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Entrectinib (solid tumours with a 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 2.5 of the dossier assessment *Entrectinib (solide Tumore mit einer neurotrophen Tyrosin-Rezeptor-Kinase [NTRK]-Genfusion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 November 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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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.

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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
ALK	anaplastic lymphoma kinase
BSC	best supportive care
CNS	central nervous system
ECOD	enrollment cut-off date
EE	efficacy evaluable
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KRAS	Kirsten Rat Sarcoma viral Oncogene Homolog
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	C-ros oncogene 1
SE	Safety Evaluable
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TRK	tyrosine receptor kinase

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 entrectinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 28 August 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of entrectinib in comparison with the appropriate comparator therapy (ACT) in adult and paediatric patients from 12 years of age 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 not yet received an NTRK inhibitor and who have no satisfactory treatment options.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of entrectinib

Therapeutic indication	**ACT[a]**
Adult and paediatric patients from 12 years of age 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 not yet received an NTRK inhibitor and ▪ who have no satisfactory treatment options	Individual treatment choosing from ▪ BSC[b] and ▪ surgical resection, which is likely to result in severe morbidity, for whom a clinical benefit is to be expected for individual patients
a. Presentation of the ACT specified by the G-BA. b. 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; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase	

The company deviates from the G-BA's specification of the ACT insofar as it cited an individual therapy choosing from best supportive care (BSC) and antineoplastic standard therapy under consideration of the respective tumour disease, disease stage and treatment setting in connection with the determination whether the standard therapies recommended

according to the state of medical knowledge have been exhausted as ACT. However, this had no influence on the study pool used by the company for the assessment of the added benefit of entrectinib, as the company only considered one non-controlled study on entrectinib, which had no comparator arm.

The assessment was conducted versus the ACT specified by the G-BA by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Study pool on entrectinib

The non-comparative study STARTRK-2 was considered for the benefit assessment.

Study STARTRK-2

The STARTRK-2 study is an ongoing, uncontrolled, open-label, multicentre study. Adult patients with locally advanced or metastatic solid tumours and NTRK1/2/3, c-ros oncogene 1 (ROS1) or anaplastic lymphoma kinase (ALK) gene rearrangement were included in the framework of a basket design independently of their tumour histology. Except for patients with non-small cell lung cancer (NSCLC), pretreatment with tyrosine receptor kinase (TRK)-, ROS1- or ALK-inhibitors was not allowed for patients with corresponding gene rearrangements. According to the inclusion criteria of the study, there were no further requirements regarding prior therapies. Moreover, patients should have had measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST).

Entrectinib was administered in line with the Summary of Product Characteristics (SPC).

Primary outcome of the study was the objective response rate. Secondary outcomes included "overall survival", outcomes on morbidity, health-related quality of life and side effects.

Data for paediatric patients from 12 years of age and older who were also covered by the therapeutic indication of entrectinib are not available.

Data cut-offs and analysis populations

Module 4 B includes analyses on 2 data cut-offs (31 May 2018 and 31 October 2018) for the STARTRK-2 study. The company used the later data cut-off for the derivation of the added benefit.

In Module 4 B, the company presented analyses on the subpopulation with NTRK gene fusion of the STARTRK-2 study separately for outcomes regarding benefit and harm. It considered the following analysis populations, from each of which patients with primary brain tumours were excluded:

- "NTRK efficacy evaluable [EE])": the company defined this population as NTRK inhibitor-naive adult patients with solid tumours with NTRK gene fusion and measurable disease according to RECIST following a blinded, independent central review and with ≥ 6 months follow-up after detection of initial response. However, due to the identical number of patients it is assumed that according to the European Public Assessment Report (EPAR) the population presented by the company in Module 4 B consists of patients with ≥ 6 follow-up after the first dose of entrectinib. For the present assessment, the EPAR definition is assumed to apply.

  The company operationalized the criterion "follow-up ≥ 6 months" by stating that only those patients were considered in the NTRK EE analysis population who were enrolled in the study until 30 April 2018 (enrolment cut-off date [ECOD]), i.e. 6 months before the data cut-off date of 31 October 2018. Thus, patients enrolled in the study after the ECOD were not included in the NTRK EE population. The company used the NTRK EE analysis population for analyses on the outcome categories "mortality", "morbidity" and "health-related quality of life" (data cut-off of 31 October 2018: N = 71).
- "NTRK compatibility set (NTRK Safety Evaluable [SE])": NTRK inhibitor-naive adult patients with solid tumours that display an NTRK gene fusion, who received at least one dose of entrectinib. The company used the NTRK SE analysis population for analyses on outcomes of the outcome category "side effects" (data cut-off: 31 October 2018: N = 108).

The company primarily used the results of the tumour histology-independent analyses to derive the added benefit. For the data cut-off of 31 October 2018, the company also presented separate analyses only for tumour entities with ≥ 10 patients in the STARTRK-2 study (see below).

Assessment of the data on the STARTRK-2 study presented by the company

The data of the STARTRK-2 study presented by the company are insufficient in the preparation presented with the dossier and are not suitable for the benefit assessment of entrectinib versus the ACT. The points of criticism of the analyses presented by the company in the dossier are listed below:

It is not ensured that the analysis populations of the company represent the relevant patient population according to the approval

According to the SPC, entrectinib is for use in adult and paediatric patients from 12 years of age with solid tumours that display an NTRK gene fusion and only for those who have no other satisfactory treatment options. For the NTRK EE and NTRK SE analysis populations of the STARTRK-2 study presented by the company, however, it is not certain that these are patients who have no satisfactory treatment options. A corresponding operationalization is neither found in the inclusion criteria of the STARTRK-2 study nor in the criteria for the formation of the analysis populations specified by the company. Moreover, the data on the study population of the STARTRK-2 study submitted by the company do not permit a delimitation of the subpopulation relevant for the research question. The extent to which the presented analysis

populations of the STARTRK-2 study with NTRK gene fusion represent the population relevant for the research question (who have no satisfactory treatment options) is thus unclear.

Formation of the NTRK EE analysis population in the STARTRK-2 study not comprehensible

The company limited the population with NTRK gene fusion of the STARTRK-2 study to patients with ≥ 6 months follow-up for analyses on the outcomes in the categories "mortality", "morbidity" and "health-related quality of life" (NTRK EE population), but not for analyses on the outcome category "side effects" (NTRK SE population). Contrary to the data provided by the company, these patients were patients with follow-up ≥ 6 months after the first dose of entrectinib and not after initial response. In view of the already small number of cases for the analysis population with NTRK gene fusion of the STARTRK-2 study and the necessary consideration by tumour entity, it is incomprehensible why patients with < 6 months follow-up were not considered. It can be seen from the EPAR that the limitation of the follow-up period results in a non-inclusion of a relevant proportion of patients with follow-up < 6 months. In addition to the exclusion criterion "follow-up < 6 months", the NTRK EE population is also limited by further exclusion criteria. However, the exclusion criteria applied by the company and thus the composition of the NTRK EE analysis population at the data cut-off of 31 October 2018 are not comprehensible on the basis of the data provided by the company in the dossier.

Results separated by tumour entity incomplete

In the present therapeutic indication, it is useful and necessary to consider results separated by tumour entity and not independently of the tumour histology.

The company presented results in the form of subgroup analyses only for the 3 entities "soft tissue sarcoma", "NSCLC" and "secretory salivary gland cancer" (with N ≥ 10 patients in the STARTRK-2 study). For a complete assessment of the therapeutic indication, results must also be presented for the other tumour entities. Moreover, the company presented results on the 3 cited tumour entities only for the outcome categories "mortality", "morbidity" and "health-related quality of life". A weighing of benefit and harm in the framework of the benefit assessment also requires the submission of results for the outcome category "side effects by tumour entity".

Comparative data presented by the company

Comparative data are required for the benefit assessment in comparison with the ACT. In its search, the company excluded studies that consider a single tumour entity as well as studies that do not provide the characteristics of the NTRK status. This approach is not adequate, because a separate consideration by tumour entity is necessary for studies on the ACT especially in the present therapeutic indication. Based on this approach, the company identified no studies with the ACT specified by it.

However, the company stated that it was trying to put the results on entrectinib for the entities "soft tissue sarcoma", "NSCLC" and "secretory salivary gland cancer" (independent of the NTRK status) "in the context of an unselected patient population treated with BSC". For the comparative data presented by the company, there is no description of the approach followed

for the search and selection of studies. Therefore, the completeness of the presented results for studies with BSC cannot be assessed, nor can selective reporting be excluded. Moreover, results on the outcome category "side effects" are missing (as with the results on entrectinib separated by tumour entity). Furthermore, there are no effect estimations on the comparison of entrectinib with the ACT. Therefore, the comparative data presented by the company are not usable for the benefit assessment of entrectinib in comparison with the ACT.

Summary

The company presented data only on adult patients with solid tumours that display NTRK gene fusion. Data for paediatric patients from 12 years of age and older who were also covered by the therapeutic indication of entrectinib are not available.

The data presented by the company are insufficient in the preparation presented with the dossier and are not suitable for the benefit assessment of entrectinib versus the ACT.

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

Table 3 shows a summary of probability and extent of the added benefit of entrectinib.

Table 3: Entrectinib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult and paediatric patients from 12 years of age 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 not yet received an NTRK inhibitor and ▪ who have no satisfactory treatment options	Individual treatment choosing from ▪ BSC[b] and ▪ surgical resection, which is likely to result in severe morbidity, for whom a clinical benefit is to be expected for individual patients	Added benefit not proven

a. Presentation of the ACT specified by the G-BA.
b. 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; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase

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 entrectinib in comparison with the ACT in adult and paediatric patients from 12 years of age with solid tumours that display a 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 not yet received an NTRK inhibitor and who have no satisfactory treatment options.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of entrectinib

Therapeutic indication	**ACT[a]**
Adult and paediatric patients from 12 years of age 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 not yet received an NTRK inhibitor and ▪ who have no satisfactory treatment options	Individual treatment choosing from ▪ BSC[b] and ▪ surgical resection, which is likely to result in severe morbidity, for whom a clinical benefit is to be expected for individual patients
a. Presentation of the ACT specified by the G-BA. b. 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; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase	

The company deviates from the G-BA's specification of the ACT insofar as it cited an individual therapy choosing from BSC and antineoplastic standard therapy under consideration of the respective tumour disease, disease stage and treatment setting in connection with the determination whether the standard therapies recommended according to the state of medical knowledge have been exhausted as ACT. However, this had no influence on the study pool used by the company for the assessment of the added benefit of entrectinib, as the company only considered one non-controlled study on entrectinib, which had no comparator arm.

The assessment was conducted versus the ACT specified by the G-BA by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

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 entrectinib (status: 26 June 2020)
- bibliographical literature search on entrectinib (last search on 9 June 2020)

- search in trial registries/trial results databases for studies on entrectinib (last search on 24 June 2020)
- search on the G-BA website for entrectinib (last search on 24 June 2020)
- bibliographical literature search on the ACT (last search on 9 June 2020)
- search in trial registries/trial results databases for the ACT (last search on 24 June 2020)
- search on the G-BA website for the ACT (last search on 24 June 2020)

To check the completeness of the study pool:

- search in trial registries for entrectinib (last search on 8 September 2020)

Concurring with the company, 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 entrectinib. The study on entrectinib identified by the company is a non-comparative study. No further study on entrectinib relevant for the research question was identified in addition to this study.

See Section 2.3.2 for the company's information retrieval on the ACT and the data it submitted for this purpose.

2.3.1 Studies on entrectinib

The study on entrectinib listed in the following Table 5 is considered in the benefit assessment.

Table 5: Study pool on entrectinib

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
Study GO40782 (STARTRK-2[c])	Yes	Yes	No	No[d]	Yes [3,4]	Yes [5]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

CSR: clinical study report

Study characteristics of the STARTRK-2 study

Table 6 and Table 7 describe the STARTRK-2 study on entrectinib.

Table 6: Characteristics of the STARTRK-2 study: (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
STARTRK-2	Uncontrolled, open-label, basket study	Patients ≥ 18 years of age with locally advanced or metastatic solid tumours that display a NTRK1/2/3, ROS1 or ALK gene rearrangement[b] ▪ with measurable tumour lesion according to RECIST[c] ▪ treatment-naive regarding TRK, ROS1 or ALK inhibitors in patients with corresponding gene rearrangement[d] ▪ ECOG PS ≤ 2 and life expectancy ≥ 4 weeks	Data cut-off: 31 May 2018 (NDA)[e] entrectinib (N = 207) subpopulations analysed by the company: ▪ NTRK EE[f] (n = 51) ▪ NTRK SE[g] (n = 63) data cut-off: 31 October 2018 (EMA)[h] entrectinib (N = 335) subpopulations analysed by the company: ▪ NTRK EE[f] (n = 71) ▫ additionally by tumour entity with N ≥ 10: - secretory salivary gland cancer (n = 12) - NSCLC (n = 12) - soft tissue sarcoma (n = 11) ▪ NTRK SE[g] (n = 108) ▫ no analyses by tumour entity	Screening: 30 days treatment: until disease progression[i], unacceptable toxicity or withdrawal of consent observation: outcome-specific, at most until death or end of study	> 150 centres in: Australia, Belgium, France, Germany, Great Britain, Hong Kong, Italy, Japan, Korea, Netherlands, Poland, Singapore, Spain, Taiwan and USA 11/2015–ongoing	Primary: objective response rate secondary: overall survival, symptoms, health-related quality of life, AEs

Table 6: Characteristics of the STARTRK-2 study: (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Further activating mutations (e.g. EGFR, KRAS) must not be present. The detection of gene rearrangements and driver mutations was performed by Foundation Medicine, a company specialized in genetic testing, by other laboratories certified for nucleic acid-based test methods according to CLIA or by equivalent certified laboratories.
c. According to the study protocol, patients with non-measurable lesions according to RECIST Version 1.1, but with clinically assessable disease, were included as "not evaluable for the primary outcome".
d. Except for patients in the tumour entity "NSCLC". Pretreatment with crizotinib was allowed for patients with NSCLC and ROS1 or ALK gene rearrangement and exclusive CNS progression.
e. The last patient was included for this analysis on 30 November 2017.
f. Analysis population for the outcome categories "mortality", "morbidity" and "health-related quality of life": patients with measurable disease according to RECIST version 1.1, NTRK gene fusion, without prior therapy with an NTRK inhibitor and with ≥ 6 months follow-up after the first dose of entrectinib. Patients with primary brain tumours were excluded.
g. Analysis population for the outcome category "side effects": patients with NTRK gene fusion without prior therapy with an NTRK inhibitor, who received at least one dose of entrectinib.
h. Data cut-off requested by EMA; last patient included for the analysis of the outcome categories "mortality", "morbidity" and "health-related quality of life" on 30 April 2018.
i. Patients could be treated with entrectinib beyond disease progression, if, at the investigator's discretion, clinical benefit continued to exist.

AE: adverse event; ALK: anaplastic lymphoma kinase; CLIA: Clinical Laboratory Improvement Amendments; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; KRAS: Kirsten rat sarcoma viral oncogene homologue; n: number of included patients in the subpopulation; N: number of included patients; NDA: New Drug Approval; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; NTRK EE: NTRK efficacy evaluable; NTRK SE: NTRK compatibility set (safety evaluable); RECIST: Response Evaluation Criteria in Solid Tumours; ROS1: c-ros oncogene 1; TRK: tyrosine receptor kinase

Table 7: Characteristics of the interventions in the STARTRK-2 study

Study	Intervention	Prior and concomitant treatment
STARTRK-2	Entrectinib 600 mg once daily, orally; in 28-day cycles dose adjustments: up to 2 dose reductions (to 400 mg and 200 mg); treatment interruption up to 4 weeks until improvement to grade 1 and discontinuation due to toxicity were possible	**Non-permitted pretreatment** ▪ TRK, ROS1 or ALK inhibitors in patients with corresponding gene rearrangement[a] ▪ chemotherapy or targeted therapy ≤ 2 weeks or 5 half-lives (whichever was shorter), radiotherapy ≤ 2 weeks and antibody-based therapy ≤ 4 weeks before the first administration of the study medication **concomitant treatment** not allowed ▪ enzyme inducing antiepileptics ▪ other approved or investigational anticancer therapies to be used with care ▪ strong inhibitors or inducers of CYP3A4 ▪ substrates of CYP2C9, CYP2D6, CYP3A4 ▪ QT interval prolonging substances ▪ drugs associated with the development of torsade de pointes arrhythmia allowed ▪ antiemetics, antidiarrhoeal drugs ▪ haematopoietic supportive therapies (G-CSF, erythropoietin) for the treatment of severe neutropenia or anaemia ▪ palliative radiotherapy or surgery (with simultaneous interruption of entrectinib treatment) ▪ bone-preserving substances for the treatment of bone metastases or osteoporosis ▪ therapies that are necessary for the wellbeing of the patient

a. For patients in the tumour entity "NSCLC". Pretreatment with crizotinib was allowed for patients with NSCLC and ROS1 or ALK gene rearrangement and exclusive CNS progression.

ALK: anaplastic lymphoma kinase; CNS: central nervous system; CYP: cytochrome P450; G-CSF: granulocyte colony-stimulating factor; NSCLC: non-small cell lung cancer; QT: time interval between the start of the Q-wave and the end of the T-wave; ROS1: c-ros oncogene 1; TRK: tyrosine receptor kinase

The STARTRK-2 study is an ongoing, uncontrolled, open-label, multicentre study. Adult patients with locally advanced or metastatic solid tumours and NTRK1/2/3, ROS1 or ALK gene rearrangement were included in the framework of a basket design independently of their tumour histology (further driver mutations, e.g. in the epidermal growth factor receptor [EGFR] or Kirsten rat sarcoma viral oncogene homologue [KRAS] gene were not allowed).

Except for patients with NSCLC, pretreatment with TRK, ROS1 or ALK inhibitors was not allowed for patients with corresponding gene rearrangements. According to the inclusion criteria of the study, there were no further requirements regarding prior therapies. Moreover, patients should have had measurable disease according to RECIST. However, patients with non-measurable tumour lesions (but with clinically assessable disease) could be included as "not evaluable for the primary outcome".

Entrectinib was administered at a dosage of 600 mg once daily according to the SPC [6] (see Table 7). Patients were treated with entrectinib until disease progression, unacceptable toxicity or withdrawal of consent. Treatment beyond disease progression was possible if, at the investigator's discretion, clinical benefit continued to exist.

Primary outcome of the study was the objective response rate. Secondary outcomes included "overall survival", outcomes on morbidity, health-related quality of life and side effects.

Data cut-offs

Module 4 B includes analyses on 2 data cut-offs (31 May 2018 and 31 October 2018) for the STARTRK-2 study. The company stated that the later data cut-off was the most relevant one for efficacy because it was requested by the European Medicines Agency (EMA) and because the STARTRK-2 study was still recruiting. The company used the later data cut-off for the derivation of the added benefit.

Analysis populations of the company

In Module 4 B, the company presented analyses on the subpopulation with NTRK gene fusion of the STARTRK-2 study separately for outcomes regarding benefit and harm. It considered the following analysis populations, from each of which patients with primary brain tumours were excluded:

- "NTRK EE": the company defined this population as NTRK inhibitor-naive adult patients with solid tumours with NTRK gene fusion and measurable disease according to RECIST following a blinded, independent central review and with ≥ 6 months follow-up after detection of initial response. However, due to the identical number of patients it is assumed that according to the EPAR the population presented by the company in Module 4 B consisted of patients with ≥ 6 follow-up after the first dose of entrectinib [7]. For the present assessment, the EPAR definition is assumed to apply.

  The company operationalized the criterion "follow-up ≥ 6 months" by considering only those patients in the NTRK EE analysis population who had been enrolled in the study until 30 April 2018 (ECOD), i.e. 6 months before the data cut-off date of 31 October 2018. Thus, patients enrolled in the study after the ECOD were not included in the NTRK EE population.

  The company used the NTRK EE analysis population for analyses on the outcome categories "mortality", "morbidity" and "health-related quality of life" (data cut-off of 31 October 2018: N = 71). For adult patients with measurable disease of the central nervous system (CNS) (referred to by the company as NTRK EE CNS RECIST population), the company presented a separate analysis for the intracranial objective response rate and for the time to CNS progression (data cut off: 31 October 2018: N = 16).
- "NTRK compatibility set (NTRK SE)": NTRK inhibitor-naive adult patients with solid tumours with an NTRK gene fusion who received at least one dose of entrectinib. The

company used the NTRK SE analysis population for analyses on outcomes of the outcome category "side effects" (data cut-off: 31 October 2018: N = 108).

The company primarily used the results of the tumour histology-independent analyses to derive the added benefit. For the data cut-off of 31 October 2018, the company also presented separate analyses only for tumour entities with ≥ 10 patients in the STARTRK-2 study (see below).

Further data on entrectinib presented by the company

In addition to the analyses on the STARTRK-2 study, the company submitted a pooled analysis of the NTRK EE analysis population of the STARTRK-2 study (N = 71) and 3 further adult patients of the STARTRK-1 and ALKA372-001 studies with solid tumours with an NTRK gene fusion who received an entrectinib dosage ≥ 600 mg, for benefit outcomes (data cut-off: 31 October 2018). The pooled analysis is not further considered, because this analysis also included patients who had received a dosage > 600 mg, which was not in compliance with the approval. Moreover, no pooled analysis was presented for the outcome category "side effects" and separated by tumour entity.

Moreover, the company presented 4 case reports of patients who were treated with entrectinib in the framework of clinical studies, namely on the following entities: "secretory salivary gland cancer", "NSCLC", "endometrial stroma sarcoma" (all of them in adults) and "infantile fibrosarcoma" (20-months-old infant, use outside the therapeutic indication). The company did not use the case reports to derive the added benefit. These case reports were also not considered further in the present benefit assessment.

Data for paediatric patients from 12 years of age and older who were also covered by the therapeutic indication of entrectinib are not available.

Assessment of the data on the STARTRK-2 study presented by the company

The data of the STARTRK-2 study presented by the company are insufficient in the preparation presented with the dossier and are not suitable for the benefit assessment of entrectinib versus the ACT. The points of criticism of the analyses presented by the company in the dossier are listed below:

It is not ensured that the analyses populations of the company represent the relevant patient population according to the approval

According to the SPC [6], entrectinib is used in adult and paediatric patients from 12 years of age and older 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, who have not yet received an NTRK inhibitor and who have no satisfactory treatment options.

For the NTRK EE and NTRK SE analysis populations of the STARTRK-2 study presented by the company, however, it is not certain that these are patients who have no satisfactory treatment options in accordance with the approved therapeutic indication. In describing the inclusion

criteria of the STARTRK-2 study in Appendix 4 E of Module 4 B, the company assumes that the patients included are patients for whom effective alternative treatment is not available or for whom standard therapy is unsuitable or who are intolerant; this assumption is solely based on the diagnosis of a locally advanced or metastatic solid tumour with NTRK gene rearrangement without further driver mutations such as EGFR or KRAS mutations. There is no corresponding operationalization, neither in the inclusion criteria according to the study protocol of the STARTRK-2 study [5] nor in the criteria set by the company for the formation of the analysis populations in Module 4 B. Thus, there is no data-based justification for this assumption. Moreover, the data on the study population of the STARTRK-2 study submitted by the company also permit no delimitation of the subpopulation relevant for the research question. The extent to which the presented analysis populations of the STARTRK-2 study with NTRK gene fusion represent the population relevant for the research question (who have no satisfactory treatment options) is thus unclear.

Formation of the NTRK EE analysis population in the STARTRK-2 study not comprehensible

As already explained, the company limited the population with NTRK gene fusion of the STARTRK-2 study to patients with follow-up ≥ 6 months for analyses on the outcomes in the categories "mortality", "morbidity" and "health-related quality of life" (NTRK EE population), but not for analyses on the outcome category "side effects" (NTRK SE population) (for information on the operationalization, see above). Contrary to the data provided by the company, these patients were patients with follow-up ≥ 6 months after the first dose of entrectinib and not after initial response. In view of the already small number of cases for the analysis population with NTRK gene fusion of the STARTRK-2 study and the necessary separate consideration by tumour entity, it is incomprehensible why patients with < 6 months follow-up were not considered. The company did not justify the exclusion of these patients. This approach means that recordings available for patients who were only included in the study after 30 April 2018 (ECOD, see above) are not taken into account and, for example, deaths among these patients in respect of the outcome "overall survival" are not included in the analysis on the data cut-off of 31 October 2018. In Module 4 B of the dossier, the company provides no information on how many patients were excluded from the analysis due to the criterion set by it. It can be seen from the EPAR that due to this limitation a relevant proportion of patients with follow-up < 6 months (18/92 = 19.6%, based on the pooled analysis of the STARTRK-1, STARTRK-2 and ALKA372-001 studies) remains unconsidered [7].

In addition to the exclusion criterion "follow-up < 6 months", the NTRK EE population is also limited by further exclusion criteria. This becomes clear from the EPAR data and the figure on the patient flow presented in the dossier. However, these data are only available for the earlier data cut-off of 31 May 2018 and only for the pooled analysis of the studies STARTRK-1, STARTRK-2 und ALKA372-001. The exclusion criteria applied by the company and thus the composition of the NTRK EE analysis population at 31 October 2018 are not comprehensible on the basis of the data provided by the company in the dossier.

Results separated by tumour entity incomplete

As already explained in detail in the dossier assessment on larotrectinib and in the justification on the G-BA's decision [8,9], it is useful and necessary to consider results separated by tumour entity and not independently of the tumour histology in the present indication. The reasons are as follows:

- Based on distinct natural histories in different tumour entities and stages, heterogeneity of prognoses is expected. For example, the analysis populations also include patients with secretory salivary gland cancer (see Appendix A), for whom - in contrast to other tumour entities - prognoses tend to be more favourable [10,11].
- The aim of the benefit assessment is a comparison with the ACT (here: individual therapy choosing from BSC and surgical resection, which is likely to result in severe morbidity, for which a clinical benefit is to be expected for individual patients). The course of the disease under the ACT also potentially depends on the tumour entities. Correspondingly (and adequately), comparative data are only available separately for tumour histology (see Section 2.3.2).
- According to the Scientific Advisory Group in Oncology, which was consulted during the approval process for larotrectinib, 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 [12].
- 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) [7,12].

The company presented results in the form of subgroup analyses only for the 3 entities "soft tissue sarcoma", "NSCLC" and "secretory salivary gland cancer" (with N ≥ 10 patients in the STARTRK-2 study). For a complete assessment of the therapeutic indication, results must also be presented for the other tumour entities. For an overview of the number of patients in the NTRK EE and NTRK SE analysis populations of the STARTRK-2 study separated by tumour entity, see Appendix A of the full dossier assessment.

Moreover, the company presented results on the 3 cited tumour entities only for the outcome categories "mortality", "morbidity" and "health-related quality of life". A weighing of benefit and harm in the framework of the benefit assessment also requires the submission of results for the outcome category "side effects by tumour entity".

2.3.2 Comparative data presented by the company

In addition to the adequate preparation of data on entrectinib (see Section 2.3.1), the benefit assessment versus the ACT requires comparative data. In its information retrieval, the company did not search for intervention and indication, but exclusively searched for "NTRK" and "cancer" in bibliographic databases and trial registries. Accordingly, the company used

identical inclusion and exclusion criteria across tumour histology for both the search for studies on entrectinib and on the ACT. The company excluded studies that consider a single tumour entity as well as studies that do not provide the characteristics of the NTRK status. The two exclusion criteria have no consequence on the search for studies on entrectinib, however, they prevent the identification of studies for potential comparison when searching for studies with the ACT chosen by the company. The company's approach was inadequate, as, for example, studies on tumour entities where the fusion is pathognomonic (e.g. secretory salivary gland cancer or secretory breast cancer) [13] cannot be identified. Moreover, as already described in Section 2.3.1, it is necessary to consider the tumour entities separately also for studies on the ACT, especially in the present therapeutic indication.

As mentioned before, the company identified no studies with the ACT specified by it in the framework of this information retrieval. However, in its reporting of results in the section on subgroup analyses, the company stated that it was trying to put the results on entrectinib for the entities "soft tissue sarcoma", "NSCLC" and "secretory salivary gland cancer" (independent of the NTRK status) "in the context of an unselected patient population treated with BSC". According to the company, a description of the efficacy of BSC for secretory salivary gland cancer cannot be found in the literature. For the entity "NSCLC", the company presented data on "overall survival" (4 studies [14-17]) and on the instrument "European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30) (1 study [16]). The company stated that the data presented on NSCLC are based on studies cited in the current S3 guideline "NSCLC" [18]. These are studies on the significance of platinum-based combination therapy versus BSC cited in the guideline and selected by the company. For the entity "soft-tissue sarcoma", the company presented data on overall survival from 2 studies [19,20] without providing information on the selection.

For the comparative data presented by the company, there is no description of the approach followed for the search and selection of studies. Therefore, the completeness of the presented results for studies with BSC cannot be assessed, nor can selective reporting be excluded. Moreover, results on the outcome category "side effects" are missing (as with the results on entrectinib separated by tumour entity). Furthermore, there are no effect estimations on the comparison of entrectinib with the ACT. Therefore, the comparative data presented by the company are not usable for the benefit assessment of entrectinib in comparison with the ACT.

2.3.3 Summary

The company presented data only on adult patients with solid tumours that display NTRK gene fusion. Data for paediatric patients from 12 years of age and older who were also covered by the therapeutic indication of entrectinib are not available.

The data presented by the company are insufficient in the preparation presented with the dossier and are not suitable for the benefit assessment of entrectinib versus the ACT. For the analysis populations presented by the company in Module 4 B, it is not certain that these are patients who have no satisfactory treatment options in accordance with the therapeutic indication.

Moreover, the formation of the NTRK EE analysis population in the STARTRK-2 study is not comprehensible. Furthermore, the preparation of the data is insufficient, in particular the lack of presentation of results for all outcome categories including the outcome category "side effects" separated by tumour entity. The comparative data presented by the company are also not usable for the benefit assessment of entrectinib in comparison with the ACT.

2.4 Results on added benefit

The data presented by the company are unsuitable to assess the added benefit of entrectinib versus the ACT in adult and paediatric patients from 12 years of age with solid tumours that display a 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 not yet received an NTRK inhibitor and who have no satisfactory treatment options. There was no hint of an added benefit of entrectinib in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of entrectinib in comparison with the ACT is summarized in Table 8.

Table 8: Entrectinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult and paediatric patients from 12 years of age 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 not yet received an NTRK inhibitor and ▪ who have no satisfactory treatment options	Individual treatment choosing from ▪ BSC[b] and ▪ surgical resection, which is likely to result in severe morbidity, for whom a clinical benefit is to be expected for individual patients	Added benefit not proven

a. Presentation of the ACT specified by the G-BA.
b. 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; 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 on the basis of the data presented by it in Module 4 B.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Hoffmann-La Roche. Basket study of entrectinib (RXDX-101) for the treatment of patients with solid tumors harboring NTRK 1/2/3 (TRK A/B/C), ROS1, or ALK gene rearrangements (fusions) (STARTRK-2): study details [online]. 2020 [Accessed: 24.09.2020]. URL: https://ClinicalTrials.gov/show/NCT02568267.

4. F. Hoffman-La Roche. An open-label, multicenter, global phase 2 basket study of entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbor NTRK1/2/3, ROS1, or ALK gene rearrangements [online]. [Accessed: 24.09.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003385-84.

5. Doebele RC, Drilon A, Paz-Ares L et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020; 21(2): 271-282. https://dx.doi.org/10.1016/S1470-2045(19)30691-6.

6. Roche. Rozlytrek [online]. 2020 [Accessed: 08.09.2020]. URL: https://www.fachinfo.de.

7. European Medicines Agency. Rozlytrek: European public assessment report [online]. 2020 [Accessed: 05.11.2020]. URL: https://www.ema.europa.eu/documents/assessment-report/rozlytrek-epar-public-assessment-report_en.pdf.

8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Larotrectinib (solide Tumore mit einer neurotrophen Tyrosin-Rezeptor-Kinase [NTRK]-Genfusion): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 15.01.2020]. URL: https://www.iqwig.de/download/A19-90_Larotrectinib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

9. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage XII: Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Larotrectinib [online]. 2020 [Accessed: 02.10.2020]. URL: https://www.g-ba.de/downloads/40-268-6479/2020-04-02_AM-RL-XII_Larotrectinib_D-495_TrG.pdf.

10. Bishop JA. Unmasking MASC: bringing to light the unique morphologic, immunohistochemical and genetic features of the newly recognized mammary analogue secretory carcinoma of salivary glands. Head Neck Pathol 2013; 7(1): 35-39. https://dx.doi.org/10.1007/s12105-013-0429-0.

11. Bissinger O, Götz C, Kolk A et al. Mammary analogue secretory carcinoma of salivary glands: diagnostic pitfall with distinct immunohistochemical profile and molecular features. Rare Tumors 2017; 9(3): 7162. https://dx.doi.org/10.4081/rt.2017.7162.

12. European Medicines Agency. Vitrakvi: European public assessment report [online]. 2019 [Accessed: 01.10.2020]. URL: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf.

13. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol 2018; 15(12): 731-747. https://dx.doi.org/10.1038/s41571-018-0113-0.

14. Thongprasert S, Sanguanmitra P, Juthapan W et al. Relationship between quality of life and clinical outcomes in advanced non-small cell lung cancer. Lung cancer (Amsterdam, Netherlands) 1999; 24(1): 17-24. https://dx.doi.org/10.1016/s0169-5002(99)00017-3.

15. Ranson M, Davidson N, Nicolson M et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2000; 92(13): 1074-1080. https://dx.doi.org/10.1093/jnci/92.13.1074.

16. Spiro SG, Rudd RM, Souhami RL et al. Chemotherapy versus supportive care in advanced non-small cell lung cancer. Thorax 2004; 59(10): 828-836. https://dx.doi.org/10.1136/thx.2003.020164.

17. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer. 2008. https://dx.doi.org/10.1200/JCO.2008.17.7162.

18. Leitlinienprogramm Onkologie, Deutsche Krebsgesellschaft, Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin. S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms [online]. URL: https://www.awmf.org/uploads/tx_szleitlinien/020-007OL_1_S3_Lungenkarzinom_2018-03.pdf.

19. Kawai A, Araki N, Sugiura H et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma. Lancet Oncol 2015; 16(4): 406-416. https://dx.doi.org/10.1016/S1470-2045(15)70098-7.

20. Gough NJ, Smith C, Ross JR et al. Symptom Burden, Survival and Palliative Care in Advanced Soft Tissue Sarcoma. Sarcoma 2011; 2011(1): 1-8. https://dx.doi.org/10.1155/2011/325189 M4 - Citavi.

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