Repotrectinib
(solid tumours with neurotrophic tyrosine receptor kinase [NTRK] gene fusion)

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 *Repotrectinib (solide Tumoren mit einer Neurotrophen-Tyrosin-Rezeptor-Kinase[NTRK]-Genfusion) – Nutzenbewertung gemäß § 35a SGB V*. 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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Keywords

Repotrectinib, Solid Tumors, Adolescent, Adult, Benefit Assessment

Medical and scientific advice

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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.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the Förderkreis für krebskranke Kinder und Jugendliche Bonn e.V. (support group for children and adolescents with cancer) for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent and the Förderkreis für krebskranke Kinder und Jugendliche Bonn e.V. were not involved in the actual preparation of the 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
ALK	anaplastic lymphoma kinase
BSC	best supportive care
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
RCT	randomized controlled trial
ROS1	c-ros oncogene 1
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book 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 repotrectinib. 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 30 April 2025.

Research question

The aim of this report is to assess the added benefit of repotrectinib in comparison with the appropriate comparator therapy (ACT) in adult and paediatric patients from 12 years of age with advanced solid tumours with neurotrophic tyrosine receptor kinase (NTRK) gene fusion.

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of repotrectinib

Research question	Therapeutic indication	ACT[a]
Monotherapy for the treatment of adult and paediatric patients 12 years of age and older with advanced solid tumours with NTRK gene fusion		
A	Who have not previously received an NTRK inhibitor and for whom treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted	Individualized treatment[b, c] choosing from: ▪ larotrectinib ▪ entrectinib ▪ BSC[d]
B	Who have previously received an NTRK inhibitor	BSC[d]

a. Presented are the respective ACTs specified by the G-BA.
b. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. For the implementation of individualized therapy in a study of direct comparison, the G-BA expects investigators to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). The decision on individualized treatment with regard to the comparator therapy was to be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). A rationale must be provided for the choice and any limitation of treatment options.
d. According to the G-BA, 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 deviated from the G-BA's ACT for both research questions.

For research question A, the company only names the two options larotrectinib and entrectinib as treatment of physician's choice.

The company does not consider the group of patients pretreated with NTRK inhibitors (research question B of the G-BA) as 1 research question, but divides it into 2 research questions (named b1 and b2 by the company). Group b1 comprises patients pretreated with NTRK inhibitors without the patient group with non-small cell lung cancer (NSCLC). Group b2 comprises the patient group with NSCLC pretreated with NTRK inhibitors. For group b1 the company names best supportive care (BSC), and for group b2 it names various immuno(chemo)therapies and chemotherapies as comparator therapies. Overall, the designation of BSC as an ACT therefore only corresponds to the G-BA's definition for the pre-treated patient group without NSCLC (subpopulation of the present research question B). The company's deviations remain without consequences for this benefit assessment, as it presents suitable data neither on the treatment options specified by the G-BA nor on those specified by itself.

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

Since no suitable data are available for either of the research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

Results

Concurring with the company, no relevant randomized controlled trial (RCT) was identified for any of the research questions that would allow a direct comparison or an adjusted indirect comparison via a common comparator of repotrectinib versus the ACT in this therapeutic indication.

For the benefit assessment, the company presented the results of the single-arm TRIDENT-1 study with repotrectinib and used them to assess the added benefit. The company did not provide any data for the ACT.

The evidence presented by the company does not allow a comparison with the ACT and is therefore not suitable for deriving the added benefit.

Results on added benefit

Since no suitable data are available for either research question of the benefit assessment, there is no hint of an added benefit of repotrectinib in comparison with the ACT in either case; 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 repotrectinib.

Table 3: Repotrectinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Monotherapy for the treatment of adult and paediatric patients 12 years of age and older with advanced solid tumours with NTRK gene fusion			
A	Who have not previously received an NTRK inhibitor and for whom treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted	Individualized treatment[b, c] choosing from: ▪ larotrectinib ▪ entrectinib ▪ BSC[d]	Added benefit not proven
B	Who have not yet received an NTRK inhibitor	BSC[d]	Added benefit not proven

a. Presented are the respective ACTs specified by the G-BA.
b. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. For the implementation of individualized therapy in a study of direct comparison, the G-BA expects investigators to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). A rationale must be provided for the choice and any limitation of treatment options.
d. According to the G-BA, 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].

I 2 Research question

The aim of this report is to assess the added benefit of repotrectinib in comparison with the ACT in adult and paediatric patients from 12 years of age with advanced solid tumours with NTRK gene fusion.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of repotrectinib

Research question	Therapeutic indication	ACT[a]
Monotherapy for the treatment of adult and paediatric patients 12 years of age and older with advanced solid tumours with NTRK gene fusion		
A	Who have not previously received an NTRK inhibitor and for whom treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted	Individualized treatment[b, c] choosing from: ▪ larotrectinib ▪ entrectinib ▪ BSC[d]
B	Who have not yet received an NTRK inhibitor	BSC[d]

a. Presented are the respective ACTs specified by the G-BA.
b. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. For the implementation of individualized therapy in a study of direct comparison, the G-BA expects investigators to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). A rationale must be provided for the choice and any limitation of treatment options.
d. According to the G-BA, 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 deviated from the G-BA's ACT for both research questions.

For research question A, the company only names the two options larotrectinib and entrectinib as treatment of physician's choice.

The company does not consider the group of patients pretreated with NTRK inhibitors (research question B of the G-BA) as 1 research question, but divides it into 2 research questions (named b1 and b2 by the company). Group b1 comprises patients pretreated with NTRK inhibitors without the patient group with NSCLC. Group b2 comprises the patient group with NSCLC pretreated with NTRK inhibitors. For group b1 the company names BSC, and for

group b2 it names various immuno(chemo)therapies and chemotherapies as comparator therapies. Overall, the designation of BSC as an ACT therefore only corresponds to the G-BA's definition for the pre-treated patient group without NSCLC (subpopulation of the present research question B). The company's deviations remain without consequences for this benefit assessment, as it presents suitable data neither on the treatment options specified by the G-BA nor on those specified by itself.

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

Since no suitable data are available for either of the research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study lists on repotrectinib (status: 6 March 2025)
- Bibliographical literature search on repotrectinib (last search on 06 March 2025)
- Search in trial registries/trial results databases for studies on repotrectinib (last search on 06 March 2025)
- Search on the G-BA website for repotrectinib (last search on 06 March 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on repotrectinib (last search on 08 May 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, no relevant RCT was identified for any of the research questions that would allow a direct comparison or an adjusted indirect comparison via a common comparator of repotrectinib versus the ACT in this therapeutic indication.

Since the company did not identify any RCT for a direct comparison or an adjusted indirect comparison via a common comparator for repotrectinib versus the ACT, it conducted an information retrieval on further studies with repotrectinib. The company identified the single-arm study TRIDENT-1 [3] and used this as the best available evidence for the assessment of added benefit in its view. The company conducted no information retrieval on further studies with the ACT.

A check for completeness of the study pool presented by the company for further investigations was foregone because the data submitted by the company under “Further investigations” were unsuitable for the benefit assessment due to the lack of comparison with the ACT. This is explained below.

Evidence provided by the company

Study TRIDENT-1

The pivotal TRIDENT-1 study is a single-arm study that is still ongoing and is divided into a dose escalation phase (phase 1) and an expansion phase (phase 2). Phase 1 of the study included adult patients with a locally advanced or metastatic solid tumour with a c-ros oncogene 1 (ROS1), NTRK1-3 or anaplastic lymphoma kinase (ALK) gene fusion. Various doses of repotrectinib were investigated, partly with the aim of establishing a recommended dose for the subsequent phase 2 of the trial.

The ongoing phase 2 of the study is intended to further investigate the efficacy, safety and pharmacokinetics of repotrectinib at the recommended dose. Adult patients and paediatric patients aged 12 years and older were included in 6 different cohorts, which differed according to the tumour entity (NSCLC or another solid tumour), the existing gene fusion (ROS1 or NTRK1-3) and their pretreatment (with or without tyrosine kinase inhibitor, chemotherapy and immunotherapy). Patients with ALK gene fusion were not further investigated in phase 2 of the study.

Patients with ROS1-positive advanced NSCLC were included in Cohorts 1 to 4, with and without prior treatment, depending on the cohort. The cohorts 5 and 6 included patients with NTRK-positive advanced solid tumours who had not yet received treatment with an NTRK inhibitor (Cohort 5) or who had already received 1 or 2 prior treatments with an NTRK inhibitor (Cohort 6). Pretreatment with chemotherapy and immunotherapy was permitted in Cohorts 5 and 6.

Depending on the age of the patients, they had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1 (≥ 18-year-olds), a Karnofsky score ≥ 50 (16- to 18-year-olds) or a Lansky score ≥ 50 (under 16-year-olds). The life expectancy of all patients had to be at least 3 months, and no surgery, radiotherapy or multimodal therapy was allowed to be a possible further treatment option.

Treatment with repotrectinib in the study was without relevant deviations from the Summary of Product Characteristics (SmPC) [4].

The primary outcome of the expansion phase of the study was the objective response rate. Secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

In the dossier, the company presented data on the data cut-off from October 2023 which was relevant for the market authorization (requested by the European Medicines Agency [EMA]). According to the company's information in Module 4 A, further data cut-offs of the TRIDENT-1 study are a data cut from June 2022 to support the US-American approval procedure, a data cut-off from December 2022 to support the European and Japanese approval procedure and a data cut-off from September 2024 that was not pre-specified as per the company.

Submitted data unsuitable for drawing conclusions on added benefit

The TRIDENT-1 study presented by the company is a single-arm study with repotrectinib. The company presents no data on the ACT. The TRIDENT-1 study does not allow a comparison with the ACT and is therefore not suitable for deriving the added benefit.

I 4 Results on added benefit

No suitable data were available for the assessment of the added benefit of repotrectinib in comparison with the ACT in adults and paediatric patients aged 12 years and older with advanced solid tumours with NTRK gene fusion. There is no hint of an added benefit of repotrectinib in comparison with the ACT for either research question; 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 repotrectinib in comparison with the ACT is summarized in Table 5.

Table 5: Repotrectinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Monotherapy for the treatment of adult and paediatric patients 12 years of age and older with advanced solid tumours with NTRK gene fusion			
A	Who have not previously received an NTRK inhibitor and for whom treatment options not targeting NTRK provide limited clinical benefit, or have been exhausted	Individualized treatment[b, c] choosing from: ▪ larotrectinib ▪ entrectinib ▪ BSC[d]	Added benefit not proven
B	Who have not yet received an NTRK inhibitor	BSC[d]	Added benefit not proven

a. Presented are the respective ACTs specified by the G-BA.
b. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. For the implementation of individualized therapy in a study of direct comparison, the G-BA expects investigators to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). A rationale must be provided for the choice and any limitation of treatment options.
d. According to the G-BA, 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 concurs with that by 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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