IQWiG Reports – Commission No. A19-90

# Larotrectinib (solid tumours with neurotrophic tyrosine receptor kinase [NTRK] gene fusion) –

## Benefit assessment according to §35a Social Code Book V[1]

## Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Larotrectinib (solide Tumore mit einer neurotrophen Tyrosin-Rezeptor-Kinase [NTRK]-Genfusion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 January 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

**Medical and scientific advice**

- Ingo Schmidt-Wolf, University Hospital Bonn, Bonn, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

**IQWiG employees involved in the dossier assessment**

- Deborah Ingenhag-Reister
- Klaus Gossens
- Elke Hausner
- Tatjana Hermanns
- Michaela Florina Kerekes
- Stefan Kobza
- Fabian Lotz
- Min Ripoll
- Beate Wieseler

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| BSC | best supportive care |
| CLIA | Clinical Laboratory Improvement Amendments |
| CNS | central nervous system |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| EMA | European Medicines Agency |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 |
| EPAR | European Public Assessment Report |
| EQ-5D | European Quality of Life-5 Dimensions |
| ESMO | European Society for Medical Oncology |
| FISH | fluorescence in situ hybridization |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| IRC | independent review committee |
| NGS | next generation sequencing |
| NSCLC | non-small cell lung cancer |
| NTRK | neurotrophic tyrosine receptor kinase |
| PedsQL | Pediatric Quality of Life Inventory |
| RCT | randomized controlled trial |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RT-PCR | reverse transcriptase polymerase chain reaction |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of Product Characteristics |
| VAS | visual analogue scale |

# 2 Benefit assessment

## 2.1 Executive summary of the benefit assessment

### Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug larotrectinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 15 October 2019.

### Research question

The aim of the present report is the assessment of the added benefit of larotrectinib as monotherapy in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in adult and paediatric patients with solid tumours that display a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options.

Table 2: Research question of the benefit assessment of larotrectinib

| **Therapeutic indication** | **ACT[a]** |
|---|---|
| Adult and paediatric patients with solid tumours that display an NTRK gene fusion[b], who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options | BSC[c] |

a. Presentation of the respective ACT specified by the G-BA.
b. The considered studies on larotrectinib are ongoing, so that patients are still being enrolled. At the time point of the data cut-off on 30 July 2018, which was considered in the present benefit assessment, information was only available on patients with the following tumour entities: soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, primary CNS tumour, lung cancer, melanoma, colorectal cancer, gastrointestinal stromal cancer, bone sarcoma, cholangiocarcinoma, congenital mesoblastic nephroma, appendix cancer, breast cancer, pancreatic cancer. Some of the tumour entities mentioned only include individual patients (see Table 9).
c. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; CNS: central nervous system; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase

The company deviated from the G-BA's specification of the ACT and chose individual treatment of physician's choice instead of BSC. This had no influence on the study pool used by the company for the assessment of the added benefit of larotrectinib, however, as the company only considered the 3 approval studies on larotrectinib, all of which were without comparator arms.

In the present benefit assessment, the assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier in comparison with the ACT BSC specified by the G-BA. Deviating from the company's approach, the comparative

data presented by the company in Module 5 and the comparative data from the European Public Assessment Report (EPAR) were considered for the benefit assessment to support the interpretation of the results achieved under larotrectinib.

**Results**

***Study pool on larotrectinib***

The 3 approval studies on larotrectinib were considered for the benefit assessment. These are the 2 phase 1/2 studies LOXO-TRK-14001 and SCOUT, and the phase 2 study NAVIGATE. Depending on the study, adult and/or paediatric patients with NTRK gene fusion with metastatic or locally advanced solid tumours were included and treated with larotrectinib.

*Study LOXO-TRK-14001*

The LOXO-TRK-14001 study is an ongoing, uncontrolled, open-label, multicentre dose escalation study. The study included adult patients with locally advanced or metastatic solid tumours that had progressed or were nonresponsive to available therapies, who were unfit for standard chemotherapy or for whom no standard or curative therapy was available.

The patients were allocated to different dose escalation cohorts and, depending on their allocation, received different doses of larotrectinib, starting from 50 mg once daily up to 200 mg twice daily (dose escalation phase of the study). Enrolment into the dose escalation phase was regardless of the presence of NTRK gene fusion, but archived tumour samples or tissue for a new biopsy had to be available for later analysis. After determination of the recommended dose of 100 mg twice daily for further clinical use, which is in compliance with the approved dosage for adults, again patients were enrolled into the study in so-called expansion cohorts (expansion phase of the study). These patients had to have confirmed alteration in one of the NTRK genes at the start of the study (gene fusion, point mutation, translocation, insertion or deletion). Starting with protocol amendment version 4.0 (25 January 2017), all patients with NTRK gene fusion, both those already enrolled and those subsequently enrolled, received 100 mg larotrectinib twice daily, regardless of the dose escalation step they had been allocated to originally.

Primary outcome of the study was the recording of adverse events (AEs), the identification of the maximum tolerated dose and the identification of a recommended dose for further clinical use. Secondary outcomes concerned tumour response.

*NAVIGATE*

The NAVIGATE study is an ongoing, uncontrolled, open-label, multicentre basket study. In the framework of the basket design, the patients were allocated to different cohorts according to tumour histology (non-small cell lung cancer [NSCLC], thyroid cancer, soft tissue sarcoma, colorectal cancer, salivary gland cancer, cholangiocarcinoma, primary tumour of the central nervous system [CNS], other solid tumours). The study included patients aged 12 years and older with locally advanced or metastatic solid tumours and evidence of NTRK gene fusion. To

be included in the study, the patients had to have received prior standard therapy appropriate for their tumour histology and disease severity, or not be candidates for such therapy.

Primary outcome of the study was tumour response; secondary outcomes included overall survival as well as outcomes on morbidity, health-related quality of life and side effects.

*SCOUT*

The SCOUT study is an ongoing, uncontrolled, open-label, multicentre study composed of a dose escalation and an expansion phase. Patients aged between 1 month and 21 years with locally advanced or metastatic solid tumours were enrolled. It was a precondition for study inclusion that the patients had recurrence, progression or nonresponse to available therapies, or that no standard or curative systemic therapies were available. Patients between 1 month and 1 year of age were only included in the study if documented evidence of NTRK gene fusion was available. Depending on the study phase, older patients were included both with and without documented NTRK gene fusion. Due to the known high prevalence of NTRK gene fusion in infantile fibrosarcoma, patients with this tumour entity did not require documented evidence of NTRK gene fusion for enrolment. Patients with locally advanced infantile fibrosarcoma could also be included if the option of potentially curative resection existed, but this would have required disfiguring surgery or limb amputation (neoadjuvant use). A physiologically-based pharmacokinetic approach was used for the dosing of larotrectinib with the intent of matching adult doses of 100 mg twice daily (cohort 1) or 150 mg twice daily (cohort 2), depending on the cohort. An approach based on body surface area of 100 mg/m$^2$ twice daily was used for cohort 3 (maximum dose of 100 mg, twice daily), which was eventually determined as the recommended dose for the expansion phase and is also in compliance with the approved dosage of larotrectinib for paediatric patients.

Primary outcome of the dose escalation phase was the recording of side effects and the identification of dose-limiting toxicity; primary outcome of the expansion phase was tumour response. Secondary outcomes of both phases included outcomes on morbidity and health-related quality of life. Further secondary outcomes of the expansion phase were overall survival and the recording of side effects.

***Analysis population***

The company primarily used the 2 analysis populations ePAS2 and SAS3 in the dossier. In the ePAS2 analysis population, all patients with NTRK gene fusion, regardless of their tumour entities (except patients with primary CNS tumours), from the studies LOXO-TRK-14001, NAVIGATE and SCOUT who met the following criteria were pooled:

- administration of ≥ 1 dose of larotrectinib
- ≥ 1 measurable lesion (as defined by Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1) at baseline as evaluated by the investigator
- independent review committee (IRC) assessment available

Thus, the analysis population presented by the company does not comprise all patients included and treated in the pooled studies. At the data cut-off from 30 July 2018 presented by the company in the dossier, the ePAS2 analysis population (N = 93) does not include 28 patients for whom an IRC assessment was not yet available at this data cut-off, although this assessment was not relevant for the patient-relevant outcomes.

The analysis population referred to as "SAS3" by the company, comprises all patients with NTRK gene fusion and primary CNS tumours.

Since the present therapeutic indication is heterogeneous and comprises different tumour entities as well as, correspondingly, patients with different prognoses, the individual tumour entities are considered separately in the present benefit assessment. According to the study protocol, this was also planned in the basket study NAVIGATE.

The ePAS2 analysis population at the data cut-off on 30 July 2018 presented by the company comprises a total of 93 patients with 14 different tumour entities: soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, lung cancer, melanoma, colorectal cancer, gastrointestinal stromal cancer, bone sarcoma, cholangiocarcinoma, appendix cancer, breast cancer, congenital mesoblastic nephroma and pancreatic cancer. In addition, there are patients with primary CNS tumours. Depending on the tumour entity, the patient populations comprise 1 to 21 patients. For the data cut-off on 30 July 2018, there are only results for patients for whom an IRC assessment was already available at this time point, as only these patients were considered in the ePAS2 analysis population (see above).

Information on demographic/clinical characteristics or on treatment/observation periods of the patients separately for tumour entities is not available except for patients with primary CNS tumours.

***Available comparative data and interpretation of the result***

The therapeutic indication of larotrectinib is heterogeneous and comprises different tumour entities and, correspondingly, patients with different prognoses. However, the documents presented by the company does not include a complete presentation of the data separated according to tumour entities. Effect estimations on the comparison of larotrectinib with the ACT BSC are neither available for a separate consideration according to tumour entity, nor for the study population pooled by the company. The derivation of an added benefit in comparison with the ACT is therefore not possible.

Nonetheless, to support the interpretation of the data on larotrectinib, available comparative data were considered. Those were study results from studies with other drugs (not BSC) identified by the company in its information retrieval. The company itself did not use these comparative data, but added them to the dossier in Module 5. The EPAR contains additional comparative data, which are also on other drugs. Although the company stated that it had produced the information retrieval described above for the centralized authorization procedure,

the results of the information retrieval differ between the documents in Module 5 and the EPAR. Both sources were therefore considered. In the consideration of the available comparative data, it was not possible to assume a sufficiently large effect that could not be based on systematic bias alone in one of the patient-relevant outcomes for any of the tumour entities.

**Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]**

Based on the results presented, probability and extent of the added benefit of the drug larotrectinib in comparison with the ACT are assessed as follows:

In summary, the added benefit of larotrectinib in comparison with the ACT BSC is not proven for patients with solid tumours that display an NTRK gene fusion.

The result of the assessment of the added benefit of larotrectinib in comparison with the ACT is summarized in Table 3.

Table 3: Larotrectinib – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Adult and paediatric patients with solid tumours that display an NTRK gene fusion[b], who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options | BSC[c] | Added benefit not proven |

a. Presentation of the respective ACT specified by the G-BA.
b. The considered studies on larotrectinib are ongoing, so that patients are still being enrolled. At the time point of the data cut-off on 30 July 2018, which was considered in the present benefit assessment, information was only available on patients with the following tumour entities: soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, primary CNS tumour, lung cancer, melanoma, colorectal cancer, gastrointestinal stromal cancer, bone sarcoma, cholangiocarcinoma, congenital mesoblastic nephroma, appendix cancer, breast cancer, pancreatic cancer. Some of the tumour entities mentioned only include individual patients.
c. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; CNS: central nervous system; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

## 2.2 Research question

The aim of the present report is the assessment of the added benefit of larotrectinib as monotherapy in comparison with BSC as ACT in adult and paediatric patients with solid tumours that display an NTRK gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options.

Table 4: Research question of the benefit assessment of larotrectinib

| **Therapeutic indication** | **ACT[a]** |
|---|---|
| Adult and paediatric patients with solid tumours that display an NTRK gene fusion[b], who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options | BSC[c] |
| a. Presentation of the respective ACT specified by the G-BA.<br>b. The considered studies on larotrectinib are ongoing, so that patients are still being enrolled. At the time point of the data cut-off on 30 July 2018, which was considered in the present benefit assessment, information was only available on patients with the following tumour entities: soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, primary CNS tumour, lung cancer, melanoma, colorectal cancer, gastrointestinal stromal cancer, bone sarcoma, cholangiocarcinoma, congenital mesoblastic nephroma, appendix cancer, breast cancer, pancreatic cancer. Some of the tumour entities mentioned only include individual patients (see Table 9).<br>c. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.<br>ACT: appropriate comparator therapy; BSC: best supportive care; CNS: central nervous system; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase | |

The company deviated from the G-BA's specification of the ACT and chose individual treatment of physician's choice instead of BSC. This had no influence on the study pool used by the company for the assessment of the added benefit of larotrectinib, however (see Section 2.7.3.2 of the full dossier assessment).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier in comparison with the ACT BSC specified by the G-BA (see Section 2.7.1 of the full dossier assessment).

## 2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on larotrectinib (status: 1 August 2019)
- bibliographical literature search on larotrectinib (last search on 1 August 2019)
- search in trial registries for studies on larotrectinib (last search on 1 August 2019)

To check the completeness of the study pool:

- search in trial registries for studies on larotrectinib (last search on 21 October 2019)

The check of the completeness of the study pool identified no randomized controlled trials (RCTs) for a direct or indirect comparison for the assessment of the added benefit of larotrectinib. All identified studies on larotrectinib were non-comparative studies. No further study on larotrectinib relevant for the research question was identified in addition to the studies identified by the company.

The company also stated that the studies identified on larotrectinib were single-arm, non-comparative studies, so that it was not possible to conduct a direct or an adjusted indirect comparison. Thus, the company stated to have conducted a comprehensive systematic information retrieval on studies of historical comparisons, which it eventually did not use for the assessment of the added benefit of larotrectinib, however (see Section 2.7.3.2 of the full dossier assessment).

Deviating from the company's approach, the available comparative data were considered for the present benefit assessment to support the interpretation of the results achieved under larotrectinib. A more detailed description of the available comparative data can be found in Section 2.3.2.

### 2.3.1 Studies on larotrectinib

The studies on larotrectinib listed in the following table are considered in the benefit assessment.

Table 5: Study pool on larotrectinib

| Study | Study category | | |
|---|---|---|---|
| | Study for approval of the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) |
| LOXO-TRK-14001 | Yes | Yes | No |
| LOXO-TRK-15002 (NAVIGATE[b]) | Yes | Yes | No |
| LOXO-TRK-15003 (SCOUT[b]) | Yes | Yes | No |
| a. Study for which the company was sponsor.<br>b. In the following tables, the study is referred to with this abbreviated form. | | | |

Section 2.6 contains a reference list for these studies.

#### 2.3.1.1 Study characteristics

Table 6 and Table 7 describe the studies on larotrectinib.

Table 6: Characteristics of the studies on larotrectinib (multipage table)

| Study | Study design | Population | Interventions (number of patients included) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| LOXO-TRK-14001 | Un-controlled, open-label, dose escalation study | Patients ≥ 18 years with locally advanced or metastatic solid tumour[b]<br>▪ with progression or nonresponse to available therapies,<br>▪ who are unfit for standard chemotherapy, or<br>▪ for whom no standard or curative therapies exist<br>▪ ECOG PS ≤ 2[c] | <u>Data cut-off 30 July 2018</u><br>larotrectinib (N = 72)<br>▪ with NTRK gene fusion (n = 10)<br>▪ without NTRK gene fusion (n = 62)<br><br>Subpopulations of patients with NTRK gene fusion analysed by the company:<br>▪ ePAS2[d] (n = 8)<br>▫ salivary gland cancer (n = 3)<br>▫ gastrointestinal stromal cancer (n = 2)<br>▫ lung cancer<br>- NSCLC (n = 1)<br>▫ soft tissue sarcoma (n = 1)<br>▫ thyroid cancer (n = 1)<br>▪ SAS3[e] (n = 0)<br><br><u>Data cut-off 19 February 2019:</u><br>▪ ESMO 2019[f] (n = 12)<br>▫ separated by tumour histology: ND<br>▪ SAS3[e] (n = 0) | Screening: 4 weeks<br><br>Treatment: until disease progression[g], unacceptable toxicity, necessity to switch treatment, withdrawal of consent, or death<br><br>Observation: ND for maximum duration | 8 centres in the USA<br><br>5/2014–ongoing | Primary: AEs, MTD, identification of recommended dose for further clinical use<br>Secondary: no relevant outcomes |

Table 6: Characteristics of the studies on larotrectinib (multipage table)

| Study | Study design | Population | Interventions (number of patients included) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| NAVIGATE | Un-controlled, open-label, basket study[h] | Patients ≥ 12[i] years with locally advanced or metastatic solid tumours with NTRK gene fusion<br>▪ after prior standard therapy appropriate for tumour histology and disease severity[j], or<br>▪ unsuitable for standard therapy<br>▪ ECOG PS ≤ 3[c] or<br>▪ Karnofsky performance score ≥ 50 (primary CNS tumour) | Data cut-off 30 July 2018:<br>larotrectinib (N = 82)<br><br>Subpopulations analysed by the company:<br>▪ ePAS2[d] (n = 58)<br>▫ salivary gland cancer (n = 14)<br>▫ thyroid cancer (n = 9)<br>▫ soft tissue sarcoma (n = 9)<br>▫ colorectal cancer (n = 6)<br>▫ melanoma (n = 6)<br>▫ lung cancer<br>- NSCLC (n = 5)<br>- SCLC (n = 1)<br>▫ gastrointestinal stromal cancer (n = 2)<br>▫ cholangiocarcinoma (n = 2)<br>▫ appendix cancer (n = 1)<br>▫ breast cancer (n = 1)<br>▫ bone sarcoma (n = 1)<br>▫ pancreatic cancer (n = 1)<br>▪ SAS3[e] (n = 4)<br><br>Data cut-off 19 February 2019:<br>▪ ESMO 2019[f] (n = 97)<br>separated by tumour histology: ND<br>▪ SAS3[e] (n = 7) | Screening: 2 weeks<br><br>Treatment: until disease progression[g], unacceptable toxicity, necessity to switch treatment, withdrawal of consent, or death<br><br>Observation: ND for maximum duration | 36 centres[k] in Denmark, Germany, France, Ireland, Japan, Portugal, Singapore, South Korea, Spain, United Kingdom, USA<br><br>10/2015–ongoing | Primary: tumour response<br>Secondary: overall survival, morbidity, health-related quality of life, AEs |

Table 6: Characteristics of the studies on larotrectinib (multipage table)

| Study | Study design | Population | Interventions (number of patients included) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| SCOUT | Un-controlled, open-label, dose escalation and expansion study | Patients aged ≥ 1 month to 21 years with locally advanced or metastatic solid tumours or CNS tumours with recurrence, progression or nonresponse to available therapies for which no standard or curative systemic therapies are available[l]<br>▪ ≥ 1 year and ≤ 21 years with or without documented NTRK gene fusion[m]<br>▪ ≥ 1 month and < 1 year only with documented NTRK gene fusion[m]<br>▪ Karnofsky (≥ 16 years) or Lansky (< 16 years) performance score ≥ 50 | Data cut-off 30 July 2018:<br>larotrectinib (N = 54)<br>▪ with NTRK gene fusion (n = 45)<br>▪ without NTRK gene fusion (n = 9)<br><br>Subpopulations of patients with NTRK gene fusion analysed by the company:<br>▪ ePAS2[b] (n = 27)<br>▫ infantile fibrosarcoma (n = 13)<br>▫ soft tissue sarcoma (n = 11)<br>▫ bone sarcoma (n = 1)<br>▫ congenital mesoblastic nephroma (n = 1)<br>▫ melanoma (n = 1)<br>▪ SAS3[e] (n = 5)<br><br>Data cut-off 19 February 2019:<br>▪ ESMO 2019[d] (n = 50)<br>separated by tumour histology: ND<br>▪ SAS3[c] (n = 11) | Screening: 4 weeks<br><br>Treatment: until disease progression[g], unacceptable toxicity, necessity to switch treatment, withdrawal of consent, complete surgical resection, or death<br><br>Observation: ND for maximum duration | 32 centres[k] in Australia, Canada, Denmark, France, Germany, Ireland, Italy, Japan, Netherlands, Poland, South Korea, Spain, Sweden, Switzerland, United Kingdom, USA<br><br>12/2015–ongoing | Primary: safety, DLT (dose escalation phase), tumour response (expansion phase)<br>Secondary: morbidity and health-related quality of life (both study phases), overall survival and AEs (expansion phase) |

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain information on potentially relevant available outcomes for this benefit assessment.
b. Enrolment into the dose escalation cohorts was regardless of the presence of NTRK gene fusion. Archived tumour samples or tissue for a new biopsy had to be available for later analysis, however. After determination of the recommended dose for further clinical use, patients were again enrolled into the study; however, all of these patients had to have confirmed alteration in one of the NTRK genes (gene fusion, point mutation, translocation, insertion or deletion). These patients were to be allocated to 2 different expansion cohorts (NTRK gene fusion, other).
c. At the start of the study, only patients with ECOG-PS ≤ 1 were enrolled into study 14001, and only patients with ECOG-PS ≤ 2 were enrolled into the NAVIGATE study. Only later in the studies, enrolment was extended to patients with ECOG PS ≤ 2 and ≤ 3 respectively.

Table 6: Characteristics of the studies on larotrectinib (multipage table)

| Study | Study design | Population | Interventions (number of patients included) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| d. The ePAS2 analysis population includes all patients with NTRK gene fusion (except patients with primary CNS tumours) who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator, and IRC assessment available. At the data cut-off on 30 July 2018, IRC assessments were only available for patients who had started treatment with larotrectinib before or on 19 February 2018. Patients who started treatment only after that time point (N = 28 at the data cut-off on 30 July 2018) are not considered in the ePAS2 analysis population.<br>e. Patients with primary CNS tumours who received ≥ 1 dose of larotrectinib and who had ≥ 1 measurable lesion as evaluated by the investigator.<br>f. The ESMO 2019 analysis population concurs with the ePAS2 analysis population at the more recent data cut-off on 19 February 2019, but additionally includes patients for whom no IRC assessment was available. According to the company, the corresponding results were presented at the ESMO Congress 2019.<br>g. Study 14001: from protocol version 4 (1/2017), NAVIGATE: from protocol version 5 (6/2016), SCOUT: from protocol version 5 (9/2016), treatment beyond disease progression was possible if the investigator considered the patient to still have a clinical benefit from it. In the SCOUT study, patients with response could discontinue larotrectinib treatment prematurely after at least 6 cycles. In case of progression, reinitiation of treatment was possible.<br>h. At enrolment, patients were allocated to 8 predefined cohorts (NSCLC, thyroid cancer, soft tissue sarcoma, colorectal cancer, salivary gland cancer, cholangiocarcinoma, primary CNS tumour, other solid tumours). With protocol amendment version 7 (24 July 2017), a 9th cohort was added, which was to include all patients who have NTRK gene fusion, but for whom the detection NTRK gene fusion had been conducted in a non-certified laboratory.<br>i. The age limit was 18 years at the start of the study and was lowered to 12 years only in the further course of the study. In some countries, younger patients were also allowed to participate (Denmark: ≥ 8 years, Korea: ≥ 5 years). In Denmark and Korea, patients under 12 years of age had to have a Lansky Performance Status of ≥ 50.<br>j. Patients with primary CNS tumours had to have prior therapy appropriate for the type of tumour in the form of radiotherapy and/or chemotherapy; radiotherapy had to be completed > 12 weeks before starting treatment with larotrectinib.<br>k. Status: 8 August 2019.<br>l. Except patients with locally advanced infantile fibrosarcoma, who could also be included despite the option of potentially curative resection, if this had required disfiguring surgery or limb amputation.<br>m. Except patients with infantile fibrosarcoma, who did not require documented evidence of NTRK gene fusion for enrolment due to the known high prevalence of NTRK gene fusion in this tumour histology. | | | | | | |
| AE: adverse event; CNS: central nervous system; DLT: dose-limiting toxicity; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ePAS: extended primary analysis set; ESMO: European Society for Medical Oncology; IRC: independent review committee; MTD: maximum tolerated dose; n: subpopulation; N: number of included patients; ND: no data; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; SAS 3: supplementary analysis set 3; SCLC: small cell lung cancer | | | | | | |

Table 7: Characteristics of the interventions in the studies on larotrectinib (multipage table)

| Study | Intervention | Prior and concomitant treatment |
|---|---|---|
| LOXO-TRK-14001 | Larotrectinib orally, as capsules or solution, in 28-day cycles<br><br>Dose escalation cohorts[a]:<br>▪ 50 mg once daily<br>▪ 100 mg once daily<br>▪ 100 mg twice daily<br>▪ 200 mg once daily<br>▪ 150 mg twice daily<br>▪ 200 mg twice daily<br><br>Expansion cohorts:<br>100 mg twice daily<br><br>Dose adjustments:<br>In case of significant toxicity, interruption for up to 4 weeks until improvement to grade 1; if interruption ≥ 4 weeks, larotrectinib was to be permanently discontinued. | **Non-permitted pretreatment**<br>▪ investigational preparation or anticancer therapy ≤ 2 weeks before first intake of study medication<br>▪ major surgery within 4 weeks before first intake of study medication<br><br>**Non-permitted concomitant treatment**<br>▪ haematopoietic growth factors for prophylaxis in cycle 1<br>▪ monoclonal antibodies, radiotherapy, immunosuppressants<br>▪ strong CYP3A4 inhibitors or inducers<br>▪ other investigational preparations<br>▪ no alternative anticancer treatment was allowed before documented progression<br><br>**Permitted concomitant treatment**<br>▪ continued treatment with standard medication administered over a minimum period of 28 days before start of the study (e.g. GnRH or LH-RH agonists in prostate cancer)<br>▪ supportive medication such as: haematopoietic growth factors for the treatment of neutropenia or thrombocytopenia, transfusions, antiemetics, antidiarrhoeal drugs, glucocorticoids (≤ 10 mg/day prednisone or equivalent), including short-term use for the treatment of asthma, COPD |

Table 7: Characteristics of the interventions in the studies on larotrectinib (multipage table)

| Study | Intervention | Prior and concomitant treatment |
|---|---|---|
| NAVIGATE | 100 mg twice daily, orally, as capsules or solution, in 28-day cycles<br><br>Dose adjustments:<br>In case of significant toxicity, interruption for up to 4 weeks until improvement to grade 1; if interruption ≥ 4 weeks, larotrectinib was to be permanently discontinued. | **Non-permitted pretreatment**<br>▪ investigational preparation or anticancer therapy ≤ 2 weeks or 5 half-lives before first intake of study medication, whichever was shorter, and recovery from clinically significant toxicities of this therapy<br><br>**Non-permitted concomitant treatment**<br>▪ other approved or investigational anticancer therapies with the treatment goal of tumour shrinkage<br>▪ strong CYP3A4 inhibitors or inducers<br>▪ haematopoietic growth factors for prophylaxis in cycle 1<br><br>**Permitted concomitant treatment**<br>▪ continued treatment with standard medication administered over a minimum period of 28 days before start of the study (e.g. GnRH or LH-RH agonists in prostate cancer, bisphosphonates, RANKL inhibitors in bone metastases)<br>▪ supportive medication such as: haematopoietic growth factors for the treatment of neutropenia or thrombocytopenia, transfusions, antiemetics, antidiarrhoeal drugs, glucocorticoids (≤ 8 mg/day dexamethasone or ≤ 50 mg/day prednisone or equivalent), including short-term use for the treatment of asthma, COPD<br>▪ anticancer drugs that can be used for the treatment of other therapeutic indications (e.g. rituximab for autoimmune disorders or methotrexate for rheumatoid arthritis) if therapeutic indication is confirmed and stable dosage for ≥ 28 days<br>▪ glucocorticoids to reduce peritumoural oedema or improve neurological deficiencies (in primary CNS tumours)<br>▪ palliative radiotherapy (only with simultaneous interruption of larotrectinib treatment)<br>▪ antiepileptics possible only under certain conditions |

Table 7: Characteristics of the interventions in the studies on larotrectinib (multipage table)

| Study | Intervention | Prior and concomitant treatment |
|---|---|---|
| SCOUT | Cohort 1[b]:<br>9.6–55.0 mg/m$^2$<br>Cohort 2[b]:<br>17.3–120.0 mg/m$^2$<br>Cohort 3:<br>100 mg/m$^2$, twice daily[c]<br>(maximum dose: 100 mg, twice daily, based on body surface area)<br>orally, as capsules or solution, in 28-day cycles<br><br>Dose adjustments:<br>In case of significant toxicity, interruption for up to 3 weeks until improvement to grade 1; if interruption ≥ 3 weeks, larotrectinib was to be permanently discontinued. | **Non-permitted pretreatment**<br>▪ major surgery within 14 days before first intake of study medication<br><br>**Non-permitted concomitant treatment**<br>▪ further chemotherapeutic regimens, investigational therapies<br>▪ haematopoietic growth factors for prophylaxis in cycle 1<br>▪ immunosuppressants (except allowed corticosteroids)<br>▪ strong CYP3A4 inhibitors or inducers<br><br>**Permitted concomitant treatment**<br>▪ continued treatment with standard medication administered over a minimum period of 28 days before start of the study<br>▪ supportive medication such as: haematopoietic growth factors for the treatment of neutropenia or thrombocytopenia, transfusions, antiemetics, antidiarrhoeal drugs, glucocorticoids (≤ 10 mg/day dexamethasone or ≤ 50 mg/day prednisone or equivalent), including short-term use for the treatment of asthma, COPD<br>▪ high-dose glucocorticoids to reduce peritumoural oedema or improve neurological deficiencies in patients with primary brain tumours<br>▪ dexamethasone in CNS tumours or metastases at a stable dose<br>▪ palliative radiotherapy (only with simultaneous interruption of larotrectinib treatment)<br>▪ antiepileptics possible only under certain conditions<br>▪ surgical resection for local tumour control or, if possible, with curative intent |

a. Starting with protocol amendment version 4.0 (25 January 2017), all patients with NTRK gene fusion received 100 mg larotrectinib twice daily, regardless of the dose escalation step they had been allocated to originally.
b. A physiologically-based pharmacokinetics model (SimCyp) was used that factored in the patient's age, body surface area, and the development of the elimination pathways of larotrectinib with the intent of matching the exposure as characterized for adults before. The dosage in cohort 1 was to be equivalent to a dose of 100 mg twice daily and the dosage in cohort 2 equivalent to a dose of 150 twice daily in adults.
c. This dose was determined as recommended dosage for paediatric patients in the framework of the study and was to be used for the expansion phase.

CNS: central nervous system; COPD: chronic obstructive pulmonary disease; CYP3A4: cytochrome P450 3A4; GnRH: gonadotropin-releasing hormone; LH-RH: luteinizing hormone-releasing hormone; NTRK: neurotrophic tyrosine receptor kinase; RANKL: receptor activator of nuclear factor kappa-B ligand

### Study LOXO-TRK-14001

The LOXO-TRK-14001 study is an ongoing, uncontrolled, open-label, multicentre dose escalation study. The study included adult patients with locally advanced or metastatic solid tumours that had progressed or were nonresponsive to available therapies, who were unfit for standard chemotherapy or for whom no standard or curative therapy was available. At the start of the study, only patients with an Eastern Cooperative Oncology Group Performance Status

(ECOG PS) of ≤ 1 were enrolled; with protocol amendment version 3.1 (1 May 2015), enrolment was extended to ECOG PS ≤ 2.

The patients were allocated to different dose escalation cohorts and, depending on their allocation, received different doses of larotrectinib, starting from 50 mg once daily up to 200 mg twice daily (see Table 7, dose escalation phase of the study). Enrolment into the dose escalation cohorts was regardless of the presence of NTRK gene fusion, but archived tumour samples or tissue for a new biopsy had to be available for later analysis. After determination of the recommended dose of 100 mg twice daily for further clinical use, again patients were enrolled into the study in so-called expansion cohorts (expansion phase of the study). These patients had to have confirmed alteration in one of the NTRK genes at the start of the study. Based on alteration (gene fusion, point mutation, translocation, insertion or deletion), the patients were to be allocated to 2 different expansion cohorts (NTRK gene fusion, other). Patients included in the expansion cohorts received exclusively the recommended dose of 100 mg twice daily, which is in compliance with the approved dosage of larotrectinib for adults [3]. Starting with protocol amendment version 4.0 (25 January 2017), all patients with NTRK gene fusion, both those already enrolled and those subsequently enrolled, received 100 mg larotrectinib twice daily, regardless of the dose escalation step they had been allocated to originally. Concomitant supportive therapies were allowed (see Table 7). All patients were to be treated until disease progression, unacceptable toxicity, necessity of a treatment switch, withdrawal of consent, or death. Treatment with larotrectinib beyond progression was possible if the investigator considered the patient to still have a benefit from it. Subsequent therapies had to be recorded during follow-up.

Primary outcome of the study was the recording of AEs, the identification of the maximum tolerated dose and the identification of a recommended dose for further clinical use. Secondary outcomes concerned tumour response.

**NAVIGATE**

The NAVIGATE study is an ongoing, uncontrolled, open-label, multicentre basket study. In the framework of the basket design, the patients were allocated to different cohorts according to tumour histology (NSCLC, thyroid cancer, soft tissue sarcoma, colorectal cancer, salivary gland cancer, cholangiocarcinoma, primary tumour of the CNS, other solid tumours). The study included patients aged 12 years and older with locally advanced or metastatic solid tumours and evidence of NTRK gene fusion. To be included in the study, the patients had to have received prior standard therapy appropriate for their tumour histology and disease severity, or not be candidates for such therapy. At the start of the study, only patients with ECOG PS ≤ 2 were enrolled; with protocol amendment version 5 (17 June 2016), enrolment was extended to ECOG PS ≤ 3. Patients with primary CNS tumours had to have a Karnofsky Performance Score of ≥ 50.

All patients received larotrectinib at a dosage of 100 mg twice daily (see Table 7). Dosing based on body surface area, as recommended in the Summary of Product Characteristics (SPC) for

paediatric patients [3], was not used. Concomitant supportive therapies were allowed (see Table 7). Treatment duration was until disease progression, unacceptable toxicity, necessity of a treatment switch, withdrawal of consent, or death. As in the LOXO-TRK-14001 study, treatment with larotrectinib beyond progression was possible if the investigator considered the patient to still have a benefit from it. Subsequent therapies had to be recorded during follow-up.

Primary outcome of the study was tumour response; secondary outcomes included overall survival as well as outcomes on morbidity, health-related quality of life and AEs.

**SCOUT**

The SCOUT study is an ongoing, uncontrolled, open-label, multicentre study composed of a dose escalation and an expansion phase. Patients aged between 1 month and 21 years with locally advanced or metastatic solid tumours were enrolled. It was a precondition for study inclusion that the patients had recurrence, progression or nonresponse to available therapies, or that no standard or curative systemic therapies were available. Patients between 1 month and 1 year of age were only included in the study if documented evidence of NTRK gene fusion was available. Depending on the study phase, older patients were included both with and without documented NTRK gene fusion. Due to the known high prevalence of NTRK gene fusion in infantile fibrosarcoma, patients with this tumour entity did not require documented evidence of NTRK gene fusion for enrolment. Patients with locally advanced infantile fibrosarcoma could also be included if the option of potentially curative resection existed, but this would have required disfiguring surgery or limb amputation (neoadjuvant use). All patients had to have a Karnofsky (≥ 16 years) or Lansky (< 16 years) performance score of ≥ 50.

Treatment of the patients was conducted according to the regimen described in Table 7. In the framework of the dose escalation phase, a dose of 100 mg/m$^2$, twice daily (maximum dose 100 mg, twice daily), as defined for cohort 3, was determined as recommended dose for the expansion phase. This dose is in compliance with the approved dosage for paediatric patients [3]. Surgical resection for local tumour control or, if possible, with curative intent was allowed. Treatment duration was until disease progression, unacceptable toxicity, necessity of a treatment switch, withdrawal of consent, complete surgical resection, or death. As in the other 2 studies, treatment with larotrectinib beyond progression was possible if the investigator considered the patient to still have a benefit from it. Subsequent therapies had to be recorded during follow-up.

Primary outcome of the dose escalation phase of the study was the recording of side effects and the identification of dose-limiting toxicity; primary outcome of the expansion phase of the study was tumour response. Secondary outcomes of both study phases comprised outcomes on morbidity and health-related quality of life. Further secondary outcomes in the expansion phase were overall survival and the recording of side effects.

**Detection of NTRK gene fusion**

NTRK gene fusion in patients enrolled into the studies on larotrectinib had to be detected by a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalently certified laboratory. In addition, archived tumour samples had to be collected at the start of the study, or – if not available and if possible – a new biopsy had to be conducted to test and confirm the NTRK status in a central laboratory.

According to the statistical analysis plan (SAP) on the pooled analysis, the following methods for detection of NTRK gene fusion were accepted: next generation sequencing (NGS), fluorescence in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR). The testing methods used cover the methods recommended by the European Society for Medical Oncology (ESMO) to detect NTRK gene fusions [4]. If NGS was used for detection, it had to be clear from the pathology report that fusion between one of the NTRK genes (*NTRK1*, *NTRK2*, *NTRK3*) and a specific partner gene had been found. If FISH was used for detection, it had to be clear from the pathology report that there had been microscopically visible colocalization of an NTRK-specific probe and a probe specific for the partner gene. Patients with infantile fibrosarcoma were an exception. Due to the high prevalence of NTRK gene fusion and the ETV6 break apart assay routinely used for diagnosis, non-existent colocalization of both ETV6 probes was sufficient for detection. If RT-PCR was used for detection, it had to be clear from the pathology report that a detectable target molecule had been amplified by the primer pair used, which, on the one hand, binds to one of the NTRK genes and, on the other, to the specific partner gene. There is no information as to which procedure was used for how many patients in the individual studies.

**Planned duration of follow-up observation**

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation in the studies on larotrectinib

| **Study**<br>**Outcome category**<br>**Outcome** | **Planned follow-up observation** |
|---|---|
| **LOXO-TRK-14001** | |
| Mortality | |
| Overall survival | ND |
| Morbidity | Not recorded |
| Health-related quality of life | Not recorded |
| Side effects | |
| AEs | No follow-up after discontinuation of study medication |
| SAEs | Up to 28 days after discontinuation of the study medication |
| **NAVIGATE** | |
| Mortality | |
| Overall survival | ND |
| Morbidity | |
| Symptoms (EORTC QLQ-C30) | No follow-up after discontinuation of study medication |
| Health status (EQ-5D VAS) | No follow-up after discontinuation of study medication |
| Health-related quality of life (EORTC QLQ C30, PedsQL Generic Core Scale) | No follow-up after discontinuation of study medication |
| Side effects | |
| All AEs | Up to 28 days after discontinuation of the study medication |
| **SCOUT** | |
| Mortality | |
| Overall survival | ND |
| Morbidity | |
| Pain (Wong-Baker FACES Pain Rating Scale) | No follow-up after discontinuation of study medication |
| Health-related quality of life (PedsQL Infant Scale and Generic Core Scale) | No follow-up after discontinuation of study medication |
| Side effects | |
| All AEs | Up to 28 days after discontinuation of the study medication |

AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; ND: no data; PedsQL: Pediatric Quality of Life Inventory; SAE: serious adverse event; VAS: visual analogue scale

In the individual studies on larotrectinib, the observation periods for the outcomes of the categories “morbidity”, “health-related quality of life” (if recorded) and “side effects” were systematically shortened because they were only recorded for the time period of treatment with the study medication (AEs/serious AEs [SAEs] partly plus 28 days). To be able to draw a reliable conclusion over the total study period, however, it would be necessary that also these outcomes are recorded over the total period. There is no information on the planned observation period for overall survival.

#### 2.3.1.2 Available data from the studies on larotrectinib

**Data cut-offs**

The company presented results on 2 data cut-offs in the dossier:

- data cut-off 30 July 2018; analysis population: ePAS2
- data cut-off 19 February 2019; analysis population: ESMO 2019

According to the company, it used the data cut-off on 30 July 2018 as primarily relevant data cut-off and presented results at the data cut-off on 19 February 2019 as supplementary information.

No interim analysis was originally planned for any of the 3 studies. The data cut-off on 30 July 2018 was produced for the European regulatory authority (European Medicines Agency [EMA]) in the framework of the approval procedure. According to information provided by the company, the results on the data cut-off from 19 February 2019 were used for a presentation at the ESMO Congress 2019. Deviating from the company, the present benefit assessment considers the tumour entities separately (see the following section for details). Results for this are only available for the data cut-off from 30 July 2018.

It can be inferred from the Module 5 documents that further unplanned interim analyses had been conducted at earlier time points (data cut-offs: 17 July 2017 and 19 February 2018).

**Analysis population**

The company primarily used the 2 analysis populations ePAS2 and SAS3 in the dossier. In the ePAS2 analysis population, all patients with NTRK gene fusion, regardless of their tumour entities (except patients with primary CNS tumours), from the studies LOXO-TRK-14001, NAVIGATE and SCOUT who met the following criteria were pooled:

- administration of ≥ 1 dose of larotrectinib
- ≥ 1 measurable lesion (as defined by RECIST version 1.1) at baseline as evaluated by the investigator
- IRC assessment available

The analysis population referred to as “SAS3” by the company, comprises all patients with NTRK gene fusion and primary CNS tumours. As supplementary information, the company presented results separately for tumour entities on the one hand and, on the other, separately for adult and paediatric patients, but pooled independently of tumour histology.

The ePAS2 analysis population comprises only patients for whom an IRC assessment was already available at the data cut-off, as only these patients were considered in the ePAS2 analysis population (see above). The study protocols did not mandate a restriction of the analysis population to patients with available IRC assessment (see Section 2.7.7.1 of the full

dossier assessment). At the time point of the data cut-off from 30 July 2018, the ePAS2 analysis population (N = 93) did not include 28 patients who had started treatment at this time point, but for whom an IRC assessment was not yet available (see Table 14 of the full dossier assessment). Information on the number of patients included in this number separated by tumour entity is not available. It can be inferred from the EPAR that 27 of these 28 patients had treatment with larotrectinib ongoing at the data cut-off on 30 July 2018 with treatment duration ranging from 0 to 4.7 months up to that time point. One patient had discontinued larotrectinib treatment after 4.3 months due to surgical resection. Whereas it may be meaningful to restrict an analysis population to patients with IRC assessment for outcomes referring to tumour imaging, it is inadequate to restrict the population in this way for the analysis of outcomes on mortality, morbidity, health-related quality of life and AEs. All patients included should be considered in the analysis of these outcomes. The company did not present such an analysis (contrary to the planning of the study) (see Section 2.7.7.1 of the full dossier assessment). For AE outcomes, the company presented results on all patients with NTRK gene fusion who had received at least one dose of larotrectinib, but not separately for tumour entities.

Deviating from the ePAS2 analysis population, patients without IRC assessment are also considered in the ESMO 2019 analysis population (see above, N = 159) at the data cut-off from 19 February 2019. The ESMO 2019 analysis population did not contain results separated by tumour entity, however.

**Consideration of the tumour entity**

Deviating from the company, the present benefit assessment considers the results separately for tumour entities and not regardless of tumour histology (within the tumour entities, the data pooled across the studies were analysed). The reasons are as follows:

- Based on the very distinct natural histories of the included tumour entities and stages, heterogeneity of prognoses is expected. The ePAS2 analysis population, for example, also includes patients with infantile fibrosarcoma, for whom – in contrast to most other tumour entities – curative resection was still a potential option at enrolment and for whom partly high survival rates can be assumed [5,6].
- The aim of the benefit assessment is the comparison with the ACT (in this case: BSC); the course of disease under BSC also potentially depends on the tumour entities.
- Correspondingly (and adequately), comparative data are only available separately for tumour histology (see Section 2.3.2).
- There is currently no scientific consensus as to whether NTRK gene fusions are universal oncogenic drivers (i.e. that they cause or promote tumour formation independently of the respective tissue or further disease characteristics [7]).
- The prognostic relevance of NTRK gene fusion is unclear, except for the tumour entities where the fusion is pathognomonic (a sufficient criterion for the diagnosis) [7].

In its dossier, the company did not address the question whether it had investigated possible heterogeneities before combining both the data from the different studies and the different tumour entities. The study protocol of the basket study NAVIGATE mandated a reporting of results separately for the respective tumour-specific cohorts.

Results separated by tumour entity are available in the form of subgroup analyses on the ePAS2 analysis population, and in the supplementary histology-specific presentation at the data cut-off from 30 July 2018 provided by the company. The data presented by the company on individual tumour entities are incomplete, however (see Section 2.4).

**Patient characteristics**

Deviating from the company, the present benefit assessment considers the patients separately for tumour entities, whereas the company pooled all patients independently of tumour histology in the ePAS2 analysis population, except patients with primary CNS tumours (referred to as "SAS3 analysis population" by the company).

Table 9 shows the number of patients included in the ePAS2 analysis population separated by tumour entity and study and pooled across all studies. Information on patients with primary CNS tumours was additionally provided, as these are not included in the ePAS2 analysis population. Clear differences are shown in the number of patients per tumour entity, ranging from one to a maximum of 21 patients.

Information on demographic and clinical characteristics (except number of received prior systemic therapies) of the patients separated by tumour entity is not available. Separate information is only available on patients with primary CNS tumours. Demographic and clinical characteristics of the patients with primary CNS tumours, supplementary to the ePAS2 analysis population, are presented in Table 19 in Appendix A of the full dossier assessment. A description of the patients treated in the individual tumour entities is therefore not possible. This is an additional difficulty in the interpretation of the results. It is also not possible to check the comparability of the patients in the studies on larotrectinib separated by tumour entity with patient populations from studies with comparator therapies.

Table 10 shows the number of prior systemic therapies received by the patients of the individual tumour entities before larotrectinib treatment. In the 4 most frequently represented tumour entities, 20% to 50% of the patients had not received prior systemic therapy. Without information on the corresponding clinical characteristics of the patients in the individual tumour entities, it cannot be checked whether the patients included in the present studies on larotrectinib concurred with the patient population described in the SPC.

Table 9: Overview of the patient populations included in the larotrectinib studies (ePAS2 analysis population, N = 93[a])

| | Studies | | | Pooled (ePAS2) n (%) |
|---|---|---|---|---|
| **Data cut-off 30 July 2018** | **LOXO-TRK-14001** | **NAVIGATE** | **SCOUT** | |
| **Tumour histology** | N = 8[b] | N = 62[b] | N = 32[b] | N = 93[a] |
| Soft tissue sarcoma | 1 | 9 | 11 | 21 (23) |
| Salivary gland cancer | 3 | 14 | 0 | 17 (18) |
| Infantile fibrosarcoma | 0 | 0 | 13 | 13 (14) |
| Thyroid cancer | 1 | 9 | 0 | 10 (11) |
| Lung cancer | 1 | 6 | 0 | 7 (8) |
| NSCLC | 1 | 5 | 0 | 6 (6[c]) |
| SCLC[d] | 0 | 1 | 0 | 1 (1) |
| Melanoma | 0 | 6 | 1 | 7 (8) |
| Colorectal cancer | 0 | 6 | 0 | 6 (6) |
| Gastrointestinal stromal cancer | 2 | 2 | 0 | 4 (4) |
| Bone sarcoma | 0 | 1 | 1 | 2 (2) |
| Cholangiocarcinoma | 0 | 2 | 0 | 2 (2) |
| Appendix cancer | 0 | 1 | 0 | 1 (1) |
| Breast cancer | 0 | 1 | 0 | 1 (1) |
| Congenital mesoblastic nephroma | 0 | 0 | 1 | 1 (1) |
| Pancreatic cancer | 0 | 1 | 0 | 1 (1) |
| Primary CNS tumour | 0 | 4 | 5 | 0[e] |

a. Number of included patients with NTRK gene fusion (except patients with primary CNS tumours) who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator, IRC assessment available. At the data cut-off on 30 July 2018, IRC assessments were only available for patients who had started treatment with larotrectinib before or on 19 February 2018. Thus, the ePAS2 does not include 28 patients who had started treatment at the time point of the data cut-off from 30 July 2018, but for whom an IRC assessment was not yet available (see Section 2.3.1.2 and Section 2.7.7.1 of the full dossier assessment).
b. Number of patients of the ePAS2 analysis population proportionally included in the individual studies, plus patients with primary CNS tumours. These are not included in the ePAS2 analysis population.
c. Institute's calculation.
d. In the NAVIGATE study, the lung cancer cohort was directed at patients with NSCLC. Nevertheless, one patient with SCLC is also included in the study population.
e. The studies included a total of 9 patients with primary CNS tumours with NTRK gene fusion who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator. Patients with primary CNS tumours are not included in the ePAS2 analysis population.

CNS: central nervous system; ePAS2: extended primary analysis set 2; IRC: independent review committee; n: number of patients with the respective tumour histology; N: number of analysed patients; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; SCLC: small cell lung cancer

Table 10: Number of prior systemic therapies received in the studies with larotrectinib (ePAS2 analysis population, N = 93[a])

| Data cut-off 30 July 2018 | N[b] | Patients with prior systemic therapy n (%) | | |
|---|---|---|---|---|
| **Tumour histology** | | **0** | **1-2** | **≥ 3** |
| Soft tissue sarcoma | 20[c] | 5 (25[d]) | 14 (70[d]) | 1 (5[d]) |
| Salivary gland cancer | 17 | 9 (53[d]) | 6 (35[d]) | 2 (12[d]) |
| Infantile fibrosarcoma | 13 | 3 (23[d]) | 7 (54[d]) | 3 (23[d]) |
| Thyroid cancer | 10 | 2 (20[d]) | 3 (30[d]) | 5 (50[d]) |
| Lung cancer | 7 | 0 | 3 (43[d]) | 4 (57[d]) |
| NSCLC | 6 | ND | ND | ND |
| SCLC | 1 | ND | ND | ND |
| Melanoma | 7 | 0 | 4 (57[d]) | 3 (43[d]) |
| Colorectal cancer | 6 | 0 | 6 (100[d]) | 0 |
| Gastrointestinal stromal cancer | 5[c] | 0 | 1 (20[d]) | 4 (80[d]) |
| Bone sarcoma | 2 | 1 (50[d]) | 0 | 1 (50[d]) |
| Cholangiocarcinoma | 2 | 0 | 1 (50[d]) | 1 (50[d]) |
| Appendix cancer | 1 | 0 | 1 (100[d]) | 0 |
| Breast cancer | 1 | 0 | 0 | 1 (100[d]) |
| Congenital mesoblastic nephroma | 1 | 1 (100[d]) | 0 | 0 |
| Pancreatic cancer | 1 | 0 | 1 (100[d]) | 0 |
| Primary CNS tumour | 9 | 0 | 8 (89) | 1 (11) |

a. Number of included patients with NTRK gene fusion (except patients with primary CNS tumours) who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator, IRC assessment available. At the data cut-off on 30 July 2018, IRC assessments were only available for patients who had started treatment with larotrectinib before or on 19 February 2018. Thus, the ePAS2 does not include 28 patients who had started treatment at the time point of the data cut-off from 30 July 2018, but for whom an IRC assessment was not yet available (see Section 2.3.1.2 and Section 2.7.7.1 of the full dossier assessment).
b. Data refer to the number of patients per tumour entity included in the ePAS2 analysis population (does not apply to patients with primary CNS tumours).
c. The deviation from the number of patients included in the ePAS2 analysis population is due to the fact that, for the ePAS2 analysis population, one patient's tumour originally classified as gastrointestinal stromal cancer was reclassified as soft tissue sarcoma.
d. Institute's calculation.

CNS: central nervous system; ePAS2: extended primary analysis set 2; IRC: independent review committee; n: number of patients with the respective tumour histology; N: number of patients in the ePAS2; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; SCLC: small cell lung cancer

### Treatment duration and observation period

There is no information on the treatment durations and observation periods for patients of the ePAS2 analysis population separated by tumour entity. For patients with primary CNS tumours, only information on treatment duration and on the median observation period for the outcome "overall survival" is available (see Table 20 in Appendix B of the full dossier assessment). The median observation period for the outcome "overall survival" in patients with primary CNS

tumours was 4.6 months. Data on the observation periods for other outcomes are also not available for these patients. Available data on the ePAS2 analysis population are presented as supplementary information in Table 20 in Appendix B of the full dossier assessment.

**Risk of bias across outcomes (study level)**

There are no effect estimations on the comparison of larotrectinib with the ACT. The risk of bias was therefore not assessed.

### 2.3.2 Available comparative data

The company itself did not use any comparative data (see Section 2.7.3.2 of the full dossier assessment). However, in Module 4 A, Section 4.2.5.6, it referred to a report in Module 5 of the dossier, which contains a description of the information retrieval on comparator studies and an extraction table of the study results identified in this information retrieval.

The document added to the dossier by the company contains an information retrieval on the following tumour entities: non-small cell lung cancer, colorectal cancer, melanoma, pancreatic cancer, thyroid cancer, glioma, cholangiocarcinoma, soft tissue sarcoma (including infantile fibrosarcoma), gastrointestinal stromal cancer, salivary gland cancer, bone sarcoma, appendix cancer, secretory breast cancer, congenital mesoblastic nephroma.

The company conducted its information retrieval in the following databases, among others: MEDLINE, EMBASE, and the Cochrane databases. Individual trial registries, conference papers and health technology assessment websites were additionally screened. Separate inclusion and exclusion criteria for the inclusion of studies were defined for each tumour entity, and indication-specific searches in bibliographic databases were carried out based on these criteria. For some tumour entities, such as non-small cell lung cancer, the inclusion of studies was limited to later lines of treatment and certain interventions. For other tumour entities, such as salivary gland cancer, on the other hand, no limitation to a specific line of treatment or intervention was made. The data on different outcomes on mortality, morbidity, health-related quality of life and AEs were presented separately for tumour entities. Due to deficiencies in the information retrieval and study selection, however, it is generally not assumed that the search results in this document are complete (see Section 2.7.3 of the full dossier assessment).

The company stated to have produced this information retrieval for the centralized authorization procedure. Section 2.5.2.1 of the EPAR on larotrectinib contains a table on comparative data with available therapies by tumour entity [7]. However, the study pool underlying the data on overall survival in this table is not the same as the study pool underlying the data on overall survival data in the report presented by the company in Module 5 of the dossier [8]. For example, 16 studies on salivary gland cancer form the study pool on results on overall survival in the EPAR table, whereas only 5 studies form the study pool on results on overall survival in the information retrieval added to Module 5 of the dossier. Of these 5 studies, only one study is also included in the corresponding study pool to which the information in the EPAR refers. It is not clear from the information available why these data sources differ so much.

Deviating from the company, the comparative data generated by the company are considered in the present benefit assessment to support the interpretation of the data on larotrectinib. For this purpose, on the one hand, the comparative data from the EPAR are considered, and, on the other, the comparative data from the information retrieval added to the dossier. The comparative data are presented in Table 21, Table 22 and Table 23 in Appendix C of the full dossier assessment.

## 2.4 Results on added benefit

### 2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.7.3.1 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms, measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30, symptom scales)
  - pain, measured with the Wong-Baker FACES Pain Rating Scale
  - health status measured with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)
- Health-related quality of life
  - health-related quality of life, measured with the EORTC QLQ-C30 (functional scales and global health status scale), Pediatric Quality of Life Inventory (PedsQL) Generic Core Scale and PedsQL Infant Scale
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3-4)
  - discontinuation due to AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.7.3.1 of the full dossier assessment). In the derivation of the added benefit, the company additionally cited case studies on the avoidance of amputations and on the regression of disfiguring or functionality-impairing tumour masses.

The avoidance of amputations cited by the company refers to the fact that the therapeutic indication also comprises patients who have a disease where surgical resection is likely to result in severe morbidity. Thus, an added benefit of larotrectinib could also be based on a patient-relevant sustained delay or even avoidance of such resections.

The therapeutic indication additionally comprises patients whose tumours have disfiguring or functionality-impairing effects due to their size and/or location. Thus, an added benefit of larotrectinib could also be based on a patient-relevant decrease in tumour size to a degree that the tumour is no longer disfiguring or impairing functionality.

No such outcomes were defined in the studies LOXO-TRK-14001 and NAVIGATE. In the SCOUT study, only the postsurgical tumour status had to be described for those patients in whom a complete surgical resection was attempted after treatment with larotrectinib. Similarly, the resection plan before and after treatment with larotrectinib had to be recorded for all patients with regard to functionality and cosmetics. An analysis was not planned. Besides, the company did not cite any such outcomes and operationalizations in Sections 4.2 and 4.3 of its dossier. Finally, no suitable operationalizations or relevant results can be derived on the basis of the available study data. The case studies presented by the company on these outcomes are described in Section 2.4.3 as supplementary information.

Table 11 shows for which outcomes results separated by tumour entity are available in the studies on larotrectinib and in the available comparative data.

Table 11: Matrix of outcomes – studies on larotrectinib and comparative data; availability of results by tumour entity (ePAS2 analysis population, N = 93[a])

| Study | Outcomes | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Overall survival** | **Symptoms (EORTC QLQ-C30, Wong-Baker FACES Pain Rating Scale)** | **Health status (EQ-5D VAS)** | **Health-related quality of life (EORTC QLQ-C30, PedsQL Infant Scale and Generic Core Scale)** | **SAEs** | **Discontinuation due to AEs** | **Severe AEs (CTCAE grade 3–4)** |
| Studies on larotrectinib, pooled (LOXO-TRK-14001, NAVIGATE, SCOUT) | Yes | No[b] | No[b] | No[b] | In part[c] | In part[c] | In part[c] |
| Comparative data[d] | Yes[e] | In part[c] | In part[c] | In part[c] | In part[c] | In part[c] | No |

a. Number of included patients with NTRK gene fusion (except patients with primary CNS tumours) who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator, IRC assessment available. At the data cut-off on 30 July 2018, IRC assessments were only available for patients who had started treatment with larotrectinib before or on 19 February 2018. Thus, the ePAS2 does not include 28 patients who had started treatment at the time point of the data cut-off from 30 July 2018, but for whom an IRC assessment was not yet available (see Section 2.3.1.2 and Section 2.7.7.1 of the full dossier assessment).
b. No data separated by tumour histology available.
c. Data are not available for all tumour entities (see Table 12 for available results on larotrectinib, and Table 21, Table 22 and Table 23 in Appendix C of the full dossier assessment for the corresponding comparative data).
d. Consideration of the available comparative data from the EPAR and the company's information retrieval on studies of historical comparisons (see Section 2.3.2 and Appendix C of the full dossier assessment).
e. Except information on the 2 tumour entities congenital mesoblastic nephroma or breast cancer.

AE: adverse event; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EPAR: European Public Assessment Report; ePAS2: extended primary analysis set 2, EQ-5D: European Quality of Life-5 Dimensions; IRC: independent review committee; NTRK: neurotrophic tyrosine receptor kinase; PedsQL: Pediatric Quality of Life Inventory; SAE: serious adverse event; VAS: visual analogue scale

### 2.4.2 Risk of bias

There are no effect estimations on the comparison of larotrectinib with the ACT. The risk of bias was therefore not assessed.

### 2.4.3 Results

Table 12 summarizes the results on larotrectinib. A Kaplan-Meier curve on the outcome "overall survival" is only available for patients with primary CNS tumour (see Appendix D of the full dossier assessment). A list of the common AEs, SAEs and severe AEs (CTCAE grade

3–4) can be found in Appendix E of the full dossier assessment, provided that separate information was available on the individual tumour entities. No list of individual events is available for the outcome "discontinuation due to AEs".

A comparison with the ACT BSC is not possible on the basis of the documents submitted by the company. The data on patient-relevant outcomes under other therapies available in the dossier are only considered to support the interpretation of the results on larotrectinib. The comparative data can be found in Appendix C of the full dossier assessment.

Table 12: Results (overall survival, side effects) – larotrectinib (ePAS2 analysis population, N = 93[a]) (multipage table)

| Tumour histology | N[b] | Median time to event in months [min, max]<br>Patients with event<br>n (%) | | | | |
|---|---|---|---|---|---|---|
| | | Overall survival | AEs | SAEs | Severe AEs (CTCAE grade 34) | Discontinuation due to AEs |
| **Pooled analysis of the studies LOXO-TRK-14001, NAVIGATE and SCOUT (data cut-off 30 July 2018)** | | | | | | |
| Soft tissue sarcoma | 21 | NA [1.2; 40.7[c]]<br>3 (14) | ND<br>20 (100)[d] | ND<br>4 (19) | ND<br>11 (52) | ND[e] |
| Salivary gland cancer | 17 | NA [4.1; 36.7[c]]<br>2 (12) | ND<br>17 (100) | ND<br>4 (24) | ND<br>9 (53) | |
| Infantile fibrosarcoma | 13 | NA [5.5[c]; 26.7[c]]<br>0 | ND | ND<br>5 (38) | ND<br>8 (62) | |
| Thyroid cancer | 10 | NA [3.0; 33.4[c]]<br>2 (20) | ND | ND<br>3 (30) | ND<br>4 (40) | |
| Primary CNS tumour | 9 | NA [0.0[c]; 9.2[c]]<br>0 | ND<br>8 (89) | ND<br>3 (33) | ND<br>2 (22) | |
| Lung cancer[f] | 7 | NA [5.5[c]; 28.5[c]]<br>1 (14) | ND | ND<br>1 (14) | ND<br>3 (43) | |
| Melanoma | 7 | 8.4 [1.4[c]; 26.1[c]]<br>2 (29) | ND | | | |
| Colorectal cancer | 6 | NA [2.2[c]; 28.8[c]]<br>2 (33) | ND | | | |
| Gastrointestinal stromal cancer | 4 | NA [12.9[c]; 37.2[c]]<br>0 | ND | | | |
| Bone sarcoma | 2 | NA [11.8[c]; 14.1[c]]<br>0 | ND | | | |
| Cholangiocarcinoma | 2 | NA [1.8; 28.6[c]]<br>1 (50) | ND | 14 (56)[g] | 16 (64)[g] | |
| Congenital mesoblastic nephroma | 1 | NA [12.5[c]; 12.5[c]]<br>0 | ND | | | |
| Appendix cancer | 1 | NA [7.7[c]; 7.7[c]]<br>0 | ND | | | |
| Breast cancer | 1 | NA [1.0[c]; 1.0[c]]<br>0 | ND | | | |
| Pancreatic cancer | 1 | 14.1 [14.1; 14.1]<br>1 (100) | ND | | | |

Table 12: Results (overall survival, side effects) – larotrectinib (ePAS2 analysis population, N = 93[a]) (multipage table)

| Tumour histology | N[b] | Median time to event in months [min, max]<br>Patients with event<br>n (%) | | | | |
|---|---|---|---|---|---|---|
| | | Overall survival | AEs | SAEs | Severe AEs (CTCAE grade 34) | Discontinuation due to AEs |
| a. Number of included patients with NTRK gene fusion (except patients with primary CNS tumours) who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator, IRC assessment available. At the data cut-off on 30 July 2018, IRC assessments were only available for patients who had started treatment with larotrectinib before or on 19 February 2018. Thus, the ePAS2 does not include 28 patients who had started treatment at the time point of the data cut-off from 30 July 2018, but for whom an IRC assessment was not yet available (see Section 2.3.1.2 and Section 2.7.7.1 of the full dossier assessment).<br>b. Data refer to the number of patients per tumour entity included in the ePAS2 analysis population (does not apply to patients with primary CNS tumours).<br>c. Censored observation.<br>d. Data refer to N = 20 patients. One patient initially diagnosed with gastrointestinal stromal cancer was reclassified to soft tissue sarcoma. No information on AEs is available for this patient.<br>e. No data by tumour histology available, except for the information that no discontinuation due to AEs had occurred in patients with primary CNS tumours.<br>f. Includes patients with NSCLC and SCLC, separate results are not available.<br>g. Separate data for the individual tumour entities are not available, only pooled across the corresponding tumour histologies.<br>AE: adverse event; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; ePAS2: extended primary analysis set 2, IRC: independent review committee; N: number of analysed patients; n: number of patients with event; NA: not achieved; ND: no data; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; SAE: serious adverse event; SCLC: small cell lung cancer | | | | | | |

## Mortality

### *Overall survival*

The present benefit assessment considers the patients separately for tumour entities (for reasons, see paragraph *Consideration of the tumour entity* in Section 2.3.1.2). Regarding the outcome "overall survival", results on larotrectinib are available for patients with the following tumour entities: soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, primary CNS tumour, lung cancer, melanoma, colorectal cancer, gastrointestinal stromal cancer, bone sarcoma, cholangiocarcinoma, congenital mesoblastic nephroma, appendix cancer, breast cancer and pancreatic cancer.

When considering the results on overall survival under larotrectinib separately according to tumour entity, the median survival time in most tumour entities had not yet been reached at the data cut-off from 30 July 2018. The proportions of patients who had died so far cannot be interpreted separately according to tumour entity due to the small number of patients and the lack of data on the median observation period.

In an attempt to evaluate the results obtained under treatment with larotrectinib for the present benefit assessment, the available comparative data were considered (see Section 2.3.2). These

are presented in Appendix C of the full dossier assessment and summarize the range of the medians on overall survival established in the underlying studies. Some of the data are available separately for treatment lines for the individual tumour entities. Since the available comparative data are not results under BSC, but under other active therapies, the results under larotrectinib were compared with those of the last available lines of treatment as an approximation. If the median was not yet reached in individual tumour entities in the results for larotrectinib, it was checked whether the time period between the minimum and maximum survival time reached so far overlaps with the comparative data. This is explained below by way of example using the tumour entity that includes the largest number of patients in the larotrectinib studies.

In the case of soft tissue sarcoma, no information is yet available on median overall survival under larotrectinib. So far, 3 of 21 patients have died. The minimum observed survival time is 1.2 months and the maximum observed survival time so far is 40.7 months (see Table 12). The comparative data available in the EPAR show median survival times of 8 to 26.5 months for patients with soft tissue sarcoma in first-line treatment, and 11.5 to 19.5 months in second-line treatment (see Table 21 of the full dossier assessment). The overview table from the company's information retrieval shows median survival times of 11 to 46.9 months (≥ first line) and 8.9 months (≥ second line) (see Table 22 of the full dossier assessment). Since in each case the time span between minimum and maximum observed survival time under larotrectinib overlaps with the above-mentioned information from the comparative data, regardless of the line of treatment, no sufficiently large effect that could not be based on systematic bias alone can be assumed for patients with soft tissue sarcoma.

Analogous to this approach, no sufficiently large effect that could not be based on systematic bias alone can be assumed for larotrectinib in the outcome "overall survival" for the patients in any tumour entity. The comparative data contained no information on median overall survival for patients with infantile fibrosarcoma. However, the studies underlying the information retrieval report survival rates ranging from 94% after 3 years to 89% after 10 years [8]. Such long-term data are not yet available for patients with infantile fibrosarcoma in the larotrectinib studies. As of the latest data cut-off from 30 July 2018, none of the 13 patients with infantile fibrosarcoma had died. No information on the median observation period is available. The minimum observed survival time is 5.5 months and the maximum observed survival time so far is 26.7 months. In view of the high survival rates shown by the comparative data, no sufficiently large effect that could not be based on systematic bias alone can be assumed for larotrectinib in the outcome "overall survival" for the patients with infantile fibrosarcoma either.

No comparative data are available for patients with congenital mesoblastic nephroma or breast cancer, as no studies reporting results on overall survival were cited in the company's information retrieval for congenital mesoblastic nephroma or for secretory breast cancer.

The separate consideration of the individual tumour entities deviates from the approach of the company, which pooled all tumour entities except patients with primary CNS tumours. For the pooled population, the company gave a median survival time of 44.4 months at the data cut-off

from 19 February 2019 and derived a dramatic effect for all patients based on this. The company did not present the corresponding Kaplan-Meier curve. Regarding patients with primary CNS tumours, the company stated that, with a median observation period of 4.6 months, all patients were still alive. From the company's point of view, the survival rates described were exceptional and not to be expected. The company did not consider comparative data in this.

Irrespective of the fact that the present benefit assessment considers the patients separately according to tumour entity, the results on the study population pooled independently of tumour histology cited by the company do not allow the derivation of an added benefit because no comparative data are available.

**Morbidity and health-related quality of life**

***Patient-reported outcomes on morbidity and health-related quality of life***

For patients under larotrectinib, no results separated by tumour entity are available regarding morbidity and health-related quality of life. Consideration by tumour entity is required also for these outcomes for the reasons stated in Section 2.3.1.2. For instance, there is heterogeneity in prognoses also for morbidity and health-related quality of life, or the course of disease under BSC can differ depending on the tumour entity. Furthermore, the comparative data do not contain results on morbidity and health-related quality of life for all tumour entities. A comparison or evaluation of the results is therefore not possible.

Considering the ePAS2 analysis population pooled independently of tumour histology, the company stated for this population that the recording of health-related quality of life and symptom burden overall showed sustained and clinically relevant improvement over time. The company did not consider comparative data in this. Besides, the company's assessment was based on analyses defined post hoc and a selective reporting of results. See Section 2.7.7.3.1 of the full dossier assessment for further details on the data presented by the company.

***Sustained delay of surgical resections that are likely to result in severe morbidity (supplementary description)***

As described above, the company did not present any relevant operationalizations of an outcome on sustained delay of surgical resections that are likely to result in severe morbidity. Besides, the company did not cite this outcome in its choice of patient-relevant outcomes, but only when deriving the added benefit.

The company described that for 22 paediatric patients, there was no curative therapy other than amputation or disfiguring surgery when they were included in the study. It stated that none of these patients had such a surgical resection in the observation period. The company based its derivation of an added benefit on these results. In the dossier, the company did not provide any supporting data that allow an evaluation of these results, however.

Documents provided by the company for the approval [9] show that 5 of the 22 paediatric patients had surgical resection with curative intent under larotrectinib treatment. This resulted

in complete remission in 3 of these patients, who were taken off larotrectinib. Complete remission was achieved if no viable tumour cells could be detected after resection and the surgical margins were negative according to the pathology report. In the other 2 patients, no negative margins were obtained from resection and larotrectinib treatment was continued. Of the 17 remaining patients, 3 had progression and subsequently discontinued treatment with larotrectinib. One further patient discontinued treatment at their own request. The remaining 13 patients were still under larotrectinib treatment (between 1 and 25 cycles) at the time point of the data cut-off (19 February 2018).

No information on the treatment and tumour status of the patients described above is available for the relevant data cut-off (30 July 2018). Hence, there is no information available as to whether sustained avoidance or delay of a surgical resection that is likely to lead to severe morbidity was achieved for these paediatric patients.

***Sustained regression of disfiguring or functionality-impairing tumour masses (supplementary description)***

As described above, the company did not present any relevant operationalizations of an outcome on sustained regression of disfiguring or functionality-impairing tumour masses. Besides, the company did not cite this outcome in its choice of patient-relevant outcomes, but only when deriving the added benefit.

Under the supplementary histology-specific presentation in Module 4 A, the company presented selected case studies on 35 adult and paediatric patients with soft tissue carcinoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, NSCLC, gastrointestinal stromal cancer, secretory breast cancer, congenital mesoblastic nephroma, pancreatic cancer and primary CNS tumour. The company did not describe the criteria it used for choosing these case studies. The description of the case studies included a photo documentation as well as brief information on age, tumour location, pretreatment, duration of treatment with larotrectinib, response to treatment, and current treatment status. The company did not quantify the results on regression of the tumour masses described by the company in the case studies, and only derived a dramatic added benefit based on the descriptive results.

Like the results of other outcomes, the case studies also impressively show the extent to which the patients pooled by the company differ with regard to demographic and disease-specific characteristics, prior therapy or the course of disease. Overall, the results of the case studies therefore support a separate consideration of the results by tumour entity. Furthermore, due to the selective presentation it is unclear to what extent the results are transferable to other patients.

**Side effects**

***Serious adverse events, severe adverse events (CTCAE grade 3–4), discontinuation due to adverse events***

The present benefit assessment considers the patients separately for tumour entities (for reasons, see paragraph *Consideration of the tumour entity* in Section 2.3.1.2). Regarding the outcomes

"SAEs" and "severe AEs (CTCAE grade 3–4)", results on larotrectinib separated by tumour histology are available only for patients with the following tumour entities: soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, primary CNS tumour and lung cancer. Only pooled results are available for patients of other tumour entities. Event rates of 14% to 56% were shown for SAEs, and event rates of 22% to 64% for severe AEs, with the maximum event rates referring to the pooled tumour entities, for which no separate results were available (see Table 12). A conclusion on how these events are distributed among the individual tumour entities cannot be drawn on the basis of the available data.

Regarding discontinuation due to AEs, no results by tumour entity are available for patients treated with larotrectinib, except for patients with primary CNS tumours. None of the patients with primary CNS tumours discontinued treatment with larotrectinib due to AEs. Only few patients of the pooled tumour entities discontinued treatment with larotrectinib due to AEs.

Information on the most common AEs in the respective tumour entities, as well as information on all SAEs and severe AEs (CTCAE grade 3–4) can be found in Appendix E of the full dossier assessment, provided that information was available on the respective tumour entity.

The consideration of the available comparative data on side effects is not considered meaningful, since no approximately comparable side effect profile to BSC can be assumed under active therapy. BSC aims to provide best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life, whereas active therapy focuses on the treatment of cancer.

Irrespective of this assessment, consideration of the available data for patients with soft tissue sarcoma and salivary gland carcinoma under larotrectinib shows that the proportion of patients with SAEs is lower than in the available comparative data (see Table 23 in Appendix C of the full dossier assessment). For patients with thyroid cancer and lung cancer, the proportions of patients with SAEs under larotrectinib overlap with those found in the comparative data. For patients with infantile fibrosarcoma and primary CNS tumour, there are no comparative data on SAEs.

The comparative data contain no information on severe AEs, as this outcome was not recorded in the comparative data. The outcome "discontinuation due to AEs" was recorded in the comparative data, but no results are available in the comparative data for patients with primary CNS tumours, for whom, as the only tumour entity, separate results on larotrectinib are available.

The company pooled the results of all tumour entities with the exception of patients with primary CNS tumours. According to the company, the study data showed that the overall tolerability of larotrectinib is good, especially considering the patients with partly several prior therapies and the particularly vulnerable patient group of children. The company cited the small proportions of severe AEs (CTCAE grade 3–4, 13%) and SAEs (5%) for the pooled population,

with the small proportions being partly due to the fact that the company considered only the subset of AEs classified as treatment-related. A consideration of the overall rates showed significantly higher proportions of severe AEs (CTCAE grade 3–4, 55%) and SAEs (33%). The company did not discuss the available results on neurologic AEs used by the company as AEs of specific interest. Against this background, the company also did not discuss the possibility of long-term complications for neurodevelopment in paediatric patients. In this respect, the EMA has requested the company to provide long-term data from the SCOUT study as soon as they become available [7].

### 2.4.4 Subgroups and other effect modifiers

Due to the small number of patients in the individual tumour entities at the time point of the data cut-off on 30 July 2018, subgroup analyses are not considered useful when considering this time point. Regardless of this, the company did not present any subgroup analyses by tumour entities.

## 2.5 Probability and extent of added benefit

Probability and extent of the added benefit are presented below. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

### 2.5.1 Overall conclusion on added benefit

The company did not present any documents for the comparison of the results under larotrectinib with results under the ACT BSC. Without conducting a comparison, it nevertheless stated that there is an added benefit of larotrectinib due to dramatic positive effects. Irrespective of the fact that the company did not draw this conclusion on the basis of a comparative assessment, the data available in the dossier and in the EPAR on treatment effects under other treatment options in the different tumour entities do not support the company's conclusion.

In summary, the added benefit of larotrectinib in comparison with the ACT BSC is not proven for patients with solid tumours that display an NTRK gene fusion.

The result of the assessment of the added benefit of larotrectinib in comparison with the ACT is summarized in Table 13.

Table 13: Larotrectinib – probability and extent of added benefit

| Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|
| Adult and paediatric patients with solid tumours that display an NTRK gene fusion[b], who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options | BSC[c] | Added benefit not proven |

a. Presentation of the respective ACT specified by the G-BA.
b. The considered studies on larotrectinib are ongoing, so that patients are still being enrolled. At the time point of the data cut-off on 30 July 2018, which was considered in the present benefit assessment, information was only available on patients with the following tumour entities: soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, primary CNS tumour, lung cancer, melanoma, colorectal cancer, gastrointestinal stromal cancer, bone sarcoma, cholangiocarcinoma, congenital mesoblastic nephroma, appendix cancer, breast cancer, pancreatic cancer. Some of the tumour entities mentioned only include individual patients (see Table 9).
c. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; CNS: central nervous system; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit for larotrectinib. For this purpose, the company referred to the presence of dramatic effects (see Section 2.7.8.2 of the full dossier assessment). It derived these dramatic effects solely on the basis of the pooled study results on larotrectinib without referring to the individual tumour entities or discussing the results in the context of available comparative data. Depending on the outcome, the dramatic effects derived by the company are addressed in Section 2.4.3 or Section 2.7.7.3.1 of the full dossier assessment.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

## 2.6 List of included studies

### LOXO-TRK-14001

Bayer. A study to test the safety of the investigational drug larotrectinib in adults that may treat cancer [online]. In: ClinicalTrials.gov. 03.10.2019 [Accessed: 28.10.2019]. URL: https://ClinicalTrials.gov/show/NCT02122913.

Hong DS, Bauer TM, Lee JJ, Dowlati A, Brose MS, Farago AF et al. Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study. Ann Oncol 2019; 30(2): 325-331.

Loxo Oncology. A phase 1 study of the oral TRK inhibitor LOXO-101 in adult patients with solid tumors: study LOXO-TRK-14001; clinical study protocol [unpublished]. 2017.

Loxo Oncology. A phase 1 study of the oral TRK inhibitor LOXO-101 in adult patients with solid tumors: study LOXO-TRK-14001; statistical analysis plan [unpublished]. 2017.

Loxo Oncology. A phase 1 study of the oral TRK inhibitor LOXO-101 in adult patients with solid tumors: study LOXO-TRK-14001; clinical study report addendum [unpublished]. 2018.

Loxo Oncology. A phase 1 study of the oral TRK inhibitor LOXO-101 in adult patients with solid tumors: study LOXO-TRK-14001; interim clinical study report [unpublished]. 2017.

**NAVIGATE**

Bayer. A study to test the effect of the drug larotrectinib in adults and children with ntrk-fusion positive solid tumors (NAVIGATE) [online]. In: ClinicalTrials.gov. 24.10.2019 [Accessed: 28.10.2019]. URL: https://ClinicalTrials.gov/show/NCT02576431.

Loxo Oncology. A phase 2 basket study of the oral TRK inhibitor larotrectinib in subjects with NTRK fusion-positive tumors: study LOXO-TRK-15002; clinical study report addendum [unpublished]. 2018.

Loxo Oncology. A phase II basket study of the oral TRK inhibitor lOXO-101 in subjects with NTRK fusion-positive tumors [online]. In: EU Clinical Trials Register. [Accessed: 28.10.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003582-28.

Loxo Oncology. A phase II basket study of the oral TRK inhibitor LOXO-101 in subjects with NTRK fusion-positive tumors); study LOXO-TRK-15002; interim statistical analysis plan [unpublished]. 2017.

Loxo Oncology. A phase II basket study of the oral TRK inhibitor LOXO-101 in subjects with NTRK fusion-positive tumors: study LOXO-TRK-15002; clinical study protocol [unpublished]. 2016.

Loxo Oncology. A phase 2 basket study of the oral TRK inhibitor larotrectinib in subjects with NTRK fusion-positive tumors: study LOXO-TRK-15002; interim clinical study report [unpublished]. 2018.

**SCOUT**

Bayer. A study to test the safety and efficacy of the drug larotrectinib for the treatment of tumors with NTRK-fusion in children (SCOUT) [online]. In: ClinicalTrials.gov. 24.10.2019 [Accessed: 28.10.2019]. URL: https://ClinicalTrials.gov/show/NCT02637687.

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