Repotrectinib (NSCLC)

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 (NSCLC) – 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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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

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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I List of tables[2]

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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 -adjusted indirect comparison
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FAS	full analysis set
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
MAIC	matching-adjusted indirect comparison
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
ROS1	c-ros oncogene 1
SAF	safety set
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics

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 patients with c-ros oncogene 1 (ROS1)-positive advanced non-small cell lung cancer (NSCLC).

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 (multipage table)

Research question	**Therapeutic indication**	**ACT**[a, b]
Monotherapy for the treatment of adult patients with ROS1-positive advanced NSCLC		
A	Who have not previously received a ROS1 inhibitor	Crizotinib
B1	Who have previously received a ROS1 inhibitor and ▪ with a PD-L1 expression ≥ 50%	▪ Pembrolizumab as monotherapy, or ▪ atezolizumab as monotherapy, or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1), or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1)

Table 2: Research questions of the benefit assessment of repotrectinib (multipage table)

Research question	Therapeutic indication	ACT[a, b]
B2	Who have previously received a ROS1 inhibitor and ▪ with a PD-L1 expression < 50%[c, e]	▪ Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1), or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells), or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1), or ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 for whom platinum-based chemotherapy is not suitable) ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed); see also Appendix VI to Section K of the Pharmaceutical Directive (only for patients with ECOG PS 2), or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG PS 2)

a. Presented are the respective ACTs specified by the G-BA. For this therapeutic indication, it is assumed as per the G-BA that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. According to the G-BA, it is also assumed that another molecularly stratified therapy (directed against ALK, BRAF, EGFR, EGFR exon 20, KRAS G12C, METex14 or RET) was not an option for the patients at the time of treatment with repotrectinib.
b. According to the G-BA, therapies that are explicitly indicated for squamous histology were not considered in the determination of the ACT since ROS1-positive NSCLC usually has a non-squamous histology.
c. According to the G-BA, it is assumed that no (further) molecularly stratified therapy against ROS1 can be considered for patients at the time of treatment with repotrectinib.
d. The ACT specified here comprises several alternative treatment options according to the G-BA. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be demonstrated versus one of these alternative treatment options. As a rule, this can be done as part of a single-comparator study. According to the G-BA, in contrast, the sole comparison with a treatment option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population.
e. The ACT specified here comprises several alternative treatment options according to the G-BA. However, the treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. b. As per the G-BA, the sole comparison with a therapy option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population.

Table 2: Research questions of the benefit assessment of repotrectinib (multipage table)

Research question	Therapeutic indication	ACT[a, b]
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1		

For research questions A and B1, the company followed the G-BA's specification of the ACT. For research question B2, the company deviated from the G-BA's specification by additionally considering atezolizumab monotherapy as an option of the ACT for patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 2 for whom platinum-based chemotherapy is not suitable. In deviation from the G-BA's specification, the company named neither gemcitabine nor vinorelbine monotherapy as an ACT. 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 benefit assessment was conducted 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.

In the summarizing description of the added benefit of repotrectinib for research question A, the company also refers to the results of a study in which a comparison of individual arms from different studies was conducted and includes the results in the derivation of the added benefit. In this comparison, the results for repotrectinib from the TRIDENT-1 study were compared with the pooled results for crizotinib from the 5 studies PROFILE 1001, OO-1201, Cohort A of METROS, EUCROSS and ROS1-Population in AcSé (hereinafter referred to as POMEA) for the treatment of patients with ROS1-positive NSCLC. It presents both a naive

comparison and matching-adjusted indirect comparison (MAIC) analyses without a common comparator for the indirect comparison of treatment with repotrectinib versus crizotinib.

Assessment of the evidence presented by the company

The consideration of single-arm data on treatment with repotrectinib from the TRIDENT-1 study allows no comparison with the ACT and is therefore not suitable for the derivation of an added benefit.

The results of a comparison of individual arms from the studies TRIDENT-1 and POMEA listed by the company in the summarizing description of the added benefit are not suitable for the benefit assessment.

Irrespective of the fact that the data presented by the company on the comparison of individual arms from different studies are insufficiently analysed, MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment. In case of non-randomized comparisons without a common comparator, meaningful comparisons for confounder adjustment are usually only those that – unlike the MAIC analysis – involve the use of individual patient data. However, the MAIC analysis only uses aggregated data in the comparator arm. Hence, the results presented by the company on the basis of MAIC analyses are unsuitable for assessing the added benefit of crizotinib. If such analyses are available, it must be examined whether there are effects for which it can be ruled out with sufficient certainty that they are not based solely on systematic bias due to confounders. There are no such effects for the outcomes considered by the company.

Overall, the data presented by the company are not suitable for the benefit assessment and do not allow an adequate comparison of repotrectinib with the ACT.

Results on added benefit

Since no relevant study is available for the present research questions of the benefit assessment, there is no hint of added benefit of repotrectinib over 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 repotrectinib.

[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)

Table 3: Repotrectinib – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
Monotherapy for the treatment of adult patients with ROS1-positive advanced NSCLC			
A	Who have not previously received a ROS1 inhibitor	crizotinib	Added benefit not proven
B1	Who have previously received a ROS1 inhibitor and ▪ with a PD-L1 expression ≥ 50%	▪ Pembrolizumab as monotherapy, or ▪ atezolizumab as monotherapy, or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1), or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1)	Added benefit not proven
B2	Who have previously received a ROS1 inhibitor and ▪ with a PD-L1 expression < 50%[c, e]	▪ Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1), or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells), or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1), or ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 for whom platinum-based chemotherapy is not suitable) ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed); see also Appendix VI to Section K of the Pharmaceutical Directive (only for patients with ECOG PS 2), or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG PS 2)	Added benefit not proven

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: Repotrectinib – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
a. Presented are the respective ACTs specified by the G-BA. For this therapeutic indication, it is assumed as per the G-BA that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. According to the G-BA, it is also assumed that another molecularly stratified therapy (directed against ALK, BRAF, EGFR, EGFR exon 20, KRAS G12C, METex14 or RET) was not an option for the patients at the time of treatment with repotrectinib. b. According to the G-BA, therapies that are explicitly indicated for squamous histology were not considered in the determination of the ACT since ROS1-positive NSCLC usually has a non-squamous histology. c. According to the G-BA, it is assumed that no (further) molecularly stratified therapy against ROS1 can be considered for patients at the time of treatment with repotrectinib. d. The ACT specified here comprises several alternative treatment options according to the G-BA. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be demonstrated versus one of these alternative treatment options. As a rule, this can be done as part of a single-comparator study. According to the G-BA, in contrast, the sole comparison with a treatment option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population. e. The ACT specified here comprises several alternative treatment options according to the G-BA. However, the treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. b. As per the G-BA, the sole comparison with a therapy option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1			

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of repotrectinib in comparison with the ACT in adult patients with ROS1-positive advanced NSCLC.

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 (multipage table)

Research question	Therapeutic indication	ACT[a, b]
Monotherapy for the treatment of adult patients with ROS1-positive advanced NSCLC		
A	Who have not previously received a ROS1 inhibitor	Crizotinib
B1	Who have previously received a ROS1 inhibitor and ▪ with a PD-L1 expression ≥ 50%[c, d]	▪ Pembrolizumab as monotherapy, or ▪ atezolizumab as monotherapy, or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1), or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1)
B2	Who have previously received a ROS1 inhibitor and ▪ with a PD-L1 expression < 50%[c, e]	▪ Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1), or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells), or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1), or ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 for whom platinum-based chemotherapy is not suitable) ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed); see also Appendix VI to Section K of the Pharmaceutical Directive (only for patients with ECOG PS 2), or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG PS 2)

Table 4: Research questions of the benefit assessment of repotrectinib (multipage table)

Research question	Therapeutic indication	ACT[a, b]
a. Presented are the respective ACTs specified by the G-BA. For this therapeutic indication, it is assumed as per the G-BA that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. According to the G-BA, it is also assumed that another molecularly stratified therapy (directed against ALK, BRAF, EGFR, EGFR exon 20, KRAS G12C, METex14 or RET) was not an option for the patients at the time of treatment with repotrectinib. b. According to the G-BA, therapies that are explicitly indicated for squamous histology were not considered in the determination of the ACT since ROS1-positive NSCLC usually has a non-squamous histology. c. According to the G-BA, it is assumed that no (further) molecularly stratified therapy against ROS1 can be considered for patients at the time of treatment with repotrectinib. d. The ACT specified here comprises several alternative treatment options according to the G-BA. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be demonstrated versus one of these alternative treatment options. As a rule, this can be done as part of a single-comparator study. According to the G-BA, in contrast, the sole comparison with a treatment option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population. e. The ACT specified here comprises several alternative treatment options according to the G-BA. However, the treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. b. As per the G-BA, the sole comparison with a therapy option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1		

For research questions A and B1, the company followed the G-BA's specification of the ACT. For research question B2, the company deviated from the G-BA's specification by additionally considering atezolizumab monotherapy as an option of the ACT for patients with ECOG PS 2 for whom platinum-based chemotherapy is not suitable. In deviation from the G-BA's specification, the company named neither gemcitabine nor vinorelbine monotherapy as an ACT. 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 benefit assessment was conducted 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.

It should be noted that the company excluded a study from its study pool with reference to a missing results report. This is an ongoing open-label RCT TRIDENT-3 [3], potentially relevant to research question A, comparing repotrectinib with crizotinib in adult patients with advanced or metastatic ROS1-positive NSCLC who have not yet received prior treatment with a tyrosine kinase inhibitor. However, results were not available at the time of the benefit assessment. According to the study design, a first interim analysis of the primary outcome progression-free survival (and possibly for the secondary outcome overall survival) is planned for the TRIDENT-3 study after approx. 117 events, which is expected after approx. 47.5 months after randomization of the first patient. According to the study registry entry, the study was started on 21 December 2023 [3].

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 [4] and used this as the best available evidence for the assessment of added benefit in its view.

It should also be noted that in the summarizing description of the added benefit of repotrectinib (Section 4.4.2 in Module 4 B) for research question A, the company refers to the results of a study which compared individual arms from different studies (further explanation

in the following section). However, the information on the comparison conducted and its results are not comprehensively processed by the company in Module 4 B. Nevertheless, the company included the results of this study in its derivation of the added benefit.

The company conducted no current 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 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).

Depending on the age of the patients, they had to have an 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) [5].

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 B, 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.

Comparison of individual arms of different studies

In the summarizing description of the added benefit, the company refers to a study comparing repotrectinib with crizotinib using a MAIC analysis. It describes that 5 available clinical trials on the treatment of patients with ROS1-positive NSCLC with crizotinib were pooled for this comparison (PROFILE 1001, OO-1201, Cohort A of METROS, EUCROSS and ROS1 population in AcSé; hereinafter referred to as POMEA) [6-8]. Based on the data cut-off from 15 October 2023, the patient-specific data from the TRIDENT-1 study were used. Aggregated data of the respective studies were used for the comparator side. The company states that the patient characteristics and results of this population are largely comparable with the assessment-relevant populations of the safety set (SAF) and the full analysis set (FAS) - each without presenting these characteristics in Module 4 B. For further details, the company refers to the corresponding report [7] and the associated publication Wolf 2025 [8].

For the comparison of repotrectinib with crizotinib, the company presents the results of a naive comparison and a MAIC analysis without a common comparator for the outcomes overall survival, tumour response and progression-free survival in tabular form. The company did not provide further data in Module 4 B.

Assessment of the evidence presented by the company

The analyses presented by the company are unsuitable for the benefit assessment of repotrectinib in comparison with the ACT. This is explained below.

Study TRIDENT-1

The consideration of single-arm data on treatment with repotrectinib from the TRIDENT-1 study allows no comparison with the ACT and is therefore not suitable for the derivation of the added benefit.

Comparisons of individual arms of different studies

The results of a comparison of individual arms from the studies TRIDENT-1 and POMEA listed by the company in the summarizing description of the added benefit are not suitable for the benefit assessment.

Irrespective of the fact that the data presented by the company in Module 4 B pertaining to the comparison of individual arms from different studies are insufficiently analysed, MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment [1]. For non-randomized comparisons without a common comparator, meaningful comparisons for confounder adjustment are usually only those that – unlike the MAIC analysis – involve the use of individual patient data [9]. However, the MAIC analysis only uses aggregated data in the comparator arm. Hence, the results presented by the company on the basis of MAIC analyses are unsuitable for assessing the added benefit of crizotinib. If such analyses are available, it must be examined whether there are effects for which it can be ruled out with sufficient certainty that they are not based solely on systematic bias due to confounders. There are no such effects for the outcomes considered by the company.

A further examination of the MAIC analysis is waived due to the overall inadequate processing in Module 4 B.

Summary

Overall, the data presented by the company are not suitable for the benefit assessment and do not allow an adequate comparison of repotrectinib with the ACT.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of repotrectinib in comparison with the ACT in adult patients with advanced ROS1-positive NSCLC. There is no hint of an added benefit of repotrectinib in comparison with the ACT for any research question of the benefit assessment; 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 (multipage table)

Research question	**Therapeutic indication**	**ACT[a, b]**	**Probability and extent of added benefit**
Monotherapy for the treatment of adult patients with ROS1-positive advanced NSCLC			
A	Who have not previously received a ROS1 inhibitor	Crizotinib	Added benefit not proven
B1	Who have previously received a ROS1 inhibitor and ▪ with a PD-L1 expression ≥ 50%[c, d]	▪ Pembrolizumab as monotherapy, or ▪ atezolizumab as monotherapy, or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1), or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1)	Added benefit not proven
B2	Who have previously received a ROS1 inhibitor and ▪ with a PD-L1 expression < 50%[c, e]	▪ Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1), or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells), or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1), or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1), or ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 for whom platinum-based chemotherapy is not suitable) ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed); see also Appendix VI to Section K of the Pharmaceutical Directive (only for patients with ECOG PS 2), or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG PS 2)	Added benefit not proven

Table 5: Repotrectinib – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
a. Presented are the respective ACTs specified by the G-BA. For this therapeutic indication, it is assumed as per the G-BA that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. According to the G-BA, it is also assumed that another molecularly stratified therapy (directed against ALK, BRAF, EGFR, EGFR exon 20, KRAS G12C, METex14 or RET) was not an option for the patients at the time of treatment with repotrectinib. b. According to the G-BA, therapies that are explicitly indicated for squamous histology were not considered in the determination of the ACT since ROS1-positive NSCLC usually has a non-squamous histology. c. According to the G-BA, it is assumed that no (further) molecularly stratified therapy against ROS1 can be considered for patients at the time of treatment with repotrectinib. d. The ACT specified here comprises several alternative treatment options according to the G-BA. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be demonstrated versus one of these alternative treatment options. As a rule, this can be done as part of a single-comparator study. According to the G-BA, in contrast, the sole comparison with a treatment option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population. e. The ACT specified here comprises several alternative treatment options according to the G-BA. However, the treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. b. As per the G-BA, the sole comparison with a therapy option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1			

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit for research question A. For research questions B1 and B2, the assessment described above corresponds to 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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