Entrectinib (solid tumours with a neurotrophic tyrosine receptor kinase [NTRK] gene fusion, > 1 month to < 12 years)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Entrectinib (solide Tumoren mit einer Neurotrophen-Tyrosin-Rezeptor-Kinase[NTRK]-Genfusion, > 1 Monat bis < 12 Jahre) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and 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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No patients or families were involved in the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CCOD	clinical cut-off date
ECOD	enrollment cut-off date
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NTRK	neurotrophic tyrosine receptor kinase
RCT	randomized controlled trial
ROS	C-ros-Oncogene
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has 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 31 July 2024.

Research question

The aim of the present report is to assess the added benefit of entrectinib in comparison with the appropriate comparator therapy (ACT) in paediatric patients (1 month to less than 12 years of age) with solid tumours that have 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 received a prior NTRK inhibitor, and who have no satisfactory treatment options other than larotrectinib.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of entrectinib

Therapeutic indication	**ACT[a]**
Paediatric patients (1 month to less than 12 years of age) with solid tumours that have a 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 not received a prior NTRK inhibitor, and who have no satisfactory treatment options other than larotrectinib	Treatment of physician's choice choosing from ▪ Larotrectinib ▪ Best supportive care[c] ▪ Surgical resection, which is likely to result in severe morbidity, but which is nevertheless expected to result in individual clinical benefit for the patient on a case-by-case basis
a. Presented is the ACT specified by the G-BA. b. Note that NTRK gene fusions can occur in various solid tumours. Presenting the data separately for each tumour entity is considered necessary and useful. c. Best supportive care 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; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase	

Deviating from the G-BA, the company only specified larotrectinib as the ACT. The benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company's deviation from the ACT specified by the G-BA will not be further commented below, as the company did not present any suitable data for the benefit assessment – neither compared with a comparator therapy designated by the company nor compared with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

The information retrieval review revealed no randomized controlled trial (RCT) for a direct comparison of entrectinib against the ACT specified by the G-BA. The company also identified no relevant RCT. The company did not present any further investigations, justifying this by stating that the three single-arm and thus non-comparative pivotal studies STARTRK-NG, TAPISTRY and STARTRK-2 do not meet the requirements of the benefit assessment. Accordingly, the company did not systematically collect information on further studies. For reasons of transparency, however, the company presented the results of the studies in the dossier in a descriptive manner.

The STARTRK-NG, TAPISTRY, and STARTRK-2 studies are non-comparative studies for the treatment of children and adolescents up to 18 years of age (STARTRK-NG), patients from birth (TAPISTRY), and adults (STARTRK-2) with entrectinib. These are not suitable for the benefit assessment, as they do not allow a comparison of entrectinib with the ACT due to the lack of a comparator arm in each case.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of entrectinib in comparison with the ACT; an added benefit is therefore not proven.

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.

[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].

Table 3: Entrectinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Paediatric patients (1 month to less than 12 years of age) with solid tumours that have a 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 not received a prior NTRK inhibitor, and who have no satisfactory treatment options other than larotrectinib	Treatment of physician's choice choosing from ▪ Larotrectinib ▪ Best supportive care[c] ▪ Surgical resection, which is likely to result in severe morbidity, but which is nevertheless expected to result in individual clinical benefit for the patient on a case-by-case basis	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Note that NTRK gene fusions can occur in various solid tumours. Presenting the data separately for each tumour entity is considered necessary and useful.
c. Best supportive care 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; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of entrectinib in comparison with the ACT in paediatric patients (1 month to less than 12 years of age) with solid tumours that have 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 received a prior NTRK inhibitor, and who have no satisfactory treatment options other than larotrectinib.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of entrectinib

Therapeutic indication	**ACT[a]**
Paediatric patients (1 month to less than 12 years of age) with solid tumours that have a 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 not received a prior NTRK inhibitor, and who have no satisfactory treatment options other than larotrectinib	Treatment of physician's choice choosing from ▪ Larotrectinib ▪ Best supportive care[c] ▪ Surgical resection, which is likely to result in severe morbidity, but which is nevertheless expected to result in individual clinical benefit for the patient on a case-by-case basis
a. Presented is the ACT specified by the G-BA. b. Note that NTRK gene fusions can occur in various solid tumours. Presenting the data separately for each tumour entity is considered necessary and useful. c. Best supportive care 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; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase	

Deviating from the G-BA, the company only specified larotrectinib as the ACT. The benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company's deviation from the ACT specified by the G-BA will not be further commented on below because the company did not present any suitable data for the benefit assessment – neither compared to a comparator therapy designated by the company nor compared to the ACT specified by the G-BA (see Chapter I 3).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

I 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: no date given)
- bibliographical literature search on entrectinib (last search on 15 May 2024)
- search in trial registries/trial results databases for studies on entrectinib (last search on 15 May 2024)
- searches on the G-BA website for entrectinib (last search on 15 May 2024)

To check the completeness of the study pool:

- search in trial registries for studies on entrectinib (last search on 12 August 2024); for search strategies, see I Appendix A of the full dossier assessment

The review revealed no randomized controlled trial (RCT) for a direct comparison of entrectinib against the ACT specified by the G-BA. The company also did not identify any relevant RCTs, however, the company considered a deviating ACT (see Chapter I 2). The company did not present any further investigations, justifying this by stating that the three single-arm and thus non-comparative pivotal studies STARTRK-NG [3], TAPISTRY [4] and STARTRK-2 [5] do not meet the requirements of the benefit assessment. Accordingly, the company did not systematically collect information on further studies. For reasons of transparency, however, the company presented the results of the STARTRK-NG, TAPISTRY, STARTRK-2 studies in the dossier in a descriptive manner.

In the following, the studies are first described and then the lack of suitability of the data presented for the benefit assessment is justified.

Evidence presented by the company

Study design

STARTRK-NG

The STARTRK-NG study is an ongoing, uncontrolled, and open-label study with paediatric patients (birth to < 18 years), which is divided into a dose escalation and an expansion phase. Patients with solid tumours or primary tumours of the central nervous system with or without NTRK1/2/3 or C-ros-Oncogene-1 (ROS1) gene fusion in different cohorts were included in the expansion phase. The gene fusion had to be detected using a validated test. Patients who have a disease that is locally advanced, metastatic or where surgical tumour resection is likely to

result in severe morbidity were able to participate in the expansion phase if no satisfactory treatment option was available.

Cohort B included patients with primary tumours of the central nervous system with NTRK1/2/3 or ROS1 gene fusion, cohort D included patients with extracranial solid tumours (including neuroblastomas) with NTRK1/2/3 or ROS1 gene fusion. Patients were not allowed to have been previously treated with an NTRK or ROS1 inhibitor.

As of 16 January 2023 (enrollment cut-off date [ECOD]), a total of 34 patients were included in cohorts B and D of the STARTRK-NG study. All patients in the study received entrectinib. Treatment with entrectinib was largely in accordance with the Summary of Product Characteristics (SPC) [6].

Primary outcome of the expansion phase was the objective response rate. According to the information in Module 4 A, secondary outcomes were recorded in the categories of mortality, morbidity, and side effects.

TAPISTRY

The TAPISTRY study is an ongoing, non-controlled, open-label platform study with an umbrella design. It included patients with advanced, metastatic, or unresectable solid tumours in whom a specific oncogenic alteration or a high tumour mutation burden (≥ 13 mutations per megabase) was detected by a validated next-generation sequencing test. Another prerequisite was disease progression under the previous treatment or a previously untreated disease without an available acceptable treatment option. There was no restriction with regard to age; paediatric patients could be included depending on the properties of the drug used and the availability of an age-appropriate formulation and dosage recommendation.

As part of the platform design, patients were assigned to different cohorts based on the presence of specific genetic alterations or biomarkers. Patients (≥ 0 years) with an NTRK1/2/3 gene fusion were assigned to cohort B. According to the cohort-specific inclusion criteria, patients were not allowed to have been treated with an NTRK inhibitor before.

A total of 10 patients were included in cohort B of the TAPISTRY study until 16 January 2023 (ECOD). All patients in cohort B received entrectinib. Treatment with entrectinib was largely in accordance with the SPC [6].

Primary outcome of the study was the objective response rate. According to the information in Module 4 A, secondary outcomes were recorded in the categories of mortality, morbidity, and side effects.

STARTRK-2

The ongoing, uncontrolled, open-label study STARTRK-2 is already known from the dossier assessment A20-74 [7] and the associated addendum A21-07 [8] to assess the added benefit of entrectinib in adult and paediatric patients aged 12 years and older with solid tumours with an NTRK gene fusion. As part of a basket design, the study included adult patients with locally advanced or metastatic solid tumours and an NTRK1/2/3, ROS1 or anaplastic lymphoma kinase (ALK) gene fusion. In Module 4 A, the company stated that while 2 paediatric patients did participate in the study (documented as a protocol violation), neither showed an NTRK gene fusion and were therefore not part of the efficacy population for the current therapeutic indication.

See dossier assessment A20-74 [7] for a detailed description of the study and intervention characteristics.

Analysis populations of the company

In the dossier, the company descriptively presented the results of pooled analyses for the assessment of the efficacy and tolerability of entrectinib, which were the basis for the approval. The company formed separate analysis populations for benefit and harm outcomes, which it referred to as efficacy and safety populations. The efficacy population comprises a total of 44 patients from the STARTRK-NG (n = 34) and TAPISTRY (n = 10) studies. The safety population comprises 91 patients from the STARTRK-NG (n = 68), TAPISTRY (n = 21) and STARTRK-2 (n = 2) studies. The patients considered were at least 1 month old and younger than 18 years at the time of study inclusion. In addition, the efficacy population is limited to patients with NTRK1/2/3 gene fusion and an observation period of at least 6 months. In contrast, the safety population also includes patients with other genetic alterations such as ALK or ROS1 gene fusion. There was also no requirement for a minimum observation period.

The company presented analyses on the data cut-off from 16 July 2023 (clinical cut-off date [CCOD]) for both populations. For the efficacy population, this means that only patients who were included in the respective study by 16 January 2023 (ECOD), i.e. 6 months before the data cut-off date of 16 July 2023, are taken into account. As a result, patients who were included in the study after the ECOD are not part of the efficacy population.

Assessment of the evidence presented by the company

STARTRK-NG, TAPISTRY, and STARTRK-2 studies unsuitable for the benefit assessment

The STARTRK-NG, TAPISTRY, and STARTRK-2 studies are non-comparative studies. Therefore, they were unsuitable to derive conclusions on the added benefit of entrectinib in comparison with the ACT. This concurs with the assessment of the company, which consequently did not use the studies to derive an added benefit either.

In addition to the missing comparison with the ACT, the STARTRK-2 study also does not include any patients relevant to the present therapeutic indication.

Further points of criticism

Irrespective of the fact that the STARTRK-NG, TAPISTRY, and STARTRK-2 studies are not suitable for the benefit assessment due to the lack of comparison with the ACT, the analysis populations formed by the company have further points of criticism, which are explained below.

Formation of the efficacy population not comprehensible

The present research question of the benefit assessment covers paediatric patients from 1 month to 12 years of age. The STARTRK-NG and TAPISTRY studies were generally able to include patients from birth to 18 years of age (STARTRK-NG) or without age restriction (TAPISTRY). The data on the efficacy population show that the youngest patient was 1.3 months old at baseline, but 13.6% were older than 12 years. This means that the proportion of patients who did not belong to the age group relevant for the benefit assessment was sufficiently low overall.

As already explained, the company restricts the population for the analyses of outcomes in the mortality and morbidity categories (efficacy population) but not for the analyses of the adverse events outcome category (safety population) to patients with an observation period of ≥ 6 months. In view of the already small number of cases for the efficacy population and the necessary separate consideration by tumour entity, it is incomprehensible why patients with an observation period of < 6 months were not considered. It is not clear from the information in the dossier how many patients were excluded from the analysis due to the criterion applied by the company.

Relevant proportion of patients in the safety population does not correspond to the research question of this benefit assessment

The research question of the present benefit assessment includes paediatric patients from 1 month to 12 years of age with solid tumours and confirmed NTRK gene fusion. However, the proportion of patients with an NTRK gene fusion in the safety population was only 55%. The remaining 45% of patients had no altered kinase or alteration of ALK or ROS1. In addition, the safety population also includes patients who were older than 12 years at baseline and are therefore not included in the present research question. Their share of the safety population is 16%. It is unclear to what extent the patient populations without NTRK gene fusion and those with an age of at least 12 years overlap. Overall, at least 45% of the patients in the safety population do not correspond to the present research question, with a maximum of 62%.

Results separated by tumour entity are missing

The company did not present analyses separated according to tumour entity. In the present therapeutic indication, however, it is sensible and necessary to consider the results separately according to tumour entity. A detailed justification for this can be found in dossier assessment A20-74 and in the supporting reasons for the G-BA's decision on entrectinib treatment of adult and paediatric patients aged 12 years and older with solid tumours with NTRK gene fusion [7,9].

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of entrectinib in comparison with the ACT for treatment of paediatric patients (1 month to less than 12 years of age) with solid tumours that have 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 received a prior NTRK inhibitor, and who have no satisfactory treatment options other than larotrectinib. There is no hint of an added benefit of entrectinib in comparison with the ACT; an added benefit is therefore not proven.

I 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 5.

Table 5: Entrectinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Paediatric patients (1 month to less than 12 years of age) with solid tumours that have a 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 not received a prior NTRK inhibitor, and who have no satisfactory treatment options other than larotrectinib	Treatment of physician's choice choosing from ▪ Larotrectinib ▪ Best supportive care[c] ▪ Surgical resection, which is likely to result in severe morbidity, but which is nevertheless expected to result in individual clinical benefit for the patient on a case-by-case basis	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. Note that NTRK gene fusions can occur in various solid tumours. Presenting the data separately for each tumour entity is considered necessary and useful. c. Best supportive care 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; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase		

The assessment described above concurs with that of the company.

The G-BA decides on the added benefit.

I 6 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.

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