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Entrectinib (NSCLC) –

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 (NSCLC) – 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
CCOD	clinical cut-off date
ECOD	enrolment cut-off date
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EE	efficacy evaluable
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FISH	fluorescence in situ hybridization
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IPTW	inverse probability of treatment weighting
KRAS	Kirsten rat sarcoma viral oncogene homologue
MAIC	matching-adjusted indirect comparison
NDA	New Drug Approval
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
PFS	progression-free survival
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

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 was to assess the added benefit of entrectinib in comparison with crizotinib as appropriate comparator therapy (ACT) in adult patients with c-ros oncogene 1 (ROS1)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an anaplastic lymphoma kinase (ALK) inhibitor.

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 patients with ROS1-positive advanced NSCLC previously not treated with a ROS1 inhibitor[b]	Crizotinib
a. Presentation of the ACT specified by the G-BA. b: For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; ROS1: c-ros oncogene 1	

The company named crizotinib as ACT and thus followed the G-BA's specification.

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

Results

The company identified no randomized controlled trials (RCTs) for direct comparisons or adjusted indirect comparisons for the comparison of entrectinib with crizotinib. The company therefore presented comparisons using individual arms from different studies.

Evidence on entrectinib presented by the company

The company included the ongoing, uncontrolled, prospective phase 2 basket study STARTRK-2 on entrectinib, in which adult patients with locally advanced or metastatic solid tumours and neurotrophic tyrosine receptor kinase (NTRK) 1/2/3, ROS1 or ALK gene rearrangement were enrolled independently of their tumour histology. In order to assess the added benefit of entrectinib in the present therapeutic indication, the company considered the subpopulation of patients with ROS1-positive, advanced NSCLC who had not been pretreated with ROS1 inhibitors (hereinafter referred to as the ROS1 population). For this subpopulation, the company used different analysis populations separated by benefit and harm outcomes; the number of considered patients varied (see Table 3).

Table 3: Data cut-offs and analysis populations of the STARTRK-2 study presented by the company in the dossier (multipage table)

Data cut-off[a] (company's designation)[b]	**Time by which patients were included in the analysis population (ECOD)**	**Analysis population[c]**	
		ROS1 EE[d] N	**ROS1 SE[e] N**
31 May 2018 (NDA)	30 April 2017[f]	37	105[g]
31 October 2018 (EMA compatibility)	31 October 2018	–	**180**
1 May 2019 (EMA-ROS1 efficacy)	30 November 2017	78 (analysis population 1[h])	–
1 May 2019 (EMA D194 ROS1 efficacy)	31 October 2018	**145**[i] (analysis population 2)	–

Table 3: Data cut-offs and analysis populations of the STARTRK-2 study presented by the company in the dossier (multipage table)

Data cut-off[a] (company's designation)[b]	**Time by which patients were included in the analysis population (ECOD)**	**Analysis population[c]**	
		ROS1 EE[d] N	**ROS1 SE[e] N**
a. Referred to by the company as clincial cut-off date (CCOD). b. Company's designation for the data cut-offs; however, since the same data cut-off may have different designations, it can be assumed that the analysis populations resulting on the basis of data cut-off, ECOD and population under consideration are meant; analysis populations whom the company considers relevant for the benefit assessment are printed in **bold**. c. According to the company, patients with ROS1-positive ROS1 inhibitor-naive NSCLC; analysis populations whom the company considered relevant for the benefit assessment are printed in **bold**. d. Patients with measurable disease according to RECIST version 1.1 based on the BICR at baseline with a follow-up ≥ 12 months after initial response reported by the company; additional criteria were used to form this population (pretreatment with a ROS1 inhibitor, ECOG PS > 2, and ROS1 biomarkers not permitted), for which it is unclear how many patients were excluded from the analysis population solely as a result of these criteria; used by the company for analyses of outcomes in the outcome category "mortality", "morbidity" and "health-related quality of life". e. Patients who received at least 1 dose of entrectinib; used by the company for analyses on outcomes in the outcome category "side effects". f. Information by the company in the dossier: 30 November 2017; the EPAR shows that patients were only included in the analysis until 30 April 2017. g. Unclear whether a follow-up of ≥ 12 months was considered for this analysis population. h: The company used analysis population 1 for the comparison with crizotinib. i. According to EPAR, this analysis considered patients with a follow-up of ≥ 6 months after initial response. BICR: blinded independent central review committee; CCOD: clinical cut-off date; ECOD: enrolment cut-off date; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; EPAR: European Public Assessment Report; N: number of patients in the analysis; NDA: New Drug Approval; NSCLC: non-small cell lung cancer; RECIST: Response Evaluation Criteria in Solid Tumours; ROS1: c-ros oncogene 1; ROS1 EE: ROS1 efficacy set (efficacy evaluable); ROS1 SE: ROS1 compatibility set (safety evaluable)		

Evidence on crizotinib presented by the company

For crizotinib, the company used individual data of adult patients with locally advanced or metastatic ROS1-positive NSCLC treated with crizotinib from a US cancer database (Flatiron Health Database). Due to the non-interventional design, this is a non-comparative retrospective cohort study. In addition, the company also included the single-arm study EUCROSS on crizotinib. Only aggregate data are available for the EUCROSS study population. Adults with locally advanced or metastatic ROS1-positive NSCLC were included in the EUCROSS study and treated with crizotinib. Pretreatment with ALK or ROS1 inhibitors was not allowed.

Comparisons of individual arms from different studies

In order to compare entrectinib with the ACT crizotinib, the company compared the results of analysis population 1 for the ROS1 population of the STARTRK-2 study at the data cut-off of 1 May 2019 (European Medicines Agency (EMA) ROS1 efficacy, N = 78, see Table 3) with the results of the cohort from the Flatiron Health Database (N = 69) by means of a propensity score analysis or the results of the EUCROSS study (N = 30) using the matching-adjusted

indirect comparison (MAIC) method. For both comparisons, the company only presented data on the outcomes "overall survival" and "progression-free survival (PFS)" in the dossier.

To derive the added benefit of entrectinib, the company primarily used the results of the comparison versus the Flatiron Health Database for the outcomes "overall survival" and "PFS". For further outcomes on morbidity and health-related quality of life, the company exclusively used the results of the STARTRK-2 study, without performing a comparison with crizotinib. For outcomes on the tolerability, the company stated to perform a "naive comparison" of entrectinib versus crizotinib. However, it compared the tolerability profile of entrectinib observed in the STARTRK-2 study with general data on crizotinib for selected AEs only.

Assessment of the evidence presented by the company

The data presented by the company in Module 4 A are unsuitable for the benefit assessment of entrectinib versus the ACT crizotinib.

Analysis populations of the STARTRK-2 study unsuitable for deriving the added benefit

As described above, the company presented different analysis populations for the benefit and harm outcomes (see Table 3). Moreover, the number of considered patients varies depending on the data cut-off and the time by which patients were included in the analysis population (enrolment cut-off date [ECOD]). Overall, the composition of the analysis populations formed by the company is not comprehensible on the basis of the data provided by the company in the dossier, among other reasons because the figure on the patient flow presented by the company in the dossier refers to the data cut-off of 31 May 2018 (new drug approval [NDA]) and the pooled analysis populations of the STARTRK-2, STARTRK-1 and ALKA-372-001 studies. A corresponding figure of the patient flow would have been useful and necessary to comprehend the formation of the corresponding analysis populations, particularly for the most recent analysis populations for the benefit outcomes (analysis population 2, data cut-off of 1 May 2019) and the harm outcomes (data cut-off of 31 October 2018). However, the company provided no such figure in the dossier.

Moreover, the company restricted the ROS1 population for analyses of outcomes of the categories "mortality", "morbidity" and "health-related quality of life" (analysis population ROS1 EE) to patients with ≥ 12 months of follow-up after initial response. The European Public Assessment Report (EPAR) shows that a follow-up of ≥ 6 months after initial response was considered for the principally relevant analysis population 2, and not ≥ 12 months after initial response as stated by the company in Module 4 A. The sole consideration of patients with a follow-up period ≥ 6 months after initial response is not adequate insofar as unresponsive patients would not be considered in the analysis population. Information on whether and if so, how many unresponsive patients were not included in this analysis population is not available.

Moreover, the effects on the analysis results for the benefit outcomes caused by the restriction of the patient population through the specification of a follow-up period are unclear, as no information is available on which patients were not included in the analysis population due to

this criterion. This approach means that recordings available for patients without a corresponding follow-up after initial response or for patients who have not shown any response yet, 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. The company did not address this issue in its dossier.

In addition to the exclusion criterion follow-up < 6 or < 12 months after initial response, the ROS1 efficacy evaluable (EE) population is also restricted by further exclusion criteria (pretreatment with a ROS1 inhibitor, ECOG PS > 2 and ROS1 biomarkers not permitted). However, the exclusion criteria applied by the company and thus the composition of the ROS1 EE analysis population are not comprehensible on the basis of the data provided by the company in the dossier (see above).

Comparisons presented by the company are unsuitable for the derivation of the added benefit

For the ROS1 population, the company compared the results of analysis population 1 of the STARTRK-2 study with the results of the cohort from the Flatiron Health Database or with the results of the EUCROSS study for crizotinib exclusively on the outcomes "overall survival" and "PFS" in order to compare entrectinib with crizotinib.

Besides the uncertainties described with regard to the restriction of the patient population of the STARTRK-2 study, both comparisons presented by the company are unsuitable for the present benefit assessment due to the following reasons:

- It is unclear why the company used analysis population 1 at the data cut-off of 1 May 2019 of the STARTRK-2 study and not the larger analysis population (analysis population 2 at the data cut-off of 1 May 2019) for both comparisons versus crizotinib, as analysis population 2 included almost twice as many patients as analysis population 1.
- Information on whether the company considered the follow-up time of ≥ 12 months after initial response specified for analysis population 1 of the STARTRK-2 study when selecting patients from the Flatiron Health Database or whether it could have considered it is not available. The follow-up time of ≥ 12 months after initial response specified in STARTRK-2 was not considered in the EUCROSS study, since data on a corresponding analysis population are not available for this study.
- Both comparisons on overall survival presented by the company are comparisons of individual arms from different studies. Although an adjustment was made in the analysis with regard to potentially relevant effect modifiers or prognostic factors, the results are subject to inherent uncertainty due to the lack of randomization, so an added benefit can only be derived if the effects are sufficiently large. For both comparisons on overall survival presented by the company, the observed effects were not large enough that they could not be caused by systematic bias alone. That there could be a systematic bias in the results is also shown by the fact that the survival time analyses of patients under treatment

with crizotinib differed notably between the Flatiron Health Database and the EUCROSS study.

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

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

Table 4 shows a summary of probability and extent of the added benefit of entrectinib.

Table 4: Entrectinib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with ROS1-positive advanced NSCLC previously not treated with a ROS1 inhibitor[b]	Crizotinib	Added benefit not proven

a. Presentation of the ACT specified by the G-BA.
b: For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; ROS1: c-ros oncogene 1

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of entrectinib in comparison with crizotinib as ACT in adult patients with ROS1-positive advanced non-small cell lung cancer (NSCLC) previously not treated with a ROS1 inhibitor.

Table 5 shows the research question of the benefit assessment and the ACT specified by the G-BA.

[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 5: Research question of the benefit assessment of entrectinib

Therapeutic indication	**ACT[a]**
Adult patients with ROS1-positive advanced NSCLC previously not treated with a ROS1 inhibitor[b]	Crizotinib
a. Presentation of the ACT specified by the G-BA. b: For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; ROS1: c-ros oncogene 1	

The company specified crizotinib as ACT and thus followed the G-BA's specification.

The assessment was conducted 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: 24 June 2020)
- bibliographical literature search on entrectinib (last search on 4 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 for the ACT (last search on 4 June 2020)
- search in trial registries/trial results databases for the ACT (last search on 24 June 2020)
- search on the GBA website for the ACT (last search on 24 June 2020)

To check the completeness of the study pool:

- search in trial registries for studies on entrectinib (last search on 8 September 2020)
- search in trial registries for studies on the ACT (last search on 10 September 2020)

Concurring with the company, the check of the completeness of the study pool identified no RCTs on the direct or indirect comparison of entrectinib versus the ACT using a common comparator.

Since the company identified no RCTs for direct comparisons or adjusted indirect comparisons, it conducted a search for further studies and presented comparisons of individual arms from different studies.

The check of the completeness of the company's study pool identified no additional potentially relevant studies on entrectinib. The check of the completeness of the study pool for crizotinib identified further potentially relevant studies on crizotinib in addition to those included by the company in its comparisons of individual arms of different studies and described in Section 2.3.1 (see Section 2.3.2).

However, overall, the data presented by the company were unsuitable to draw conclusions on the added benefit of entrectinib in comparison with crizotinib. This is justified below.

2.3.1 Evidence provided by the company

For entrectinib, the company included the uncontrolled, prospective phase 2 basket study STARTRK-2 [3-7] and used the subpopulation of adult patients with ROS1-positive advanced NSCLC who had not been pretreated with ROS1 inhibitors (hereinafter referred to as the ROS1 population). In Module 4 A, the company presented the single-arm entrectinib studies STARTRK-1 [8], ALKA-372-001 [8] and STARTRK-NG [9] as supplementary information.

For crizotinib, the company used data from a US cancer database (Flatiron Health Database). Due to the non-interventional design, this is a non-comparative retrospective cohort study. Moreover, the company also included the single-arm study EUCROSS on crizotinib [4,10-14].

Evidence on entrectinib

STARTRK-2 study

The STARTRK-2 study is an ongoing, uncontrolled, open-label and multicentre study. Adult patients with locally advanced or metastatic solid tumours and NTRK 1/2/3, ROS1 or ALK gene rearrangement were included within 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). Patients had to have an ECOG PS ≤ 2 and a life expectancy of at least 4 weeks. The number of prior lines of treatment was not restricted in the study, but pretreatment with tyrosine receptor kinase or ROS1 or ALK inhibitors was not allowed for patients with the corresponding gene rearrangement (with the exception of patients with NSCLC). Moreover, patients had to have measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST). However, patients with non-measurable tumour lesions (but with clinically assessable disease) could be included as "non-evaluable for the primary outcome".

For the assessment of the added benefit of entrectinib in the present therapeutic indication, the company considered the subpopulation of patients with ROS1-positive advanced NSCLC who had not been pretreated with ROS1 inhibitors (ROS1 population). For this subpopulation, the company used different analysis populations separated by benefit and harm outcomes; the number of considered patients varied (see Table 6).

Entrectinib was administered in line with the summary of product characteristics (SPC) [14]. Patients were treated with entrectinib until disease progression, unacceptable toxicity or

withdrawal of consent. Treatment could be continued beyond disease progression at the investigator's discretion if clinical benefit continued to exist.

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

Further information on the characteristics of the study can be found in Appendix A of the full dossier assessment.

Data cut-offs and analysis populations

For the STARTRK-2 study, the company presented different data cut-offs (clinical cut-off dates [CCOD] 31 May 2018, 31 October 2018 and 1 May 2019) and analysis populations for the ROS1 population separated by benefit (ROS1 EE) and harm outcomes (ROS1 SE) (see Table 6) in Module 4 A.

Table 6: Data cut-offs and analysis populations of the STARTRK-2 study presented by the company in the dossier

Data cut-off[a] (company's designation)[b]	**Time by which patients were included in the analysis population (ECOD)**	**Analysis population[c]**	
		ROS1 EE[d] N	**ROS1 SE[e] N**
31 May 2018 (NDA)	30April 2017[f]	37	105[g]
31 October 2018 (EMA compatibility)	31 October 2018	–	**180**
1 May 2019 (EMA-ROS1 efficacy)	30 November 2017	78 (analysis population 1[h])	–
1 May 2019 (EMA D194 ROS1 efficacy)	31 October 2018	**145**[i] (analysis population 2)	–

a. Referred to by the company as CCOD.
b. Company's designation for the data cut-offs; however, since the same data cut-off may have different designations, it can be assumed that the analysis populations resulting on the basis of data cut-off, ECOD and population under consideration are meant; analysis populations whom the company considers relevant for the benefit assessment are printed in **bold**.
c. According to the company, patients with ROS1-positive ROS1 inhibitor-naive NSCLC; analysis populations whom the company considered relevant for the benefit assessment are printed in **bold**.
d. Patients with measurable disease according to RECIST version 1.1 based on the BICR at baseline with a follow-up ≥ 12 months after initial response reported by the company; additional criteria were used to form this population (pretreatment with a ROS1 inhibitor, ECOG PS > 2 and ROS1 biomarkers not permitted), for which it is unclear how many patients were excluded from the analysis population solely as a result of these criteria; used by the company for analyses of outcomes in the outcome category "mortality", "morbidity" and "health-related quality of life".
e. Patients who received at least 1 dose of entrectinib; used by the company for analyses on outcomes in the outcome category "side effects".
f. Information by the company in the dossier: 30 November 2017; the EPAR [15] shows that patients were only included in the analysis until 30 April 2017.
g. Unclear whether a follow-up of ≥ 12 months was considered for this analysis population (see running text).
h: The company used analysis population 1 for the comparison with crizotinib.
i. According to EPAR [15], this analysis considered patients with a follow-up of ≥ 6 months after initial response.

BICR: independent central review committee; CCOD: clinical cut-off date; ECOD: enrolment cut-off date; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; EPAR: European Public Assessment Report; N: number of patients in the analysis; NDA: New Drug Approval; NSCLC: non-small cell lung cancer; RECIST: Response Evaluation Criteria in Solid Tumours; ROS1: c-ros oncogene 1; ROS1 EE: ROS1 efficacy evaluable; ROS1 SE: ROS1 compatibility set (safety evaluable);

Analysis populations

- ROS1 EE: The company defines this population as patients with measurable disease according to RECIST after a blinded, independent central review at baseline with a follow-up ≥ 12 months after initial response. However, due to the identical number of patients it is assumed that according to the EPAR [15] the analysis population 2 (see Table 6) at the data cut-off from 1 May 2019 presented by the company in Module 4 A consists of patients with follow-up periods ≥ 6 months after initial response. For the present assessment, the EPAR definition is assumed to apply.

The dossier provides no clear description of how the company operationalized the criterion "≥ 6 or ≥ 12 months follow-up after initial response". In the following, it is assumed that only those patients were included in the ROS1 EE analysis population who had been included in the study by the ECOD of the respective data cut-off (see Table 6) and who subsequently had at least one confirmed tumour response with ≥ 6 or ≥ 12 months of follow-up.

Moreover, further criteria (pretreatment with a ROS1 inhibitor, ECOG PS > 2 and ROS1 biomarker not permitted) were used to form the analysis population, for which it is unclear how many patients were excluded solely as a result of these criteria.

The company used the ROS1 EE analysis population for analyses on the outcome categories “mortality”, “morbidity” and “health-related quality of life”. For patients with measurable lesions of the central nervous system (CNS) (referred to by the company as ROS1 EE CNS RECIST population), the company presented a separate analysis for the intracranial objective response rate.

- ROS1 SE: Patients who received at least 1 dose of entrectinib. The company used this analysis population for analyses on outcomes of the outcome category “side effects”.

Data cut-offs and consideration of patients in the analysis populations

- Data cut-off of 31 May 2018 (CCOD): In the dossier, the company refers to this data cut-off as the “NDA data cut-off”. According to the information provided by the company in Module 4 A, the patients were included in the analysis population by the ECOD of 30 November 2017. However, according to the information in the EPAR [15], patients were only included in the analysis population until the ECOD of 30 April 2017. Analyses are available for the ROS1 EE (N = 37) and ROS1 EE CNS RECIST (N = 17) populations.

  However, for the ROS1 safety evaluable (SE) population at this data cut-off (N = 105), the information provided by the company in the dossier does not state whether, as with the data cut-off the company refers to as EMA tolerability (see Table 6), all patients who have received at least 1 dose of entrectinib are included in the analysis or whether a follow-up of ≥ 12 months after the first dose was considered.
- Data cut-off of 31 October 2018 (CCOD): In the dossier, the company refers to this data cut-off as the EMA tolerability data cut-off; it was also requested by the EMA. Analyses are available for the ROS1 SE population (N = 180). The ECOD corresponds to the CCOD.
- Data cut-off of 1 May 2019 (CCOD): For this data cut, which was also requested by the EMA, there are 2 analysis populations in the dossier depending on the ECOD.
  - Analysis population 1: In the dossier, the company refers to this analysis population as the EMA ROS1 efficacy data cut-off. Patients were included in the analysis population until the ECOD of 30 November 2017. Analyses are available for the ROS1 EE (N = 78) and ROS1 EE CNS RECIST (N = 31) populations.

- Analysis population 2: In the dossier, the company refers to this analysis population as the EMA D194 ROS1 efficacy data cut-off. Patients were included in the analysis population until the ECOD of 31 October 2018. Analyses are available for the ROS1 EE (N = 145) and ROS1 EE CNS RECIST (N = 43) populations.

For the harm outcomes, the company considered the data cut-off of 31 October 2018 (EMA tolerability) as relevant for the benefit assessment. For the benefit outcomes, the company considers analysis population 2 at the data cut-off of 1 May 2019 to be the most relevant population for the analysis, as this was the last one requested by the EMA, and the STARTRK-2 study was still recruiting. Moreover, the analysis contained the most data. However, the company used analysis population 1 at the data cut-off of 1 May 2019 for the comparison with crizotinib (see Section 2.3.2). The company did not provide a reason for this approach.

In Module 4 A, the company presents results of all available outcomes for analysis population 2 (EMA D194 ROS1 efficacy). Moreover, it presents the results of analysis population 1 (EMA ROS1 efficacy) and the results for the data cut-off of 31 May 2018 (NDA) as supplementary information.

Further data on entrectinib presented by the company

In Module 4 A, Appendix 4-G, the company presents pooled analyses of STARTRK-2 with individual patients from the studies STARTRK-1, ALKA-372-001 and STARTRK-NG as supplementary information in addition to the analyses on the STARTRK-2 study. All 3 studies are single-arm dose-ranging studies for entrectinib.

The studies STARTRK-1 and ALKA-372-001 included adult patients with locally advanced or metastatic solid tumours and an NTRK1/2/3, ROS1 or ALK gene rearrangement who were then treated with different doses of entrectinib. The pooled analyses of the studies STARTRK-2, STARTRK-1 and ALKA-372-001 for benefit outcomes included 94 patients (pooled ROS1 EE), those for harm outcomes included 210 patients (pooled ROS1 SE). From the STARTRK-2, the data cut-off of 1 May 2019 (analysis population 1, EMA ROS1 efficacy, N = 78) was used for the benefit outcomes and the data cut-off of 31 October 2018 (EMA tolerability, N = 180) was used for the harm outcomes. From the studies STARTRK-1 and ALKA-372-001, the data cut-off of 31 May 2018 (NDA) was used for both analyses. Patients with ROS1-positive, ROS1 inhibitor-naive NSCLC who received a dosage of ≥ 600 mg entrectinib were included in the pooled analysis. The pooled analyses are not further considered, because it is unclear whether this analysis also included patients who had received a dosage > 600 mg, which was not in compliance with the approval.

The STARTRK-NG study included paediatric patients with locally advanced or metastatic solid tumours or primary tumours of the central nervous system (CNS tumours). As paediatric patients are not included in the present therapeutic indication of entrectinib [14], the study is not considered further.

Evidence on the ACT crizotinib

Flatiron Health Database

The Flatiron Health database includes treatment data on about 160 000 patients with lung cancer from 265 oncology clinics in the USA. Individual data on overall survival and PFS of adult patients with locally advanced or metastatic ROS1-positive NSCLC treated with crizotinib (N = 69) were used for the comparison with entrectinib (the presence of other driver mutations such as ALK, EGFR or KRAS was not allowed). To be included in the analysis, patients had to have an ECOG PS ≤ 2. Patients whose ECOG PS was unknown ≤ 30 days before the first treatment with crizotinib were also included [15,16]. The disease was diagnosed between 1 Januar 2011 and 30 June 2018 and the patients were observed until the end of treatment, death or last known activity as stated by the company in the dossier. It can be assumed that the duration of the planned follow-up period was specified on an outcome-specific basis. The number of prior lines of treatment was not restricted, but pretreatment with crizotinib was not allowed [16]. Detailed information on the crizotinib dosage in the patients included in the analyses is not available.

Further information on the characteristics of the study can be found in Appendix A of the full dossier assessment.

Study EUCROSS

EUCROSS is a single-arm study including adults with locally advanced or metastatic ROS1-positive NSCLC who were then treated with crizotinib. Patients had to have an ECOG PS ≤ 2 and a life expectancy of at least 12 weeks. The number of prior lines of treatment was not restricted, but pretreatment with ALK or ROS1 inhibitors was not allowed. Moreover, patients had to have a measurable disease according to RECIST. Only aggregate data are available for the EUCROSS study population.

34 patients were included in the study. Treatment with crizotinib was in compliance with the SPC [17].

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

Further information on the characteristics of the study can be found in Appendix A of the full dossier assessment.

Comment on the completeness of the study pool on crizotinib

Concurring with the company, the check of the completeness of the study pool on the ACT crizotinib identified the studies METROS [18], PROFILE1001 [19], AcSé [20] and NCT01945021 [21] as potentially relevant. However, the company did not include them in the benefit assessment. All studies included adults with ROS1-positive, ROS1 inhibitor-naive advanced NSCLC. The company justified the exclusion of the studies stating that there were

deviations from the entrectinib study STARTRK-2 pertaining to significant clinical characteristics and prognostic factors: no information on the proportion of brain metastases (PROFILE1001 study), 29% of the patients had been pretreated with EGFR inhibitors (AcSé study), purely Asian population (NCT01945021 study), and the ROS1 patients were only tested with fluorescence in situ hybridization (FISH) and not confirmed by sequencing (METROS study). These deviations made the studies unsuitable for comparison.

The company's justifications alone are insufficient for an exclusion of the studies. For example, the exclusion of the METROS study solely based on the applied FISH test method is not appropriate, as patients could also be tested with the FISH method in the Flatiron Health Database used by the company for the comparison of entrectinib with crizotinib (see Table 11 of the full dossier assessment). However, the fact that the company did not consider these potentially relevant studies remains without consequence for the present assessment, as the overall conclusion on the added benefit would not change if the data available in these studies were taken into account.

Comparisons of individual arms from different studies

In order to compare entrectinib with the ACT crizotinib, the company compared the results of analysis population 1 for the ROS1 population of the STARTRK-2 study at the data cut-off of 1 May 2019 (EMA ROS1 efficacy, N = 78) with the results of the cohort from the Flatiron Health Database (N = 69) or the results of the EUCROSS study (N = 30).

For the comparison of the ROS1 population of the STARTRK-2 study with the Flatiron Health Database based on individual data, the company conducted a propensity score analysis using inverse probability of treatment weighting (IPTW). The company compared the aggregated data of the EUCROSS study with the results of the ROS1 population of the STARTRK-2 study based on individual data using the MAIC method. For both comparisons, the company only presented data on the outcomes "overall survival" and "PFS" in the dossier.

To derive the added benefit of entrectinib, the company primarily used the results of the comparison versus the Flatiron Health Database for the outcomes "overall survival" and "PFS". It justifies this approach by stating that the comparison of entrectinib versus crizotinib based on individual data represents the best possible clinical evidence and that the comparison using the MAIC method has a higher risk of bias compared to the propensity score method. As a sensitivity analysis, the company additionally presented the results of a comparison of the arms without adjustment for both comparisons. For further outcomes on morbidity and health-related quality of life, the company exclusively used the results of the STARTRK-2 study, without performing a comparison with crizotinib. For outcomes on the tolerability, the company stated to perform a "naive comparison" of entrectinib versus crizotinib. However, it compared the tolerability profile of entrectinib observed in the STARTRK-2 study with general data on crizotinib for selected AEs only. Overall, the company derived a hint of a non-quantifiable added benefit for entrectinib.

2.3.2 Assessment of the evidence presented by the company

The data presented by the company in Module 4 A are unsuitable for the benefit assessment of entrectinib versus the ACT crizotinib. This is explained below.

Analysis populations of the STARTRK-2 study unsuitable for deriving the added benefit

As described in Section 2.3.1, the company presented different analysis populations for the benefit and harm outcomes. Moreover, the number of considered patients varies depending on the data cut-off and the time by which patients were included in the analysis population (ECOD). Overall, the exact composition of the analysis populations formed by the company is not comprehensible on the basis of the data provided by the company in the dossier, among other reasons because the figure on the patient flow presented by the company in the dossier refers to the data cut-off of 31 May 2018 (NDA) and the pooled analysis populations of the STARTRK-2, STARTRK-1 and ALKA-372-001 studies. A corresponding figure of the patient flow would have been useful and necessary to comprehend the formation of the corresponding analysis populations, particularly for the most recent analysis populations for the benefit outcomes (analysis population 2, data cut-off of 1 May 2019) and the harm outcomes (data cut-off of 31 October 2018). However, the company provided no such figure in the dossier.

Moreover, as described in Section 2.3.1, the company restricted the patient population with ROS1-positive NSCLC of the STARTRK-2 study to patients with follow-up ≥ 12 months after initial response for analyses on the outcomes in the categories "mortality", "morbidity" and "health-related quality of life" (ROS1 EE analysis population), but not for analyses on the outcome category "side effects" (ROS1 SE population). The EPAR [15] shows that a follow-up of ≥ 6 months after initial response was considered for the principally relevant analysis population 2, and not ≥ 12 months after initial response as stated by the company in Module 4 A. The sole consideration of patients with a follow-up period ≥ 6 months after initial response is not adequate insofar as unresponsive patients would not be considered in the analysis population, which may have a relevant impact on the results. Information on whether and if so, how many unresponsive patients were not included in this analysis population is not available.

Moreover, the effects on the analysis results for the benefit outcomes caused by the restriction of the patient population through the specification of a minimum follow-up period are unclear, as no information is available on which patients were not included in the analysis population due to this criterion. This approach means that recordings available for patients without a corresponding follow-up after initial response or for patients who have not shown any response yet 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. The company did not address this issue in its dossier.

In addition to the exclusion criterion follow-up < 6 or < 12 months after initial response, the ROS1 EE analysis population is also restricted by further exclusion criteria (pretreatment with a ROS1 inhibitor, ECOG PS > 2 and ROS1 biomarkers not permitted). However, the exclusion

criteria applied by the company and thus the composition of the ROS1 EE analysis population are not comprehensible on the basis of the data provided by the company in the dossier (see above).

Comparisons presented by the company are unsuitable for the derivation of the added benefit

As described in Section 2.3.1, in order to compare entrectinib with the ACT crizotinib in adults with ROS1-positive, ROS1 inhibitor-naive advanced NSCLC, the company compared the results of analysis population 1 of the STARTRK-2 study at the data cut-off of 1 January 2019 with the results of the cohort from the Flatiron Health Database or the EUCROSS study on crizotinib for the outcomes "overall survival" and "PFS" only. To derive the added benefit of entrectinib, the company primarily used the results of the comparison versus the Flatiron Health Database for the outcomes "overall survival" and "PFS".

Both comparisons presented by the company are unsuitable for the present benefit assessment for the following reasons:

In addition to the described uncertainties regarding the restriction of the patient population of the STARTRK-2 study (see above), it is unclear why the company used analysis population 1 of the STARTRK-2 study (N = 78) and not the larger analysis population (analysis population 2 at the data cut-off of 1 May 2019, N = 145) for both comparisons versus crizotinib, as analysis population 2 included almost twice as many patients as analysis population 1. Although in the dossier, the company states that it considers analysis population 2 to be the most relevant one, it does not justify its approach of using analysis population 1 of the STARTRK-2 study for both comparisons.

Moreover, information on whether the company considered the follow-up time of ≥ 12 months after initial response specified for analysis population 1 of the STARTRK-2 study when selecting patients from the Flatiron Health Database or whether it could have considered it is not available. The follow-up time of ≥ 12 months after initial response specified in STARTRK-2 was not considered in the EUCROSS study, since data on a corresponding analysis population are missing for this study.

Irrespective of this, this was a comparison of individual arms from different studies in each case. Although an adjustment was made in the analysis with regard to potentially relevant effect modifiers or prognostic factors, the results are subject to inherent uncertainty due to the lack of randomization, so an added benefit can only be derived if the effects are sufficiently large. For both comparisons on overall survival presented by the company, the observed effects were not large enough that they could not be caused by systematic bias alone. That there could be a systematic bias in the results is also shown by the fact that the survival time analyses of patients differed notably between the Flatiron Health Database and the EUCROSS study. For example, patients from the Flatiron Health Database have a significantly worse prognosis under treatment with crizotinib than patients treated with crizotinib in the EUCROSS study.

2.4 Results on added benefit

There are no suitable data for the assessment of the added benefit of entrectinib in the comparison with the ACT crizotinib in adult patients with ROS1-positive advanced NSCLC who had not been pretreated with ROS1 inhibitors. Hence, this resulted in no hint of an added benefit of entrectinib in comparison with crizotinib; 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 crizotinib is summarized in Table 7.

Table 7: Entrectinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with ROS1-positive advanced NSCLC previously not treated with a ROS1 inhibitor[b]	Crizotinib	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. b: For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; ROS1: c-ros oncogene 1		

The assessment described above differs from that of the company, which, on the basis of the results of the STARTRK-2 study and the comparison of single-arm studies (primarily based on the comparison of STARTRK-2 vs. the Flatiron Health Database), derived a hint of a non-quantifiable added benefit for entrectinib for the outcomes “overall survival” and “tumour response” (PFS and intracranial response).

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.

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