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

Addendum to Commission A19-90[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ePAS	extended primary analysis set
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFS	infantile fibrosarcoma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRC	independent review committee
NTRK	neurotrophic tyrosine receptor kinase
SAE	serious adverse event

1 Background

On 25 February 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-90 (Larotrectinib – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") primarily used the pooled results of the studies LOXO-TRK-14001, NAVIGATE and SCOUT for the extended primary analysis set 2 (ePAS2) at the data cut-off from 30 July 2018 for the assessment of larotrectinib in adult and paediatric patients with solid tumours that display a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options.

In its comment from 5 February 2020, the company presented a more recent summarizing analysis of the studies on the data cut-off from 15 July 2019 [3,4].

The G-BA commissioned IQWiG with the assessment of the results on individual tumour entities from the presented data at the data cut-off from 15 July 2019.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment of the data on larotrectinib subsequently submitted

- Section 2.1 describes the data cut-off and the analysis population on the data subsequently submitted.
- Section 2.2 summarizes the relevant results of the data subsequently submitted.
- Section 2.3 summarizes the conclusion on the added benefit under consideration of the data subsequently submitted.

Analogous to its approach in the dossier, the company did not provide a presentation of the results for all outcomes separated by tumour entities for the new data cut-off from 15 July 2019. Effect estimations on the comparison of larotrectinib with the appropriate comparator therapy (ACT) best supportive care (BSC) were neither available for a consideration separated by tumour entity, nor for the population pooled according to tumour entities, nor for patients with primary tumours of the central nervous system (CNS). The derivation of an added benefit in comparison with the ACT is therefore not possible.

In its comments, as in its dossier, the company primarily addressed a pooled analysis of all tumour entities (without patients with primary CNS tumours). In contrast to the company's approach, the present addendum also considers the results separated by tumour entity for the reasons stated in Section 2.3.1.2 of the dossier assessment [1]. However, the data subsequently submitted contained such a separate presentation of the results for all tumour entities only for one outcome (overall survival). The presentation available for the outcome "adverse events (AEs)" was only partly separated by tumour entity.

2.1 Description of the data cut-off and of the analysis population

In its comments, the company presented summarizing analyses of the studies LOXO-TRK-14001, NAVIGATE and SCOUT for the data cut-off on 15 July 2019. As in the dossier, the company based its analyses and conclusions primarily on the ePAS population, which it referred to as "ePAS4" for the current data cut-off. It was not clear from the information provided in the comments how the company operationalized the ePAS4 population. It is assumed for the present addendum that the operationalization concurred with that used in the dossier, i.e. that the ePAS4 population comprises all patients with NTRK gene fusion, regardless of their tumour entities (except patients with primary CNS tumours), from the studies LOXO-TRK-14001, NAVIGATE and SCOUT who met the following criteria:

- administration of ≥ 1 dose of larotrectinib
- ≥ 1 measurable lesion (as defined by Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1) at baseline as evaluated by the investigator
- independent review committee (IRC) assessment available

According to information in the comments, the median observation period for overall survival was 15.8 months for the ePAS4. The median treatment period with larotrectinib for the ePAS4 population was 11.2 months.

In addition to the ePAS4, the company also presented results on 24 patients with primary CNS tumours. The median observation period for overall survival for this population was 6 months. The median treatment period with larotrectinib for the population with primary CNS tumours was 5.5 months.

The company used a different population for AEs. This analysis population referred to as "safety population" comprised all patients with NTRK gene fusion who had received at least one dose of larotrectinib (including patients with primary CNS tumours). 208 patients were analysed in this population.

2.1.1 Patient characteristics

Table 1 shows the proportions of patients included in the ePAS4 separated by tumour entity.

Table 1: Overview of the patient populations included in the larotrectinib studies (ePAS4 analysis population)

	Pooled analysis of the studies LOXO-TRK-14001, NAVIGATE and SCOUT (ePAS4) (data cut-off 15 July 2019) n (%)
Total	N = 164[a]
Soft tissue sarcoma	36 (22)
Infantile fibrosarcoma	32 (20)
Thyroid cancer	27 (16)
Salivary gland cancer	21 (13)
Lung cancer	13 (8)
NSCLC	ND
SCLC	ND
Colorectal cancer	8 (5)
Melanoma	7 (4)
Breast cancer	5 (3)
Gastrointestinal stromal tumour	4 (2)
Bone sarcoma	2 (1)
Cholangiocarcinoma	2 (1)
Pancreatic cancer	2 (1)
Appendix cancer	1 (< 1)
Congenital mesoblastic nephroma	1 (< 1)
Liver carcinoma	1 (< 1)
Prostate cancer	1 (< 1)
Cancer of unknown primary	1 (< 1)
Primary CNS tumour	0[b]

a. Number of included patients with NTRK gene fusion (except patients with primary CNS tumours) who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator, IRC assessment available.
b. The studies included a total of 24 patients with primary CNS tumours with NTRK gene fusion who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator. Patients with primary CNS tumours are not included in the ePAS4 analysis population.

CNS: central nervous system; ePAS: extended primary analysis set; IRC: independent review committee; n: number of patients with the respective tumour histology; N: number of analysed patients; ND: no data; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; SCLC: small cell lung cancer

At the data cut-off from 15 July 2019, the ePAS4 population included 164 patients, and hence 71 more than the ePAS2, which was the basis for the dossier assessment. In addition, the new data cut-off included 24 patients with primary CNS tumours, which were not part of the ePAS4 analysis population.

Also at the new data cut-off, notable differences were shown regarding the proportions of the patients included per tumour entity, based on 1 to at most 36 patients. As was the case for the

previous data cut-off, proportions of > 10% each were shown only for the tumour entities "infantile fibrosarcoma (IFS)", "thyroid cancer", "salivary gland cancer" and "soft tissue sarcoma".

There was no information on demographic and clinical characteristics of the patients separated by tumour entity. Demographic and clinical characteristics of the patients with primary CNS tumours, as well as on the pooled ePAS4 analysis population, are presented in Table 5 in Appendix A.

2.1.2 Risk of bias

There are no effect estimations on the comparison of larotrectinib with the ACT. The risk of bias across studies and the outcome-specific risk of bias are therefore not assessed.

2.2 Results

Table 2 and Table 3 summarize the results on the data subsequently submitted on larotrectinib. A Kaplan-Meier curve on the outcome "overall survival" separated by tumour entity is only available for patients with primary CNS tumours (see Appendix B). There are no lists of common adverse events (AEs), serious AEs (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4) separated by tumour entity. The company again did not conduct any comparative analyses versus the ACT.

Table 2: Results (overall survival) – larotrectinib, ePAS4 population (multipage table)

Tumour histology	N[a]	Median time to event in months [min, max] Patients with event n (%)
Overall survival		
Pooled analysis of the studies LOXO-TRK-14001, NAVIGATE and SCOUT (data cut-off 15 July 2019)		
Total	164	NA [0.46[b]; 51.58[b]] 25 (15)
Soft tissue sarcoma	36	NA [0.46[b]; 51.58[b]] 4 (11)
Infantile fibrosarcoma	32	NA [4.63[b]; 38.31[b]] 0 (0)
Thyroid cancer	27	27.79 [1.18[b]; 45.40[b]] 6 (22)
Salivary gland cancer	21	NA [4.07; 48.30[b]] 2 (10)
Lung cancer[c]	13	NA [4.76[b]; 39.59[b]] 2 (15)
Colorectal cancer	8	36.47 [2.17[b]; 36.47] 3 (38)
Melanoma	7	NA [1.41[b]; 37.52[b]] 2 (29)
Breast cancer	5	NA [0.95[b]; 11.99[b]] 0 (0)

Table 2: Results (overall survival) – larotrectinib, ePAS4 population (multipage table)

Tumour histology	N[a]	Median time to event in months [min, max] Patients with event n (%)
Overall survival		
Pooled analysis of the studies LOXO-TRK-14001, NAVIGATE and SCOUT (data cut-off 15 July 2019)		
Gastrointestinal stromal tumour	4	44.35 [21.42[b]; 44.35] 1 (25)
Bone sarcoma	2	NA [14.06[b]; 23.85[b]] 0 (0)
Cholangiocarcinoma	2	17.63 [1.84; 33.41] 2 (100)
Pancreatic cancer	2	14.13 [7.85[b]; 14.13] 1 (50)
Appendix cancer	1	NA [7.66[b]; 7.66[b]] 0 (0)
Congenital mesoblastic nephroma	1	NA [23.69[b]; 23.69[b]] 0 (0)
Liver carcinoma	1	1.12 [1.12; 1.12] 1 (100)
Prostate cancer	1	NA [6.44[b]; 6.44[b]] 0 (0)
Cancer of unknown primary	1	11.96 [11.96; 11.96] 1 (100)
Primary CNS tumour[d]	24	NA [1.9[b]; 21.4[b]] 1 (4)

a. Data are based on the ePAS4 population: patients with NTRK gene fusion (except patients with primary CNS tumours) who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator, IRC assessment available.
b. Censored observation.
c. Includes patients with NSCLC and SCLC, separate results are not available.
d. SAS3 population, not part of the ePAS4.

CNS: central nervous system; ePAS: extended primary analysis set; N: number of analysed patients; n: number of patients with event; NA: not achieved; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; SCLC: small cell lung cancer

Table 3: Results (side effects) – larotrectinib, safety population with NTRK gene fusion

Tumour histology	Patients with event n (%)				
	N[a]	AEs	SAEs	Severe AEs (CTCAE grade 3–4)	Discontinuation due to AEs
Pooled analysis of the studies LOXO-TRK-14001, NAVIGATE and SCOUT (data cut-off 15 July 2019)					
Total	208	205 (99)			
Soft tissue sarcoma	39	38 (97)			
Infantile fibrosarcoma	34	34 (100)			
Salivary gland cancer	23	23 (100)			
Lung cancer[b]	15	15 (100)			
Colorectal cancer	8	8 (100)			
Thyroid cancer	89[c]	87 (98)[c]	64 (31)[c]	106 (51)[c]	10 (5)[c]
Melanoma					
Breast cancer					
Gastrointestinal stromal tumour					
Bone sarcoma					
Cholangiocarcinoma					
Pancreatic cancer					
Appendix cancer					
Congenital mesoblastic nephroma					
Liver carcinoma					
Prostate cancer					
Cancer of unknown primary					
Primary CNS tumour					

a. Information is based on the safety population with NTRK gene fusion (Overall NTRK Fusion Cancers Safety Set). This comprises all patients with NTRK gene fusion who had received ≥ 1 dose of larotrectinib (including patients with primary CNS tumours).
b. Includes patients with NSCLC and SCLC, separate results are not available.
c. No separate data available for individual tumour histologies, only pooled data across the corresponding tumour histologies.

AE: adverse event; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with event; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; SAE: serious adverse event; SCLC: small cell lung cancer

Mortality

Overall survival

In the ePAS4 analysis population, a total of 25 patients had died at the data cut-off from 15 July 2019. In about half of the tumour entities presented by the company, the median overall survival was reached at the present data cut-off (see Table 2). As was the case in the dossier assessment, the proportions of the patients who had died by then are not interpretable due to the low number of patients and the missing information on the median observation period separated by tumour entity.

Regardless of the fact that the company presented results on overall survival on the ePAS4 separated by tumour entity, the results cited by the company do not allow a classification of the results, as no comparative data are available.

Morbidity and health-related quality of life

Patient-reported outcomes on morbidity and health-related quality of life

Analogous to the approach in the dossier, the company provided the prespecified descriptive presentation of the respective total scores and of the mean changes from baseline for the individual documentation times pooled across all tumour entities for patient-reported outcomes also for the ePAS4. In addition, the company presented post hoc analyses on the best change from baseline or on responder analyses. The presentation of the post hoc analyses was selective and thus incomplete, however.

The company presented analyses separated by tumour entity only for 2 scales (fatigue and physical functioning) of the European Organisation for Research and Treatment of Cancer-Core 30 (EORTC QLQ-C30) and for one scale (mobility) of the European Quality of Life-5 Dimensions (EQ-5D), for example. The analyses presented did not resolve the problems described in the dossier assessment.

Due to the lack of comparative data, the selective and thus incomplete presentation, which was not completely separated by tumour entity, it cannot be inferred from the analyses presented whether larotrectinib has an advantage or a disadvantage over BSC.

Sustained delay of surgical resections that are likely to result in severe morbidity

In the data subsequently submitted, the company presented a descriptive list of over 31 paediatric patients, for whom there was no curative therapy other than amputation or disfiguring surgery when they were included in the SCOUT study. As in the dossier, the company did not describe how it operationalized the outcome “sustained delay of a surgical resection that is likely to result in severe morbidity”. Besides, not all data provided in the list are comprehensible and the company again did not provide any supportive information to help interpret or classify these data. Hence, the data are only described briefly below.

The company’s list on the available data cut-off included 21 paediatric patients with IFS and 10 with soft tissue sarcoma. The median treatment period of all 31 patients at the available data cut-off was about 12 months. The company did not provide any observation periods for these patients. At the time point of the available data cut-off, 11 patients had discontinued treatment with larotrectinib, and 6 patients had had progression.

The information provided by the company also showed that 11 of the 31 paediatric patients had surgery after treatment with larotrectinib. In one case, the surgical resection led to motor and sensory deficits; the company did not report on the severity of this morbidity. R0 resection was achieved in 7 of the 11 patients operated on. One patient had 2 operations with the respective documentation of R1 and R0. 20 patients had not had surgery until the available data cut-off.

Side effects

Serious adverse events, severe adverse events (CTCAE grade 3–4), discontinuation due to adverse events

In the data subsequently submitted, the company did not present any results separated by tumour entity for any of the patient-relevant outcomes (SAEs, severe AEs [CTCAE grade 3–4], discontinuation due to AEs) of the category of side effects (see Table 3). Only for the overall rate of AEs, separate data were available for the tumour entities "soft tissue sarcoma", "salivary gland cancer", "lung cancer", "colon cancer" and "IFS". These data did not refer to the ePAS4 analysis population, but to all patients with NTRK gene fusion who had received at least one dose of larotrectinib. For patients with other tumour entities than the ones mentioned and for the outcomes "SAEs", "severe AEs (CTCAE grade 3–4)" and "discontinuation due to AEs", only results pooled according to tumour entities and studies were available.

Due to the lack of comparative data, the selective and thus incomplete presentation, which was not completely separated by tumour entity, the results on side effects of larotrectinib cannot be classified.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of larotrectinib from dossier assessment A19-90.

The therapeutic indication of larotrectinib is heterogeneous and comprises different tumour entities and, correspondingly, patients with different prognoses. However, the documents presented by the company do not include a presentation of the data completely separated according to tumour entities. Effect estimations on the comparison of larotrectinib with the ACT BSC are neither available for a separate consideration according to tumour entity, nor for the ePAS4 study population pooled by the company. The derivation of an added benefit in comparison with the ACT is therefore not possible.

The following Table 4 shows the result of the benefit assessment of larotrectinib under consideration of dossier assessment A19-90 and the present addendum.

Table 4: Larotrectinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult and paediatric patients with solid tumours that display an NTRK gene fusion[b], who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options	BSC[c]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. The considered studies on larotrectinib are ongoing, so that patients are still being enrolled. At the time point of the data cut-off on 15 July 2019, information was only available on patients with the following tumour entities: soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, primary CNS tumour, lung cancer, melanoma, colorectal cancer, gastrointestinal stromal tumour, bone sarcoma, cholangiocarcinoma, congenital mesoblastic nephroma, appendix cancer, breast cancer, pancreatic cancer, liver carcinoma, prostate cancer. Some of the tumour entities mentioned only include individual patients (see Table 1).
c. 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; CNS: central nervous system; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase

The G-BA decides on the added benefit.

3 References

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

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4. Bayer Vital. Stellungnahme zum IQWiG-Bericht Nr. 866: Larotrectinib (solide Tumore mit einer neurotrophen Tyrosin-Rezeptor-Kinase [NTRK]-Genfusion); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-90. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/502/#beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A – Characteristics of the ePAS4 analysis population and of the patients with primary CNS tumours

Table 5: Characteristics of the ePAS4 analysis population and of the patients with primary CNS tumours – larotrectinib (multipage table)

Study	**Larotrectinib (15 July 2019)**	
Characteristics	**ePAS4**	**Primary CNS tumour**
Category	**N[a] = 164**	**N[b] = 24**
LOXO-TRK-14001	13 (8)	0 (0)
NAVIGATE	98 (60)	7 (29)
SCOUT	53 (32)	17 (71)
Age category, n (%)		
Toddlers and infants (28 days – < 24 months)	31 (19)	1 (4)
Children (2 – < 12 years)	19 (12)	13 (54)
Adolescents (12 – < 18 years)	5 (3)	6 (25)
Adults	109 (66)	4 (17)
Sex [F/M], %	51/49	54/46
Family origin, n (%)		
White	126 (77)	19 (79)
Asian	9 (5)	2 (8)
Black	5 (3)	2 (8)
Other[c]	24 (15)	1 (4)
ECOG PS, n (%)		
0	80 (49)	15 (63)
1	62 (38)	7 (29)
2	19 (12)	1 (4)
3	3 (2)	1 (4)
Disease stage at initial diagnosis, n (%)		
I	22 (13)	0 (0)
II	29 (18)	0 (0)
III	38 (23)	1 (4)
IV	47 (29)	0 (0)
Unknown/not reported	28 (17)	23 (96)
Time since initial diagnosis [years]		
Mean (SD)	3.8 (5.3)	2.2 (2.0)
Median [min; max]	1.7 [0.02; 31.5]	1.8 [0.32; 9.6]
Disease stage at start of study, n (%)		
Locally advanced	42 (26)	0 (0)
Metastatic	122 (74)	0 (0)
Other	0 (0)	24 (100)

Table 5: Characteristics of the ePAS4 analysis population and of the patients with primary CNS tumours – larotrectinib (multipage table)

Study	**Larotrectinib (15 July 2019)**	
Characteristics	**ePAS4**	**Primary CNS tumour**
Category	**N[a] = 164**	**N[b] = 24**
Prior therapy, n (%)		
Prior anticancer treatment	154 (94)	24 (100)
Prior surgery	125 (76)	16 (67)
Prior radiotherapy	75 (46)	11 (46)
Prior systemic treatment	127 (77)	21 (88)
0	36 (22)	3 (13)
1–2	84 (51)[d]	16 (67)[d]
≥ 3	44 (27)	5 (21)
Number of prior systemic regimens		
Mean (SD)	1.8 (1.8)	1.8 (1.6)
Median [min; max]	1.0 [0; 10]	1.0 [0; 6]
Treatment discontinuation, n (%)	74 (45)	15 (63)
Study discontinuation, n (%)	ND	ND

a. Number of included patients with NTRK gene fusion (except patients with primary CNS tumours) who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator, IRC assessment available.
b. Number of included patients with primary CNS tumours with NTRK gene fusion who meet the following criteria: administration of ≥ 1 dose of larotrectinib, ≥ 1 measurable lesion at baseline as evaluated by the investigator.
c. Institute's calculation, includes the categories: native Americans and Alaskans, Hawaiians and other Pacific Islanders, multiple family origin, others, and not reported.
d. Institute's calculation.

CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ePAS: extended primary analysis set; F: female; IRC: independent review committee; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of analysed patients; ND: no data; NTRK: neurotrophic tyrosine receptor kinase; SD: standard deviation

Appendix B – Kaplan-Meier curve at the data cut-off on 15 July 2019

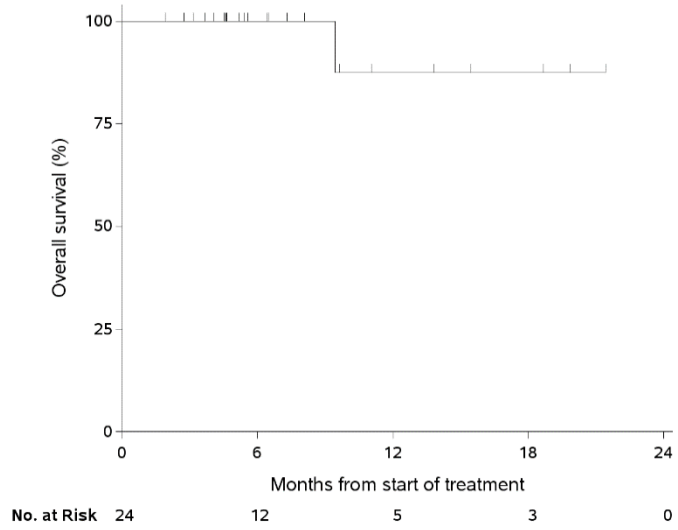

Figure 1: Kaplan-Meier curve on the outcome “overall survival” for patients with primary CNS tumours at the data cut-off from 15 July 2019