hypotheses.

	All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable. For time-to-event endpoints, such as OS, descriptive summaries of Kaplan–Meier (KM) estimates with 95% CIs and KM curves will be presented. Patients who took at least one dose of larotrectinib will be included in the safety analysis set. Patients who took at least one dose of larotrectinib, did not violate a major inclusion/exclusion criterion, and had at least one post baseline assessment after receiving larotrectinib will be included in the full analysis set. Safety data will be analyzed on the safety analysis set, effectiveness data on the full analysis set. Demographic and baseline data will be described for both full and safety analysis sets. All analyses will be performed for the total study population (overall analysis) and separately for each cohort as appropriate. Additional analyses may be done by participating country if patient numbers are sufficient and if required for local reasons. Whenever reasonable, data will be presented by subgroups (e.g. age, gender, baseline characteristics, and prior therapy).	
Milestones	First patient first visit:	Q4 2019
	Last patient first visit for all cohorts	Q4 2022
	Last patient last visit for all cohorts excluding pediatric cohort	Q4 2024
	Last patient last visit for the pediatric cohort	Q4 2027
	Final report for all cohorts excluding pediatric cohort	Q2 2025
	Final report for the pediatric cohort	Q2 2028

5. Amendments

None

6. Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrollment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document (Annex 1) that is available upon request.

Table 1: Milestones

Milestone*	**Planned date**
Start of data collection (first patient first visit)	Q4 2019
Registration in the EU PAS register	Q3 2019
Annual safety report	2020 - 2023
Interim review	Interim reviews for safety and effectiveness will be performed after approximately 50 patients pooled across tumor types complete at least 6 months of treatment or discontinue treatment. Subsequent reviews will be performed after approximately 150 and 300 patients have met the same conditions
Cohort review(s)	Reviews by cohort type will be performed after approximately 10 patients per cohort complete at least 6 months of treatment or discontinue treatment. The various reviews may be combined if they are expected to occur within approximately 1 month of each other
Last patient first visit for all cohorts	Q4 2022
Last patient last visit for all cohorts except the pediatric cohort	Q4 2024
End of data collection (data base clean) for all cohorts except the pediatric cohort	Q1 2025

Milestone*	Planned date
Final report of study results for all cohorts except the pediatric cohort	Q2 2025
Last patient last visit for the pediatric cohort	Q4 2027
End of data collection (data base clean) for the pediatric cohort	Q1 2028
Final report of study results for the pediatric cohort	Q2 2028

*Study, interim and cohort reviews may be combined if they are expected to occur within one month of each other

7. Rationale and background

TRK fusion cancer, caused by *NTRK* gene fusions, is rare (occurring in less than 1% of cancers [1]) and is present in many types of pediatric and adult solid tumors. *NTRK* gene fusions occur frequently in a number of rare tumors, such as mammary analogue secretory carcinoma of the salivary glands (almost 100% incidence of *NTRK* gene fusion) and infantile fibrosarcoma (90.9%), and infrequently in some more common cancers, such as lung adenocarcinoma (3.3%) and colorectal cancer (0.7%) [2,3,4,5]. Selective inhibition of the constitutively active TRK fusion proteins is a promising therapeutic target [6].

Larotrectinib is an oral selective inhibitor of tropomyosin-related kinases (TRKA, TRKB, and TRKC). It has low nanomolar potency against all three TRK family members in enzyme and cellular assays, with 100 to 1,000-fold selectivity relative to other kinases.

The efficacy and safety of larotrectinib were evaluated in three multicenter trials: a phase 1 study involving adults (NCT02122913), a phase 1–2 study (SCOUT trial – NCT02637687) involving children, and a phase 2 study (NAVIGATE trial – NCT02576431) involving adolescents and adults. Pooled data from the first 55 patients with advanced, progressive cancers harboring *NTRK* gene fusions who enrolled to these 3 multicenter trials represented 17 unique cancer diagnoses and demonstrated an overall response rate of 75% including a complete response (CR) rate of 22% (assessed by an independent radiology review committee). Safety data from 19 February 2018 on 176 patients exposed to larotrectinib showed that the most common treatment-related AEs (≥20%) were fatigue, nausea, dizziness, vomiting, anemia, increased AST, cough, increased ALT, constipation, and diarrhea. No grade 3 treatment-related AEs occurred in more than 4% of the patients and only one patient had a grade 4 treatment-related AE (pyrexia) [7].

The purpose of this non-interventional study is to describe in a real-world setting the safety and effectiveness of larotrectinib in patients with locally advanced or metastatic TRK fusion cancer, who have limited effective treatment options, especially in advanced disease. As a therapy for rare disease, larotrectinib is approved with a relatively small number of patients enrolled to one of three early phase trials. The results indicated clinical effectiveness for larotrectinib in patients with TRK fusion cancer; but the available safety data – with respect to patient numbers and longer-term exposure – are relatively limited. This post-approval study will generate additional safety data in a

larger population, and may enable subgroup analysis by primary tumor type (in addition to other patient subsets that were not possible in the prior studies). The study will also provide information on treatment and management patterns, as well as outcomes for patients, in the real-world setting. It will also collect baseline information, including retrospective data on prior systemic therapy in patients treated with larotrectinib.

8. Research questions and objectives

8.1 Primary objective

The primary objective of this international, non-interventional study is to describe the safety of larotrectinib in patients with locally advanced or metastatic TRK fusion cancer, including incidences of all treatment-emergent adverse events (TEAEs) in real-world practice conditions.

8.2 Secondary objective(s)

The secondary objectives of this study are:

- To describe the effectiveness of larotrectinib, including overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) by local investigator assessments.
- To describe the patterns of larotrectinib treatment, including actual doses, duration of treatment (DOT), and other dosing parameters
- To describe the effectiveness of larotrectinib in subgroups of patients, including but not limited to: by age, *NTRK* gene, *NTRK* gene partner, testing methodology, country/region, prior therapy (type and/or number of lines of therapy), and/or by other patient (baseline) characteristics. Additional subgroups may be explored as needed
- To describe long-term effects of larotrectinib on growth (height and weight), neurological outcomes, developmental milestones, and sexual development (Tanner scale) in the pediatric cohort.

8.3 Further objective(s)

Additional exploratory objectives include:

- To describe the effectiveness of larotrectinib, including overall response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), progression-free survival (PFS) based on radiological assessments of tumor response as determined by a Blinded Independent Review Committee (BIRC) as applicable
- To determine procedures avoided because of the use of larotrectinib (e.g. amputation or other disfiguring procedure) in infantile fibrosarcoma
- To determine the number of patients who underwent surgery for a curative intent (excluding amputation) because of the use of larotrectinib
- To describe systemic treatment prior to larotrectinib treatment, including doses, duration of treatment, best response, and reasons for discontinuation, as appropriate

9. Research methods

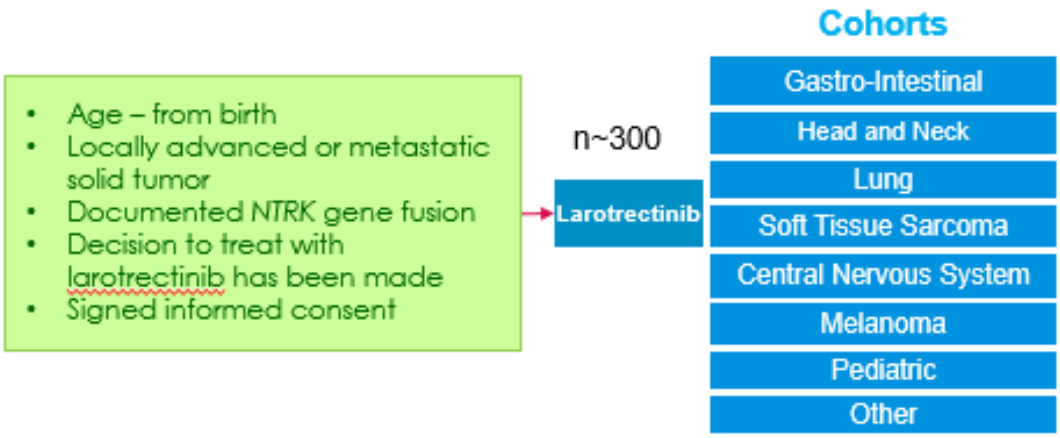
9.1 Study design

This is an international, prospective, open-label, multicenter, multi-cohort, non-interventional study. Patients with locally advanced or metastatic TRK fusion cancer for whom a decision to treat with larotrectinib has been made before enrollment will be eligible for the study. Cohorts will be defined by the tumor types in adult patients recruited, including gastrointestinal (GI), head and neck (H&N), lung, soft tissue sarcoma (STS), primary central nervous system (CNS), melanoma, or 'other'. All pediatric patients regardless of tumor type will be enrolled under a 'pediatric' cohort.

Detection of NTRK gene fusion will be by next-generation sequencing (NGS), fluorescent in situ hybridization (FISH), reverse-transcription polymerase chain reaction (rt-PCR) or any other genomic testing able to detect NTRK gene fusion. The decision on the dose and duration of treatment is solely at the discretion of the treating physician, based on the recommendations written in the local product information. Examinations and the laboratory monitoring schedule will follow local label recommendations in line with local standard of care.

This study is designed to describe safety and tolerability in patients treated with larotrectinib. It will also collect data to describe the effectiveness of larotrectinib in TRK fusion cancer, patterns of treatment, and the influence of baseline characteristics and treatment history.

Figure 1: Study Design



Data will be collected from up to 300 patients with NTRK gene fusion globally over a total study period of 5 years (8 years for pediatric cohort), including 36 months' enrollment and a minimum of 24 months' observation time from study entry for all cohorts but pediatric cohort. A minimum of 30 pediatric patients will be enrolled with at approx. 10 patients in each following categories: < 2 years of age, 2-<12 years of age, and ≥ 12 years of age. Pediatric patients will be followed up for at least 60 months from larotrectinib initiation, unless the patient discontinued due to lost to follow-up, withdrawal, or death. The end of the study is the date at which the final pediatric patient has been in the study for 60 months or has discontinued due to lost to follow-up, withdrawal, or death, whatever comes first.

Patient enrolled in ON-TRK study with a testing report not mentioning any NTRK gene fusion will be replaced.

Safety reviews will be performed annually with the first review starting 1 year after first patient is enrolled into the study. Interim reviews for safety and effectiveness will be performed after approximately 50 patients pooled across tumor types complete at least 6 months of treatment or discontinue treatment. Subsequent reviews will be performed after approximately 150 and 300 patients have met the same conditions. In addition, reviews by cohort type will be performed after approximately 10 patients per cohort complete at least 6 months of treatment or discontinue treatment. The various reviews may be combined if they are expected to occur within approximately 1 month of each other.

Physicians participating in this study are recommended to include consecutive patients; the study initiator may limit or halt the recruitment of patients with a particular tumor type if one cohort risks becoming over-represented within the overall study population. The data for this study will be collected using an electronic case report form (eCRF).

The international, non-interventional study design enables data to be collected from patients treated under local standard of care clinical practice; all decisions in terms of diagnostic procedures, treatments, management of the disease, and resource utilization are fully dependent on mutual agreement between the patient and the attending physician, without interference by the study initiator or study protocol. This will enable assessment of treatment and subsequent outcomes based on local standards and is likely to encompass a wider range of therapeutic decisions compared with the stricter, defined limits on therapy required by investigational study protocols. Decisions and outcomes made in real-world conditions are likely to be more applicable to wider clinical practice than those from interventional studies.

This study population is larger and is likely to be more diverse than that observed in prior interventional trials, with potentially a broader range of tumor types, disease severity, prior treatments, comorbidities, and concomitant medications. The sample size will enable comprehensive characterization of the larotrectinib safety profile of all treated patients; analysis of safety and effectiveness should also be possible among different patient subsets (e.g. by tumor type, prior treatment history). Owing to the rarity of TRK fusion cancer, single group studies can be considered well adapted to the investigation of rare clinical scenarios [8].

9.1.1 Primary endpoint(s)

The primary endpoint is the safety of larotrectinib in patients with locally advanced or metastatic TRK fusion cancer, defined as the frequency, severity according to CTCAE v.5, seriousness, reasonable causal relationship between larotrectinib and an AE, and action taken related to larotrectinib treatment.

Safety will be assessed in all patients who receive at least one dose of larotrectinib.

9.1.2 Secondary endpoint(s)

The secondary endpoints for the study are shown below (full definitions are provided in 9.7 Data Analysis):

- Objective response rate (ORR), based on investigator assessment preferably using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [9] or Response Assessment in Neuro-Oncology (RANO) [10] as appropriate by local investigator assessment
- Disease control rate (DCR)
- Duration of response (DOR)
- Time to response (TTR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Total dose, starting and ending dose, dose modification during treatment and duration of treatment (DOT);
- Effectiveness (ORR, DCR, DOR, TTR, PFS, OS) by patient subgroup(s)
- Change in height and weight from baseline by visit; neurological abnormalities (normal/abnormal), developmental milestones abnormalities (normal/abnormal) and Tanner stage abnormalities (pediatric cohort only)

9.1.3 Further endpoints

As an exploratory endpoint, effectiveness including ORR, DCR, DOR, TTR, and PFS will be assessed based on radiological assessments of tumor response as determined by the BIRC as applicable

The exploratory endpoints for patients who received systemic therapy prior to larotrectinib are:

- Duration of prior systemic treatment, defined as the time interval from the start of treatment to the day of permanent discontinuation
- Response to prior systemic treatment, as assessed by investigators
- Time from discontinuation of prior systemic treatment to start of larotrectinib

Other exploratory endpoints include:

- Amputation considered avoided due to the use of larotrectinib in the infantile fibrosarcoma patient population
- Number of patients who underwent a surgery for a curative intent while on larotrectinib (excluding amputation), by tumor type (and overall)

9.2 Setting

9.2.1 Eligibility

Female and male patients with a locally advanced or metastatic solid tumor harboring *NTRK* gene fusion (detected by NGS, FISH, rt-PCR or any other genomic testing able to detect NTRK gene fusion) and for whom a decision to treat with larotrectinib has been made by the treating physician will be eligible for enrollment into the study. Patients who met the eligibility criteria recently can be enrolled only if the initial visit (larotrectinib start date) occurred within one month before signing the patient informed consent and all details necessary for data collection for the visit are available. Also, any AEs

that occurred in patients who started larotrectinib treatment during that period must be documented retrospectively.

Patient enrolled in ON-TRK study with a testing report not mentioning any NTRK gene fusion will be replaced.

9.2.1.1 Inclusion criteria

- Adult and pediatric (from birth to 18 year old) patients
- Patients with locally advanced or metastatic solid tumor harboring an *NTRK* gene fusion. *NTRK* (*NTRK1*, *NTRK2*, and *NTRK3*) gene fusions will be identified locally. Acceptable methods of detection of *NTRK* gene fusion include NGS, fluorescence in situ hybridization (FISH), reverse-transcription polymerase chain reaction (rt-PCR) or any other genomic testing able to detect NTRK gene fusion. If a pan-TRK IHC method is used, this result needs to be accompanied with the results using one of the other methods noted above.
- Life expectancy of at least 3 months based on clinical judgement
- Decision to treat with larotrectinib made by the treating physician prior to study enrollment
- Signed informed consent form
- For patients under legal age, signed assent by the patient (where applicable) and parental/legal guardian signed informed consent is required

9.2.1.2 Exclusion criteria

- Any contraindications as listed in the local approved product information
- Pregnancy
- Participation in an investigational program with interventions outside of routine clinical practice
- Prior treatment with larotrectinib or other kinase inhibitor with TRK inhibition
- Patients with NTRK gene amplification or NTRK point mutation

9.2.1.3 Rationale for specific exclusion criteria

Patients previously treated with larotrectinib or other TRK inhibitor therapy are excluded because of the potential for such patients to have acquired resistance to TRK inhibitors and for this to affect study outcomes.

9.2.2 Withdrawal

In this non-interventional study, withdrawal from the study is independent of the underlying therapy and will not affect the patient's medical care. Each patient, or their parent/legal guardian for patients under legal age may withdraw from the study at any time and without giving a reason. If a patient wants to terminate the study participation, no further data will be collected. In case a patient, or their parent/legal guardian, would like to withdraw the consent given earlier, he/she should inform his/her

doctor and the site should document the withdrawal in the eCRF as well as in the patient medical records.

9.2.3 Replacement

Enrollment will stop when the target sample size is reached. Patients who drop out (e.g. withdrawal, lost to follow-up) will not be replaced.

9.2.4 Representativeness

The patients documented in the study should be selected based only on eligibility according to the inclusion and exclusion criteria(section 9.2.1). No further selection should be applied. Physicians will be asked to sample consecutive patients whenever possible to avoid selection bias and thus increase the likelihood of representativeness. At each site, all screened patients will be documented consecutively in an anonymous screening log with reasons for non-participation (without recording patient-specific data).

9.2.5 Visits

The start of the study is the date from which information on the first patient in the study can be first recorded in the study dataset (i.e. first informed consent obtained). The end of the study is the date at which the final pediatric patient has been in the study for 60 months after initiation of larotrectinib treatment, or when the final adult patient has been in the study for 24 months after initiation of larotrectinib, or when no patient is still under observation due to lost to follow-up, withdrawal, or death, whatever occurs last.

A visit is defined as any status assessment or new treatment decision the treating physician takes in the presence of the patient. The time interval between two documented status assessments is assumed to be 8 weeks, although this will be at the discretion of the treating physician.

The treating physician will document the initial visit, treatment visits, follow-up visits, and the final information collection for each patient in the eCRF. The initial visit corresponds to the initiation of larotrectinib treatment. Documentation at the initial visit will include the baseline information, even if data were collected at a prior visit. Patients who met the eligibility criteria recently can be enrolled only if the initial visit (larotrectinib start date) occurred within one month before signing the patient informed consent and all details necessary for data collection for the visit are available. Also, any AEs that occurred in patients who started larotrectinib treatment during that period must be documented retrospectively. Treatment visits will occur during period of treatment with larotrectinib, and follow-up visits after end of larotrectinib treatment. Visits will occur during routine practice; the study protocol does not define exact referral dates for these.

The final information collection for a patient is at the end of study, at patient's withdrawal of consent, lost to follow-up, or death (whatever is earlier).

A patient is regarded as 'Lost to follow-up' in case no further information can be expected from the patient at a given point in time. In case no information was obtained from a patient within 12 month since the last data collection time point the site personnel is requested to apply due diligence – within the applicable legal limits – to contact patients to ascertain the reason. In case no information can be retrieved, the site should confirm that the patient is lost to follow-up and document the end of observation.

If the documentation is stopped prematurely, the reasons for the end of observation must be given. If a patient joins an interventional clinical study during the course of observation, information on survival will still be collected up to the end of this study.

The observation period for adult patients covers the period from initiation of larotrectinib treatment to loss to follow-up, withdrawal of consent, death, or when the final adult patient has been in the study for 24 months after initiation of larotrectinib. The observation period for pediatric patients covers the period from initiation of larotrectinib treatment to loss to follow-up, withdrawal of consent, death, or when the final pediatric patient has been in the study for 60 months after initiation of larotrectinib. The study will be closed 60 months after the last pediatric patient has started treatment with larotrectinib or when no patient is still under observation due to lost to follow-up, withdrawal, or death. For all patients still under observation at time of study closure, a last disease-status documentation will be required along with the completion of the final information collection. Typical information to be collected at the visits are summarized in Table 2.

Table 2: Tabulated overview on data collected during the study

	Initial visit[1]	**Treatment visit(s)**	**Follow-up visit(s)**	**Final information collection**
Date/time/type of visit	X	X	X	X
Eligibility and informed consent	X			
Demography	X			
Height[2] and weight	X	X	X	
Vital signs	X	X	X	
Disease history	X			
Documentation of positivity for *NTRK* gene fusion[3]	X			
Co-morbidities (medical history, concomitant diseases)	X			
Anti-cancer therapy	X	X	X	X
Medication (excluding anti-cancer therapy)	X	X	X	X

	Initial visit[1]	**Treatment visit(s)**	**Follow-up visit(s)**	**Final information collection**
Cancer-related procedures	X	X	X	X
Radiotherapy	X	X	X	X
Larotrectinib exposure	X	X		X[4]
Performance status[5]	X	X	X	X
Tumor assessment	X	X	X	X
Laboratory parameters	X	X		X
Adverse events	X[6]	X[7]		X[7]
Survival assessment			X	X
End of observation				X
Tanner scale (sexual development)[2]	X	X	X	X
Neurological examination[2]	X	X	X	X
Developmental milestones[2]	X	X	X	X

[1]Initial visit is the visit when treatment with larotrectinib is started, and will include baseline information

[2]In pediatric patients only

[3]Date and methodology for identification of *NTRK* gene fusion; recommended methods are next-generation sequencing (NGS), fluorescent in situ hybridization (FISH), reverse-transcription polymerase chain reaction (rt-PCR) or any other genomic testing able to detect NTRK gene fusion

[4]If patient is still on treatment at the end of observation

[5]Eastern Cooperative Oncology Group (ECOG) score, Lansky performance status for patients aged less than 16 years old, or Karnofsky score for patients in the pediatric cohort > 16 years old

[6]Adverse events at initial visit only after administration of first dose of larotrectinib

[7]Adverse events recorded up to 30 days after the final dose of larotrectinib

9.3 Variables

The treating physician collects the study relevant data for each patient (as described in section 9.3.2) and documents it in the eCRF. The eCRF and a detailed description of variables collected in this study are kept as stand-alone documents (see Annex 1) and are available upon request.

9.3.1 Variables to determine the primary endpoint(s)

The variables for the primary endpoint are:

- Incidence of TEAEs, including severity, seriousness, outcome, and causality assessment.

9.3.2 Variables to determine the secondary endpoints

The outcome variables for secondary endpoints are:

- Demographic and baseline characteristics (vital signs)
- Disease history including pathology report at baseline and subsequently as applicable
- Comorbidities
- Method for detecting NTRK gene fusion including testing report at baseline and subsequently as applicable
- Larotrectinib use
  - Initiation and termination dates
  - Dosage and dose modification
- Tumor assessments
- Date of radiological or clinical progression on larotrectinib
- Eastern Cooperative Oncology Group (ECOG), Lansky, or Karnofsky performance status
- Neurological examination
- Developmental milestones
- Age at adrenarche, if applicable (males)
- Age at menarche. if applicable (females)
- Tanner scale (see Annex 3)
- Laboratory examination data
- Date of death/last follow-up

9.3.3 Variables to determine the further endpoints

Additional outcome variables for exploratory endpoints include:

- Tumor assessments according to BIRC as applicable
- Previous systemic therapy
  - Initiation and termination dates

  - Best tumor response to therapy
  - Date of radiological progression on therapy
- In patients with infantile fibrosarcoma, whether an amputation was considered for the patient prior to treatment with larotrectinib
- Surgery (with curative intent) while on larotrectinib

9.4 Data sources

The treating physician collects historic data (demographic, clinical characteristics and medical history) from medical records, or else by interviewing the patient or, for patients under the age of 18 years, their parent/legal guardian. Likewise, the treating physician collects treatment-related data during visits that take place in routine practice.

Laboratory tests will be performed according to local standard of care.

Each patient is identified by a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the patient's treating physician or authorized site personnel are able to identify the patient based on the patient identification code.

Any visit in clinics or practices other than the study center should be documented. If needed and appropriate, the treating physician participating in this study should make every effort to contact other physicians who may be co-managing the patient's health, the patient's family or caregivers to retrieve relevant information for the study (with documented consent from the patient or legal representative). The treating physician and clinic staff will be trained on the importance of obtaining such relevant information.

9.5 Study size

Considering that TRK fusions occur more commonly in rare tumor types, such as salivary-gland cancer and infantile fibrosarcoma, it might not be feasible to enroll a large number of patients into this study in a reasonable time. As such, this study plans to enroll 300 patients among these tumor specific cohorts: GI, H&N, lung, STS, primary CNS, melanoma, pediatric, or 'other'.

The primary objective of this study is to describe the incidence of TEAEs in a real world setting, and as such, the sample size was based on the probability of observing at least one event for a range of true incidence rates, including some of the uncommon events.

The probability of observing at least one event for a range of true incidences from 0.1% to 5% for a sample size ranging from 100 to 400 patients in an arm are shown in Figure 2. As seen here, for a true event incidence of 1% and a sample size of 300 patients, the probability of observing at least one event is 95%. Therefore, a total of approximately 300 patients is sufficient to observe at least one AE for even uncommon events.

Figure 2: Probability of observing at least one adverse event by sample size

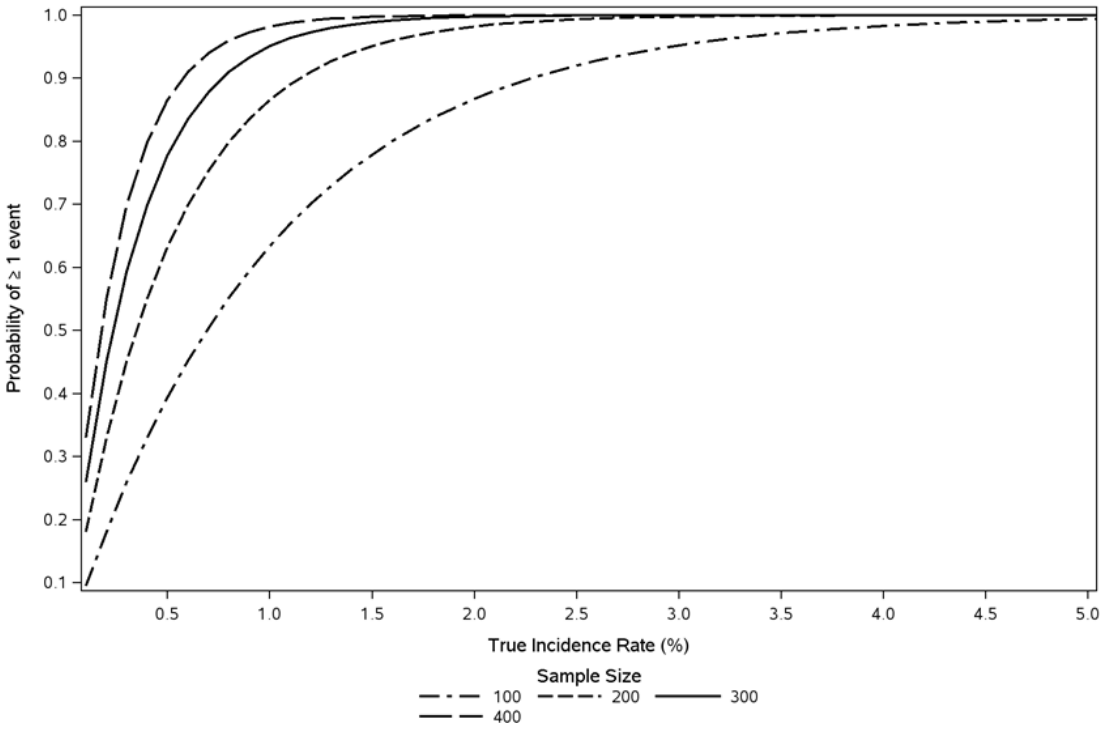


Table 3 shows the width of a 95% confidence interval (CI) for the rate of adverse events (based on exact binomial distribution) for different observed incidence rates with 300 patients.

Table 3: Estimated incidence rates and 2-sided 95% confidence intervals for N=300

Number of cases	Observed incidence rates	LCL	UCL	Width (%)
3	1%	0.21	2.89	2.69
15	5%	2.83	8.11	5.29
30	10%	6.85	13.97	7.12

With 300 patients, if the observed incidence rate is between 1% and 10%, the width of a 95% CI for the rate of AE will be approximately 2.69% to 7.12%.

9.6 Data management

A Contract Research Organization (CRO) will be selected and assigned for Electronic Data Capture (EDC) system development. The eCRF will be part of the EDC system which allows documentation of all variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request (Annex 1). Detailed information on data management, including procedures for data collection, retrieval, and preparation are given in the Data Management Plan (DMP), which is available upon request (Annex 1).

For information on quality control, refer to section 9.8.

9.7 Data analysis

9.7.1 Statistical considerations

Statistical analyses will be of explorative and descriptive nature. The study is not designed to support any formal statistical testing. Unless otherwise stated, all CIs will be given at a 2-sided 95% level.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

Patients who took at least one dose of larotrectinib will be included in the safety analysis set.

Patients who took at least one dose of larotrectinib, did not violate a major inclusion/exclusion criterion, and had at least one post baseline assessment after receiving larotrectinib will be included in the full analysis set.

Safety data will be analyzed on the safety analysis set, effectiveness data on the full analysis set. Demographic and baseline data will be described for both full and safety analysis sets.

All analyses will be performed for the total study population (overall analysis) and also by cohorts, as appropriate. Additional analyses may be performed separately for each participating country if patient numbers are sufficient and if required for local reasons. Whenever reasonable, data will be summarized by subgroups (e.g. age, gender, baseline characteristics).

All therapies will be coded using the World Health Organization Drug Global:

- Medication
- Anti-cancer therapy

Any diagnoses/diseases/event terms documented in the following forms will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version:

- Co-morbidities (medical history, concomitant diseases)
- Adverse events

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). Additional analyses might be conducted as deemed appropriate. The SAP will be finalized before study database lock. The SAP is available upon request (see Annex 1).

9.7.2 Analysis of population characteristics

All background data such as patient demographics, diagnosis and prior treatment, past medical history, concomitant diseases, and concomitant medication will be described by presenting frequency distributions and/or basic summary statistics.

9.7.3 Analysis of primary variable(s)

Adverse events will be summarized for the safety population using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 as well as the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Incidence proportions will be calculated based on the total number of patients valid for safety. Incidence proportions will be calculated by MedDRA system organ class, preferred term, and worst CTCAE grade, for the MedDRA-based analyses, and by Event Category/NCI CTC Term, and worst grade for the CTCAE-based analyses. These analyses will be performed for TEAEs, drug-related TEAEs, treatment-emergent SAEs, drug-related treatment-emergent SAEs, and TEAEs leading to dose reduction, dose interruption, or permanent dose discontinuation.

For vital signs, descriptive statistics will be calculated by visit. Where possible, laboratory data will be graded using the mapping provided within the NCI-CTCAE manual version that is valid at the time of analysis. CTCAE severity grading for laboratory abnormalities is mainly based on applicable laboratory threshold values outlined in NCI-CTCAE manuals. Frequency of laboratory abnormalities will be tabulated by NCI-CTCAE category and worst grade. Laboratory abnormalities will be summarized by severity. Frequency and incidence rates (in specific abnormality categories, high/low ranges) will be provided. Frequency tables will also be provided for changes in severity from baseline to worst value post-baseline.

9.7.4 Analysis of secondary variables

All summaries with respect to effectiveness data will be descriptive. The primary data source for effectiveness endpoints ORR, DCR, DOR, TTR, and PFS will be based on tumor response as assessed by the investigator. The estimates of overall response rate and disease control rate and the corresponding CIs will be provided. For the time to event variables, DOR, TTR, PFS, and OS, the medians and survival rates at various time points with 95% CI will be estimated by Kaplan and Meier (1958) methodology. Radiologically or clinically documented progression of tumor will be considered as disease progression. Subgroup analyses stratified with prognostic, predictive, or other factors collected at baseline as mentioned earlier may be explored. Further details will be described in the SAP.

- ORR is defined as the proportion of patients with a best overall response (BOR) of CR or partial response (PR) assessed by investigators. BOR is defined as the best response designation [in the order of CR, PR, stable disease (SD), progressive disease (PD), or not evaluable (NE)] for each patient that is recorded between the date of the first dose of treatment and the date of documented disease progression per investigators, preferably using RECIST 1.1 or RANO as appropriate
- DCR is defined as the proportion of patients with a BOR of CR, PR, or SD for at least 16 weeks from larotrectinib initiation
- DOR is determined for patients with BOR of CR or PR and is defined as time (months) from the start of CR or PR (whichever response is recorded first) to the date of observed disease progression or death due to any cause, whichever is earlier. Sensitivity analysis will be performed for radiological progression only
- Time to response (TTR) is determined as time from the start of larotrectinib treatment until the first evidence of CR or PR. Time to response will be calculated for responders only.

- PFS is defined as the time (months) from the start of larotrectinib treatment to the date of first observed disease progression (radiological or clinical, whichever is earlier) or death due to any cause, if death occurs before progression is documented. Sensitivity analysis will be performed for radiological progression only
- Overall survival (OS) is defined as the time (months) from the start of larotrectinib treatment to the date of death, due to any reason. Patients alive or lost to follow-up at the time of analysis will be censored at their last date of follow-up

Duration of larotrectinib treatment is defined as the time (months) from the start of larotrectinib treatment to the day of permanent discontinuation of larotrectinib (including death). For larotrectinib treatment, descriptive statistics will be calculated for the treatment duration, starting dose, and average dose. The following data will be summarized for larotrectinib treatment: the number of patients with dose modification (e.g. reduction, interruption, re-challenge at protocol dose), number of dose modifications, and frequencies of reasons for dose modifications.

For pediatric cohort only, change in height and weight from baseline will be summarized at each visit. Age at adrenarche for males and age at menarche for females will be summarized. In addition, number and percentage of patients with abnormal Tanner stage, abnormal neurological assessments, and abnormal developmental milestones will be presented.

Patient baseline characteristics will be reported descriptively. Effectiveness of larotrectinib will be described by subgroups such as by age, NTRK gene, NTRK gene partner, testing methodology, country/region, prior therapy (type and/or number of lines of therapy), and/or by other patient (baseline) characteristics. Planned subgroup analyses will be outlined in the SAP.

9.7.5 Analysis of safety data

Safety data comprise the primary endpoint of the study and the analysis is detailed in section 9.7.3.

9.7.6 Analysis of other data

Effectiveness variables including ORR, DCR, DOR, TTR, and PFS will be also determined by the BIRC based on radiological assessments of tumor response as applicable. These effectiveness variables will determined by the BIRC for patients who have technically adequate baseline and on-treatment radiological assessments of tumor response that have been able to be centrally collected at the imaging core laboratory.

In patients who had systemic anti-cancer therapy prior to the study, the treatment data will be summarized descriptively.

- Dosing of other treatment used prior to the study, including start/stop date, duration of treatment, given doses, reasons for discontinuation, and time from discontinuation of the treatment to start of larotrectinib will be retrospectively collected and summarized descriptively in the population enrolled in this study

For patients with infantile fibrosarcoma, number and percentage of patients who avoided amputation will be reported.

Also, the number and percentage of patients who underwent a surgery for a curative intent while being treated for larotrectinib (excluding amputation) will be presented.

9.8 Quality control

9.8.1 Data quality

Before study start at the sites, all investigators will be sufficiently trained on the background and objectives of the study, and ethical as well as regulatory obligations. Investigators will have the chance to discuss and develop a common understanding of the NIS protocol and the eCRF.

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis, and data transfer to Bayer.

All observations will be recorded in a standardized eCRF. After data entry, missing or implausible data will be queried and the data will be validated. A check for multiple documented patients will be done.

Detailed information on checks for completeness, accuracy, plausibility, and validity are given in the Data Management Plan (DMP). The DMP is available upon request (see Annex 1).

Medical Review of the data will be performed according to the Medical Review Plan (MRP). The purpose of the Medical Review is to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on the Medical review will be described in the MRP, which is available upon request (see Annex 1).

National and international data protection laws as well as regulations on non-interventional studies will be followed. Electronic records used for capturing patient documentation (eCRF) will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) [11]. 21CFR Part 11 regulations describe the criteria to consider electronic records, including e-signatures, to be reliable and generally equivalent to paper records and handwritten signatures. They mandate access controls to ensure that only authorized individuals can use the system, additionally a computer-generated audit trail has to be in place to record the date and time of any actions to create, modify, or delete electronic records. The documentation is available upon request (see Annex 1).

9.8.2 Quality review

Quality review will be done in two steps: in the first step the site's training status will be assessed via standardized telephone interviews. In the second step, source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the NIS protocol and verification with source documents.

Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request (Annex 1).

9.8.3 Storage of records and archiving

Bayer will ensure that all relevant documents of this study will be stored after the end or discontinuation of the study for at least 25 years. Any data as well as programs from statistical programming performed to generate results will be stored within the programming system for at least 25 years.

The investigators participating in the study are required to archive documents at their sites according to local requirements, considering possible audits and inspections from the study initiator and funder and/or local authorities.

9.8.4 Certification/qualification of external parties

Not applicable

9.9 Limitations of the research methods

Because of the non-interventional study design and limitations inherent to non-interventional studies, findings generated from this study are subject to biases, such as selection bias, limitations to availability of historical medical data, and differences in treatment or reporting owing to local guidelines.

Results for secondary effectiveness variables such as PFS must be interpreted carefully because of the uncontrolled setting: time periods between follow-up visits are more variable than in controlled clinical studies, in which a fixed visit schedule is maintained. The quality of the tumor status evaluation will differ from that in controlled clinical studies.

Results for the exploratory effectiveness variables assessed by Blinded Independent Review Committee will be limited to the availability of radiological scans collected for this assessment and therefore results would need to be interpreted carefully.

Comparison of outcomes after treatment with larotrectinib versus treatment with an internal comparator cannot be performed in this study, and as such it is not possible to distinguish the effects of treatment versus the natural course of disease or effects from other unknown factors. Comparisons can only be performed with historical comparison group from clinical or non-interventional studies, which is prone to bias and confounding. Historical patient data collected with respect to prior treatments may be incomplete and/or differ relating to larotrectinib use and standard of care in local practice. Historical data provided by patient interview is prone to errant recall.

Although the study aims to include participants from a variety of geographic regions, there may be local limitations that reduce the representativeness of patients recruited, such as patient access to recruiting physicians (including differences in patient profile in specialized recruiting sites versus local general practice), larotrectinib availability and reimbursement, and decisions relating to local standard of care.

Due to the rarity of patients with cancer harboring *NTRK* gene fusions and the fact that *NTRK* testing varies by tumor types, institutions, and countries, it could lead to an over-representation of a tumor type, institution(s), and patients from specific country(ies).

9.10 Other aspects

Not applicable

10. Protection of human subjects

10.1 Ethical conduct of the study

This study is a non-interventional study where larotrectinib is prescribed in the customary manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a

particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA, FDA, and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012 [12]). Recommendations given by other organizations will be followed as well (e.g. EFPIA [13], ENCePP [14]).

In addition, the guidelines on good pharmacovigilance practices (GVP module VI) [15] and since the study qualifies as a PASS, GVP module VIII [16,17] will be followed.

10.3 Independent ethics committee (IEC) or institutional review board (IRB)

In all countries where reference to an IEC/IRB is required, documented approval from appropriate IECs/IRBs will be obtained for all participating centers prior to study start. When necessary, an extension, amendment, or renewal of the IEC/IRB approval must be obtained and also forwarded to the study initiator and funder. The IEC/IRB must supply to the study initiator and funder, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to applicable laws and regulations.

10.4 Patient information and consent

Before documentation of any patient data, informed consent is obtained by the patient in writing. For patients under legal age, signed assent by the patient (where applicable) and parental / legal guardian signed informed consent will be obtained. Informed consent forms will be provided for persons who are capable to give their consent. For adult patients and for children not capable to give their consent, the legal representative should give the consent. In countries where required by law or regulation, the investigator must have the IECs/IRB written approval/favorable opinion of the written informed consent form(s) and any other written information to be provided to patients prior to the beginning of the observation.

10.5 Patient insurance

In this non-interventional study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the investigators and, respectively, the institutions involved provide sufficient protection for both patient and investigator.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10.6 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

All records identifying the patient will be kept confidential and will not be made publicly available. Patient names will not be supplied to Bayer AG. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to Bayer AG. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the investigator.

11. Management and reporting of adverse events/adverse reactions

11.1 Definitions

An Adverse Event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product [18].

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

As mentioned above no causal relationship with a product is implied by the use of the term "adverse event".

A Treatment Emergent Adverse Event (TEAE) defines as an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.

An Adverse Reaction (AR) is defined as a response to a medicinal product which is noxious and unintended. An AR is any AE judged as having a reasonable suspected causal relationship to larotrectinib.

An adverse event (AE) or adverse reaction (AR) is serious (SAE) if it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- Is medically important

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is 'sudden death' where no cause has been established. In this instance, 'sudden death' should be regarded as the AE and 'fatal' as its reason for being 'serious'.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as serious, unless the admission is:

- planned before patient's inclusion in the study (i.e. elective or scheduled surgery) or
- ambulant (shorter than 12 hours) or
- part of the normal treatment or monitoring of the studied disease (i.e. not due to a worsening of the disease)

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery
- The father was exposed to a medicinal product prior to conception

Other medically important serious event: any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

11.2 Collection

Starting with the first application of larotrectinib within the frame of the study (i.e. up to one month prior to signing ICF),, all non-serious adverse events (AE) must be documented on the AE Report Form or in the CRF/EDC system and forwarded to the MAH within 7 calendar days of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within one business day of awareness). For each AE, the investigator must assess and document the seriousness, duration, relationship to product, action taken and outcome of the event. For patients enrolled retrospectively (i.e. signing the ICF within one month after start of larotrectinib treatment), all AEs after start of larotrectinib treatment have to be documented in the CRF retrospectively.

If a pregnancy occurs during the study, although it is not a serious adverse event itself, it should be documented and forwarded to the MAH within the same time limits as a serious adverse event. The result of a pregnancy will be followed-up according to applicable Bayer SOPs. Any data on abnormal findings concerning either the mother or the baby will be collected as adverse events.

The documentation of any AE/SAE ends, at the latest, 30 days after the completion of the observation period of the patient; that is, any AE/SAE – regardless of the relationship and the seriousness – occurring up to 30 days after the last dose of larotrectinib within the patient's observation period has to be documented and forwarded to the MAH within the given timelines.

Worsening of a pre-existing medical condition, (i.e., diabetes, migraine headaches, gout) should be considered an AE if there is either an increase in severity, frequency, or duration of the condition or an association with significant worse outcomes. Disease progression in and of itself is not considered an AE or SAE, but signs and/or symptoms of fatal disease progression should be recorded as fatal SAEs. Disease progression is an efficacy finding and will not be reported as an AE or SAE unless the disease progression results in death within 30-day post last dose of study treatment reporting period (in which case, signs and/or symptoms associated with disease progression should be recorded as fatal SAE (s)). All other deaths due to disease progression occurring after the 30-day window and during the follow-up will not be reported as an AE or SAE.

For patients that started larotrectinib treatment before the ICF signature, all AEs /SAEs occurred up to one month before the ICF signature have to be collected as part of the study data. Events occurred earlier are part of the patient's medical history and do not have to be reported as AEs /SAEs.

For any serious product-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

11.3 Management and reporting

Non-serious AEs

The outcome of all reported AEs will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with larotrectinib that qualify for expedited reporting will be submitted to the relevant authorities according to EU PV legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU, Module VI [15]) and according to national regulations by the MAH; however, all investigators must obey local legal requirements.

For non-serious ARs occurring under non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the CRF/EDC system will be forwarded immediately (within one business day of awareness) to the pharmacovigilance country person being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant authorities according to national regulations will be done by the MAH for SAEs related to larotrectinib treatment; however, all investigators must obey local legal requirements.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

For SAEs that occurred while administering non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

11.4 Evaluation

Whenever new important safety information is received, e.g. case reports from an investigator, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case reports, refer to section 11.2 and 11.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

12. Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov" and in the EU PAS register at "http://www.encepp.eu/encepp_studies/indexRegister.shtml". Results will be disclosed in a publicly available database within the standard timelines.

The results of this non-interventional study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP3 Guidelines [19], STROBE [20]). No individual investigator may publish on the results of this study, or their own patients, without prior approval from the MAH.

13. References

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Annex 1: List of stand-alone documents

Document Name

- Investigator list
- Country & Site list
- Steering Committee Members
- Steering Committee Charter
- eCRF
- Detailed list of variables
- EDC System
- EDC System Validation
- DMP
- SAP
- QRP
- MRP
- IRC

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Revision 5; 19/08/2019

Study title: ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib

EU PAS Register® number: Not yet available
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7,8,9
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7.1

Comments:

This is a prospective, non-interventional study, so no hypothesis is being tested

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1/9.2.1
4.2	Is the planned study population defined in terms of:				9.1/9.2.1
	4.2.1 Study time period	☒	☐	☐	9.1
	4.2.2 Age and sex	☒	☐	☐	9.2.1
	4.2.3 Country of origin	☒	☐	☐	9.1
	4.2.4 Disease/indication	☒	☐	☐	9.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

This is a non-interventional study, and all treatment decisions (including dosing and exposure) will be made by the treating physician without influence from the sponsor

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.7
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Health Technology Assessment endpoints are not included in the non-interventional data collected

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.7
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.8

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.8
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.8
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5/9.1

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.6

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: PPD

Date: 04/Sept PPD

Signature: _____

Annex 3: Tanner Scale

CRITERIA FOR DISTINGUISHING TANNER STAGES 1 TO 5 DURING PUBERTAL STAGES IN GIRLS

Tanner Stage	Breast	Pubic Hair
1 (prepubertal)	No palpable glandular tissue or pigmentation of areola; elevation of areola only	No pubic hair; short, fine vellus hair only
2	Glandular tissue palpable with elevation of breast and areola together as a small mound; areolar diameter increased	Sparse, long, pigmented terminal hair chiefly along the labia majora
3	Further enlargement without separation of breast and areola; although more darkly pigmented, areola still pale and immature; nipple generally at or above midplane of breast tissue when individual is seated upright	Dark, coarse, curly hair, extending sparsely over mons
4	Secondary mound of areola and papilla above breast	Adult-type hair, abundant but limited to mons and labia
5 (adult)	Recession of areola to contour of breast; development of Montgomery's glands and ducts on areola; further pigmentation of areola; nipple generally below midplane of breast tissue when individual is seated upright; maturation independent of breast size	Adult-type hair in quantity and distribution; spread to inner aspects of the thighs in most racial groups

Data from Ross GT: Disorders of the ovary and female reproductive tract. In Wilson JD, Foster DW (eds): Textbook of Endocrinology, 7th ed. Philadelphia, WB Saunders, 1985, p 206;

CRITERIA FOR DISTINGUISHING TANNER STAGES 1 TO 5 DURING PUBERTAL STAGES IN BOYS

	Pubic Hair	Genital
Stage 1	Absence of pubic hair	Childlike penis, testes, and scrotum (testes 2 mL)
Stage 2	Sparse, lightly pigmented hair mainly at the base of the penis	Scrotum enlarged with early rugation and pigmentation; testes begin to enlarge (3–5 mL)
Stage 3	Hair becomes coarse, darker, and more curled and more extensive	Penis has grown in length and diameter; testes now 8–10 mL; scrotum more rugated
Stage 4	Hair adult in quality, but distribution does not include medial aspect of thighs	Penis further enlarged with development of the glans; scrotum and testes (10–13 mL) further enlarged
Stage 5	Hair is adult and extends to thighs	Penis and scrotum fully adult; testes 15 mL and greater

Modified from Marshall WA, Tanner JM: Variation in pattern of pubertal changes in boys. Arch Dis Child 1970;45:13–23.

Annex 4: Description of amendments

None

Annex 5: Signature pages

Signature Page - NIS Conduct Responsible

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 2019-09-06, PPD

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 9 September 2019, PPD

Signature Page - MAH Contact Person (Regulatory Affairs)

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Name: PPD

Date, Signature: 2019-09-05, PPD

Signature Page - NIS Medical Expert

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: Sept 11th 2019, PPD

Signature Page - NIS Safety Lead

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 9 Sep 2019, PPD

Signature Page - NIS Statistician

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 09 SEP 2019, PPD

Signature Page - NIS Data Manager

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 17. Sep. 2019 , PPD

Signature Page - NIS Epidemiologist

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: Sept. 4, 2019 PPD

Signature Page - NIS Health Economics and Outcomes Research (HEOR) Responsible

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 9/17/19 , PPD

Signature Page - NIS Regulatory Affairs Responsible

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

PPD

Date, Signature: Sep 9, 2019,

Signature Page - Real World Evidence (RWE) & Outcomes Data Generation (ODG) Responsible

Title	ON-TRK: PrOspective Non-interventional study in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib
Protocol version and date	v2.0; 04-SEP-2019
IMPACT study number	20324
Study type / Study phase	Non-interventional, post approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	BAY2731953, larotrectinib
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 9/9/2019 , PPD