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Addendum

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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum:²

- Christoph Schürmann
- Beate Wieseler

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List of abbreviations

Abbreviation	Meaning
ALK	anaplastic lymphoma kinase
BSC	best supportive care
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	<i>Gemeinsamer Bundesausschuss</i> (Federal Joint Committee)
HRQoL	health-related quality of life
IQWiG	<i>Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen</i> (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
RCT	randomized controlled trial

1 Background

On 15 November 2012 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a benefit assessment of crizotinib pursuant to § 35a Social Code Book V (Commission No. A12-15). The assessment was made on the basis of a dossier of the pharmaceutical company (hereinafter abbreviated to “the company”). On 15 February 2013 the G-BA published IQWiG’s dossier assessment of 13 February 2013 [1] for comment.

In the commenting procedure, on 7 March 2013 the company submitted further data to the G-BA. On 2 April 2012 the G-BA commissioned IQWiG with the assessment of the results on the outcomes of symptoms (morbidity) and health-related quality of life (HRQoL) under consideration of the information from the dossier and from the comment of the company.

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

The present addendum to Commission A12-15 was made on the basis of the following data sources:

- The company’s dossier of 15 November 2012 [2]
- Documents subsequently submitted during the commenting procedure by the company on 7 March 2013 (in particular the clinical study report for Study PROFILE 1007, as well as additional analyses of this study prepared by the company for its comment on the dossier assessment; citations 17 und 23 in [3]).

The present addendum initially describes the analyses presented by the company and justifies the selection of analyses for the determination of the extent of added benefit for the outcomes of symptoms (as a characteristic of morbidity) and HRQoL. Then the results are described and the extent of added benefit at outcome level is determined for symptoms and HRQoL.

2 Results on symptoms and health-related quality of life

With the comment on IQWiG's dossier assessment the company presented additional information on results for the questionnaires EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D from Study PROFILE 1007.

Besides HRQoL, QLQ-C30 covers general symptoms of cancer; QLQ-LC13 complements this questionnaire with specific symptoms of lung cancer. EQ-5D is a questionnaire on HRQoL.

The symptom scales of QLQ-C30 and QLQ-LC13 are used for the assessment of morbidity (symptoms). The further scales of QLQ-C30, as well as EQ-5D, are used for the assessment of HRQoL.

As already described in the dossier assessment, Study PROFILE 1007 is suited to investigate the added benefit of crizotinib versus chemotherapy (docetaxel/pemetrexed) in the chemotherapy population. This is a population of patients with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) in whom chemotherapy is indicated (in particular, this can refer to patients with Eastern Cooperative Oncology Group [ECOG] performance status 0, 1, and potentially 2). The study cannot provide any conclusions regarding the comparison of crizotinib und best supportive care (BSC) in the BSC population in whom chemotherapy is not indicated (in particular, this can refer to patients with ECOG performance status 4, 3, and potentially 2). The company presented no new data for this population in its comment. The present addendum can therefore exclusively provide conclusions on the chemotherapy population.

2.1 Selection of analyses for benefit assessment

The company presented analyses for different operationalizations for the symptom scales QLQ-C30 and QLQ-LC13. The statistical analysis plan envisaged the analysis of a combined outcome, namely, the time to first occurrence of a deterioration of the symptoms of pain (chest), cough or dyspnoea. Deterioration was regarded to be a negative change of at least 10 points on one of the relevant scales of questionnaire QLQ-LC13. The company assessed a change of 10 points to be relevant; this was adequately explained by reference to a study that has demonstrated this on an empirical basis [4]. In addition to the results for the combined outcome the single components are also presented. As the combined outcome only covers part of the symptoms, the results do not describe a general added benefit with regard to symptoms, but exclusively an added benefit related to the symptoms included.

Beyond the analysis of this combined outcome, analyses of mean changes from the start to the end of the study are available for both the symptom subscales of QLQ-C30 and for QLQ-LC13 in accordance with the analysis plan (continuous effect measure "difference in means"). A justified irrelevance threshold for the group difference is not available. For the interpretation of relevant effects for the single symptoms, in addition to the analysis plan the

company used responder analyses with the validated response criterion of 10 points [4]. The company presented 2 types of analyses in which this response criterion of 10 points was used to assess the improvement of symptoms. In the first analysis, the proportion of patients was investigated who achieved a mean improvement during the course of the study of at least 10 points over all time points at which they filled in the questionnaire. This analysis in the form of a responder analysis represents an adequate approach to the interpretation of scales [5]. In the second analysis the frequencies of treatment cycles were considered in which a patient achieved an improvement of at least 10 points. The company presented the differences in frequencies (rates) between treatment groups (however, data are missing on the rates in the respective treatment groups). In the present addendum the originally planned analysis of continuous data is at first shown. To assess added benefit, the responder analyses following the definition named first is then used. It should also be noted that, regarding the significance of results, the results of these responder analyses are consistent with those of the differences in rates and thus seem consistent (not presented further).

Aspects of HRQoL were investigated with the questionnaires EORTC QLQ-C30 and EQ-5D. As with the symptom-related scales (see above), analyses of differences in means, responder analyses and differences in rates were investigated with the relevant subscales of QLQ-C30. Accordingly, only responder analyses were used for assessment of added benefit. For EQ-5D analyses were available for the single components for which the proportion of patients was calculated who selected the respective response categories (no problems, some problems, extreme problems). However, the present results of the analysis only refer to a small number of patients, namely those who terminated treatment during the study (about 40% of the patients included). Because of the high proportion of patients who were not considered in the analysis, these analyses cannot be used for the assessment of added benefit. In addition, the company presented analyses of differences in means for the sum score and the visual analogue scale. These results are not considered for the assessment either. The sum score can only be interpreted as a “utility value” and not as an actual benefit parameter. The visual analogue scale represents the global health status. The related result is not assessed, as the aspects are already represented by the corresponding subscale of QLQ-C30. It should also be noted that the effect estimates of both scales are consistent with regard to statistical significance and clinical relevance.

In all analyses named above, observations of patients were only considered at most to the first of the following events: a) progression, b) termination of treatment, c) termination of observation under treatment. Consequently the effects observed cannot be transferred to the time after progression and only describe the treatment effects as long as no progression occurs according to the criteria of the study.

2.2 Risk of bias

Table 1 shows the risk of bias at study level (for reasons see dossier assessment A12-15 [1]) as well as the risk of bias of the results on symptoms and HRQoL. The risk of bias is already high at study level. The outcome-related risk of bias is to be regarded as high, due in particular to the lack of blinding and the high proportion of patients who prematurely discontinued chemotherapy.

Table 1: Risk of bias at study and outcome level – RCT, direct comparison - crizotinib versus chemotherapy, chemotherapy population

Study	Study level	Outcomes			
		Deterioration of symptoms ^a	Improvement of symptoms ^b	Health-related quality of life (disease-specific instruments) ^c	Health-related quality of life (generic instruments EQ-5D) ^e
PROFILE 1007	high	high ^d	high ^d	high ^d	- ^e
<p>a: Time to deterioration of at least one of the symptoms “pain (chest)”, “dyspnoea” or “cough”, measured as deterioration of at least 10 points on one of the relevant scales of EORTC QLQ-LC13.</p> <p>b: Measured via the symptom scales of disease-specific instruments (EORTC QLQ-C30 and QLQ-LC13); 2 analyses: continuous data and responder analysis (response was defined as the mean improvement of at least 10 points during the observation period compared with the start of study).</p> <p>c: Measured via quality-of-life scales of the disease-specific instrument EORTC QLQ-C30.</p> <p>d: The risk of bias is already high at study level. In particular the outcome-related bias is to be regarded as high due to the lack of blinding and the high proportion of patients who prematurely discontinued chemotherapy.</p> <p>e: For the single components of EQ-5D, results were only available in which a high proportion of patients (> 30%) had not been taken into account. The results for the sum score and visual analogue scale are not considered in this benefit assessment.</p> <p>EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D: European Quality of Life-5 Dimensions; QLQ-LC13: Quality of Life Questionnaire-LC13; RCT: randomized controlled trial</p>					

As only one study was available for the assessment of symptoms and HRQoL and the validity was additionally weakened by a high risk of bias, at best “hints” could be inferred from the data.

2.3 Results

Table 2 displays the continuous data for symptom scales and HRQoL. Table 3 and Table 4 show the responder analyses for symptoms (all scales) and for HRQoL, as well as the combined outcome on symptoms.

Table 2: Results (continuous data) on morbidity (symptoms) and health-related quality of life – RCT, direct comparison – crizotinib versus chemotherapy, chemotherapy population

Outcome category		Crizotinib			Chemotherapy		Crizotinib vs. chemotherapy	
Outcome	N ^a	Values at start of study ^b mean [95% CI]	Change from start of study ^c mean [95% CI]	N ^a	Values at start of study ^b mean [95% CI]	Change from start of study ^c mean [95% CI]	Difference in means ^c [95% CI]; p-value	Hedges' g [95% CI]; p-value
PROFILE 1007								
Morbidity								
EORTC QLQ C30 symptom scales ^e								
Fatigue	162	38.3 [34.5; 42]	-7.18 [-10.12; -4.24]	151	36.1 [32.2; 40]	4.73 [0.94; 8.51]	-11.91 [-16.7; -7.12] p < 0.001	-0.55 [-0.78; -0.33] p < 0.001
Nausea and vomiting	162	8.4 [6.2; 10.6]	1.96 [0.11; 3.82]	151	11.7 [8.9; 14.4]	1.38 [-1.35; 4.11]	0.58 [-2.72; 3.89] p = 0.729	0.04 [-0.18; 0.26] p = 0.728
Pain	162	23.9 [20.1; 27.7]	-10.19 [-12.93; -7.45]	151	28.0 [23.8; 32.2]	2.70 [-0.88; 6.28]	-12.89 [-17.4; -8.38] p < 0.001	-0.63 [-0.86; -0.41]; p < 0.001
Dyspnoea	162	31.1 [26.8; 35.5]	-10.66 [-13.75; -7.58]	150	32.5 [28.2; 36.9]	2.22 [-1.86; 6.31]	-12.89 [-18.01; -7.77] p < 0.001	-0.56 [-0.78; -0.33] p < 0.001
Insomnia	161	22.6 [18.5; 26.6]	-7.03 [-9.59; -4.48]	151	27.8 [23.6; 32]	1.57 [-1.86; 5]	-8.61 [-12.88; -4.33] p < 0.001	-0.45 [-0.67; -0.22] p < 0.001
Appetite loss	162	24.4 [20; 28.9]	-5.23 [-7.83; -2.64]	151	23.3 [18.9; 27.7]	-0.07 [-3.52; 3.38]	-5.17 [-9.48; -0.85] p = 0.019	-0.27 [-0.49; -0.04] p = 0.019

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Table 2: Results (continuous data) on morbidity (symptoms) and health-related quality of life – RCT, direct comparison – crizotinib versus chemotherapy, chemotherapy population (continued)

Outcome category		Crizotinib			Chemotherapy		Crizotinib vs. chemotherapy	
Outcome	N ^a	Values at start of study ^b mean [95% CI]	Change from start of study ^c mean [95% CI]	N ^a	Values at start of study ^b mean [95% CI]	Change from start of study ^c mean [95% CI]	Difference in means ^c [95% CI]; p-value	Hedges' g [95% CI]; p-value
Morbidity								
EORTC QLQ C30 symptom scales ^d								
Constipation	161	14.8 [11; 18.7]	9.28 [6.27; 12.3]	150	16.9 [13; 20.7]	1.50 [-2.71; 5.71]	7.78 [2.61; 12.96] p = 0.003	0.33 [0.11; 0.56] p = 0.003
Diarrhoea	162	9.7 [6.8; 12.6]	9.60 [6.86; 12.35]	150	7.8 [5.3; 10.3]	-1.39 [-5.02; 2.23]	11.00 [6.46; 15.53] p < 0.001	0.54 [0.31; 0.76] p < 0.001
<i>Financial difficulties^g</i>	<i>162</i>	<i>28.5 [23.4; 33.6]</i>	<i>-8.08 [-11.07; -5.08]</i>	<i>149</i>	<i>27.3 [22.5; 32.1]</i>	<i>-3.74 [-7.58; 0.09]</i>	<i>-4.33 [-9.2; 0.53] p = 0.081</i>	<i>-0.20 [-0.42; 0.02] p = 0.080</i>
EORTC QLQ LC13 symptom scales ^e								
Dyspnoea	161	27.2 [23.8; 30.5]	-7.34 [-9.86; -4.82]	150	26.9 [23.2; 30.5]	5.01 [1.89; 8.12]	-12.34 [-16.34; -8.34] p < 0.001	-0.67 [-0.91; -0.46] p < 0.001
Pain (chest)	160	18.8 [15.3; 22.3]	-11.51 [-13.94; -9.09]	148	24.0 [19.7; 28.3]	1.60 [-1.58; 4.78]	-13.11 [-17.11; -9.11] p < 0.001	-0.73 [-0.96; -0.50] p < 0.001
Pain (arm and shoulder)	161	16.3 [12.5; 20.0]	-9.66 [-12.17; -7.15]	149	19.5 [15.1; 23.8]	1.58 [-1.71; 4.87]	-11.24 [-15.39; -7.10] p < 0.001	-0.60 [-0.83; -0.38] p < 0.001
Pain (other)	160	23.1 [18.9; 27.3]	-10.12 [-13.24; -7]	145	31.4 [26.7; 36.2]	0.55 [-3.54; 4.63]	-10.67 [-15.82; -5.52] p < 0.001	-0.46 [-0.68; -0.24] p < 0.001

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Table 2: Results (continuous data) on morbidity (symptoms) and health-related quality of life – RCT, direct comparison – crizotinib versus chemotherapy, chemotherapy population (continued)

Outcome category		Crizotinib			Chemotherapy		Crizotinib vs. chemotherapy	
Outcome	N ^a	Values at start of study ^b mean [95% CI]	Change from start of study ^c mean [95% CI]	N ^a	Values at start of study ^b mean [95% CI]	Change from start of study ^c mean [95% CI]	Difference in means ^c [95% CI]; p-value	Hedges' g [95% CI]; p-value
Morbidity								
EORTC QLQ LC13 symptom scales ^e								
Cough	161	38.2 [34; 42.4]	-17.83 [-20.53; -15.13]	150	42.2 [37.3; 47]	-5.23 [-8.73; -1.73]	-12.60 [-17.02; -8.18] p < 0.001	-0.63 [-0.86; -0.41] p < 0.001
Oral pain	161	5.5 [3.1; 7.9]	1.46 [-0.38; 3.30]	150	6.4 [3.5; 9.2]	6.85 [4.54; 9.17]	-5.39 [-8.35; -2.44] p < 0.001	-0.41 [-0.63; -0.18] p < 0.001
Dysphagia	161	7.1 [4.6; 9.6]	0.23 [-1.35; 1.82]	150	8.6 [5.4; 11.9]	3.20 [0.99; 5.40]	-2.96 [-5.68; -0.24] p = 0.033	-0.24 [-0.46; -0.02] p = 0.033
Peripheral neuropathy	161	14.0 [10.6; 17.4]	1.73 [-1.43; 4.88]	150	17.7 [13.5; 21.9]	9.19 [5.15; 13.22]	-7.46 [-12.58; -2.34] p = 0.004	-0.32 [-0.55; -0.10] p = 0.004
Alopecia	160	17.4 [12.6; 22.1]	-11.47 [-14.39; -8.55]	150	16.9 [12.3; 21.5]	4.27 [0.25; 8.28]	-15.74 [-20.7; -10.77] p < 0.001	-0.70 [-0.93; -0.48] p = < 0.001
Haemoptysis	161	2.4 [1.0; 3.9]	-1.37 [-2.84; 0.10]	150	3.7 [1.8; 5.6]	2.25 [0.37; 4.13]	-3.62 [-6.01; -1.23] p = 0.003	-0.34 [-0.56; -0.11] p = 0.003

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Table 2: Results (continuous data) on morbidity (symptoms) and health-related quality of life – RCT, direct comparison – crizotinib versus chemotherapy, chemotherapy population (continued)

Outcome category		Crizotinib			Chemotherapy		Crizotinib vs. chemotherapy	
Outcome	N ^a	Values at start of study ^b mean [95% CI]	Change from start of study ^c mean [95% CI]	N ^a	Values at start of study ^b mean [95% CI]	Change from start of study ^c mean [95% CI]	Difference in means ^c [95% CI]; P-value	Hedges' g [95% CI]; P-value
Health-related quality of life								
EORTC QLQ C30^f								
Global health status / HRQoL	162	57.2 [53.9; 60.5]	4.41 [1.65; 7.16]	151	58.1 [54.6; 61.5]	-5.43 [-8.93; -1.93]	9.84 [5.39; 14.28] p < 0.001	0.49 [0.27; 0.72] p < 0.001
Physical function	162	76.3 [73.1; 79.5]	4.34 [1.88; 6.80]	151	75.8 [72.4; 79.2]	-5.76 [-8.91; -2.61]	10.11 [6.12; 14.10] p < 0.001	0.56 [0.34; 0.79] P < 0.001
Role function	162	69.3 [64.9; 73.7]	1.92 [-1.24; 5.08]	151	66.6 [61.9; 71.2]	-6.83 [-10.94; -2.71]	8.75 [3.57; 13.92] p < 0.001	0.38 [0.15; 0.60] p = 0.001
Emotional factors	162	74.5 [71.3; 77.8]	6.85 [4.41; 9.30]	151	73.7 [70.4; 76.9]	1.80 [-1.37; 4.96]	5.06 [1.06; 9.06] p = 0.013	0.28 [0.06; 0.50] p = 0.013
Cognitive function	162	85.6 [82.7; 88.4]	0.05 [-2.27; 2.38]	151	83.6 [80.2; 87.1]	-3.61 [-6.65; -0.57]	3.67 [-0.16; 7.49] p = 0.061	0.21 [-0.01; 0.43] p = 0.060
Social function	162	68.0 [63.7; 72.2]	6.31 [2.96; 9.67]	151	67.1 [62.6; 71.6]	-2.45 [-6.64; 1.75]	8.76 [3.40; 14.12] p = 0.001	0.36 [0.14; 0.59] p = 0.001
EQ-5D		No evaluable data available						

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Table 2: Results (continuous data) on morbidity (symptoms) and health-related quality of life – RCT, direct comparison – crizotinib versus chemotherapy, chemotherapy population (continued)

a: Number of patients in the analysis at the end of study for the “PRO evaluable” analysis population; values at the start of the study may be based on other patient numbers.

b. Values at the start of study from an analysis of the “PRO evaluable population” (crizotinib : N = 165, chemotherapy: N = 162, in single scales deviations of +/- 1 patient in each treatment group.

c: Estimates from a mixed-effect model repeated measures (MMRM) with the following variables: intercept, therapy, therapy-time interaction, baseline EORTC QLQ C30 or LC13 score (plus duration since administration of first dose as a random effect).

d: EORTC QLQ C30 symptom scales, range 0-100, lower (decreasing) scores signify fewer symptoms; negative scores in the group comparison signify an advantage of Crizotinib.

e: EORTC QLQ LC13 symptom scales, range 0-100, lower (decreasing) scores signify fewer symptoms; negative scores in the group comparison signify an advantage of crizotinib.

f: EORTC QLQ C30 function scales, range 0-100, higher (increasing) scores signify better functionality; positive effects in the group comparison signify an advantage of crizotinib.

g: Financial difficulties are a component of the questionnaire but are not considered as part of morbidity (symptoms).

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C 30; EQ-5D: EuroQol-5D; HRQoL: health-related quality of life; N: number of analysed patients; RCT: randomized controlled trial

Table 3: Results (responder analyses) for morbidity (symptoms) and health-related quality of life – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Instrument	Crizotinib		Chemotherapy		Crizotinib vs. chemotherapy
Subscale	N	Patients with events ^a n (%)	N	Patients with events ^a n (%)	RR [95% CI] ^b ; p-value ^c
Morbidity					
EORTC QLQ-C30 symptom scales (improvement of symptoms)					
Fatigue	162	75 (46.3)	151	31 (20.5)	2.26 [1.58; 3.22] p < 0.001
Nausea and vomiting	162	25 (15.4)	151	28 (18.5)	0.83 [0.51; 1.36] p = 0.463
Pain	162	71 (43.8)	151	31 (20.5)	2.13 [1.49; 3.06] p < 0.001
Dyspnoea	162	66 (40.7)	151	31 (20.5)	1.98 [1.38; 2.86]; p = < 0.001
Insomnia	161	53 (32.9)	151	39 (25.8)	1.27 [0.90; 1.81] p = 0.170
Appetite loss	162	53 (32.7)	151	31 (20.5)	1.59 [1.09; 2.34] p = 0.015
Constipation	161	22 (13.7)	150	31 (20.7)	0.66 [0.40; 1.09] p = 0.101
Diarrhoea	162	22 (13.6)	150	23 (15.3)	0.89 [0.52; 1.52] p = 0.660
<i>Financial difficulties^d</i>	<i>162</i>	<i>51 (31.5)</i>	<i>149</i>	<i>30 (20.1)</i>	<i>1.56 [1.06; 2.31] p = 0.023</i>
EORTC QLQ-LC13 symptom scales (improvement of symptoms)					
Dyspnoea	161	63 (39.1)	150	26 (17.3)	2.26 [1.51; 3.36] p < 0.001
Pain (chest)	160	64 (40.0)	148	33 (22.3)	1.79 [1.26; 2.56] p = 0.001
Pain (arm or shoulder)	161	54 (33.5)	149	29 (19.5)	1.72 [1.16; 2.55] p = 0.005
Pain (other)	160	62 (38.8)	145	46 (31.7)	1.22 [0.90; 1.66] p = 0.200
Cough	161	89 (55.3)	150	50 (33.3)	1.66 [1.27; 2.16] p < 0.001
Oral pain	161	12 (7.5)	150	11 (7.3)	1.02 [0.46; 2.23] p = 0.968
Dysphagia	161	22 (13.7)	150	12 (8.0)	1.71 [0.88; 3.33] p = 0.110
Peripheral neuropathy	161	25 (15.5)	150	24 (16.0)	0.97 [0.58; 1.62] p = 0.909

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Table 3: Results (responder analyses) for morbidity (symptoms) and health-related quality of life – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population (continued)

Instrument	Crizotinib		Chemotherapy		Crizotinib vs. chemotherapy
Subscale	N	Patients with events ^a n (%)	N	Patients with events ^a n (%)	RR [95% CI] ^b ; p-value ^c
Morbidity					
EORTC QLQ-LC13 symptom scales (improvement of symptoms)					
Alopecia	160	45 (28.1)	150	29 (19.3)	1.45 [0.97; 2.19] p = 0.070
Haemoptysis	161	9 (5.6)	150	9 (6.0)	0.93 [0.38; 2.28] p = 0.877
Health-related quality of life					
EORTC QLQ-C30 (improvement of HRQoL)					
Global health status	162	69 (42.6)	150	31 (20.7)	2.06 [1.44; 3.00] p < 0.001
Physical function	162	44 (27.2)	151	18 (11.9)	2.28 [1.38; 3.76] p = 0.001
Role function	162	50 (30.9)	151	22 (14.6)	2.12 [1.35; 3.32] p = 0.001
Emotional function	162	60 (37.0)	150	36 (24.0)	1.54 [1.09; 2.19] p = 0.013
Cognitive function	162	31 (19.1)	150	28 (18.7)	1.03 [0.65; 1.62] p = 0.916
Social function	162	67 (41.4)	150	40 (26.7)	1.55 [1.12; 2.13] p = 0.006
EQ-5D					
Single components			No evaluable results available		
a: An event was a mean improvement of at least 10 points during the observation period compared with the start of the study.					
b: Institute’s calculations (asymptotic).					
c: Chi-square test (asymptotic).					
d: Financial difficulties are a component of the questionnaire, but are not considered as part of morbidity (symptoms).					
CI: confidence interval; HRQoL: health-related quality of life; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk					

Table 4: Results (time to event) for morbidity (symptoms) – RCT, direct comparison – crizotinib versus chemotherapy, chemotherapy population

Outcome category Outcome	Crizotinib		Chemotherapy		Crizotinib vs. chemotherapy HR [95% CI]; p-value
	N	Patients with events n (%) Median time without deterioration in months [95% CI]	N	Patients with events n (%) Median time without deterioration in months [95% CI]	
Morbidity					
Deterioration ^a regarding pain (chest), cough or dyspnoea					
	162	91 (56.2) 5.6 [3.4; 11.0]	151	111 (73.5) 1.4 [1.0; 1.8]	0.54 [0.40; 0.71]; p < 0.001
Deterioration ^b regarding pain (chest)					
	162	39 (24.1) 20.8 [18.7; n.c.]	151	62 (41.1) 9.9 [4.9; n.c.]	0.36 [0.24; 0.54]; p < 0.001
Deterioration ^b regarding cough					
	162	49 (30.2) 18.8 [12.5; 22.9]	151	48 (31.8) n. b. [8.8. n.c.]	0.73 [0.49; 1.09]; p = 0.123
Deterioration ^b regarding dyspnoea					
	162	71 (43.8) 13.8 [6.2; 18.8]	151	87 (57.6) 2.5 [1.8; 4.2]	0.55 [0.40; 0.76]; p < 0.001
a: Operationalized as time to first occurrence of deterioration of at least 10 points in at least one of the corresponding scales of the EORTC QLQ-LC13.					
b: Operationalized as time to first occurrence of deterioration of at least 10 points in the corresponding scale of the EORTC QLQ-LC13.					
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; n. c.: not calculable					

Results for symptoms

For EORTC QLQ-C30, a statistically significant effect was shown in the group comparison of continuous data (Table 2) to the advantage of crizotinib with regard to fatigue, pain, dyspnoea, insomnia and appetite loss. A statistically significant effect to the disadvantage of crizotinib was shown for constipation and diarrhoea. No statistically significant differences were shown for nausea and vomiting.

The EORTC QLQ-LC13 showed a statistically significant effect to the advantage of crizotinib for all symptoms recorded in this questionnaire, i.e. for pain (chest, arm and shoulder, other), dyspnoea, cough, oral pain, dysphagia, peripheral neuropathy, alopecia, and haemoptysis. In the overlapping areas, the results of QLQ-LC13 are thus consistent with those of QLQ-C30.

Responder analyses were used for the interpretation of results on symptoms for describing an added benefit (Table 3). As the response criterion used in Table 3 is only achieved with an

improvement in symptoms, no effects with regard to deterioration in symptoms can be made visible. The responder analyses therefore do not represent the statistically significant disadvantage of crizotinib for constipation and diarrhoea that is visible in the analysis of continuous data. On average the analysis of continuous data on constipation and diarrhoea showed a clear deterioration whereas on average these symptoms hardly changed in the chemotherapy group. An evaluation of the effect size of continuous data on the basis of Hedges' *g* additionally showed a relevant effect for diarrhoea, as the 95% confidence interval lay completely above the irrelevance threshold of 0.2 (see Table 2). As the effects for constipation and diarrhoea are already represented under adverse events (see dossier assessment of 13 February 2013 [1]), the consideration of the improvement of symptoms in the responder analysis is regarded as sufficient.

The responder analyses describing the proportion of patients with an improvement of symptoms showed a statistically significant advantage of crizotinib over chemotherapy for the following symptoms: fatigue, pain, dyspnoea, appetite loss (from QLQ-C30) as well as dyspnoea, pain (chest, arm, shoulder) and cough (from QLQ-LC13), (Table 3). In the chemotherapy population there is thus a hint of an added benefit of crizotinib versus chemotherapy for the above-mentioned symptoms.

The time to deterioration of symptoms, which is determined by the combined outcomes of pain (chest), cough or dyspnoea (Table 4), also showed a statistically significant advantage of crizotinib. This analysis also provides a hint of an added benefit in the chemotherapy population with regard to the symptoms contained in the combined outcome.

In Study PROFILE 1007, in each case symptoms were only recorded until progression of disease. The conclusions on added benefit therefore only apply for the period to the progression of the disease. Under crizotinib the analyses therefore showed a higher number of patients who achieved an improvement of symptoms in the time to progression of disease. Furthermore, the time to deterioration of symptoms before progression of disease was prolonged.

Results on health-related quality of life

EORTC QLQ-C30 is an instrument developed for cancer patients and contains 6 subscales on quality of life. These were analysed separately. Results on quality of life measured by means of this disease-specific instrument were therefore initially considered separately. They are however interpreted in the overall assessment of the results of the single scales.

The comparison of the mean change in HRQoL between treatment groups showed a statistically significant advantage of crizotinib for all scales, with the exception of cognitive function (Table 2).

The responder analysis QLQ-C30 (Table 3) describes the proportion of patients who on average achieved an improvement of at least 10 points on the respective scales in the

observation period. With the exception of cognitive function, the analysis showed a statistically significant advantage of crizotinib for all HRQoL scales. Overall, in the chemotherapy population there is thus a hint of an added benefit of crizotinib versus chemotherapy with regard to HRQoL. As HRQoL was only recorded up to progression of disease this conclusion only applies for the period up to progression.

3 Extent of added benefit at outcome level

The assessment of extent of added benefit regarding symptoms and HRQoL is based on the data presented in Section 2.3. For the assessment the different outcome categories and effect sizes are considered. The methods used for this purpose are described in Appendix A of Benefit Assessment A11-02 [6].

For adult patients with previously treated ALK-positive advanced NSCLC in whom chemotherapy is indicated (chemotherapy population), the assessment provided a hint of an added benefit for symptoms (morbidity) and for HRQoL. On the basis of these results, the extent of added benefit at outcome level was assessed in each case (see Table 5).

In order to assess the extent of added benefit, initially by means of the degree of symptoms, it was decided whether the symptoms investigated in the included study were of a severe or non-severe degree. As baseline values of 33 in the symptom scales of the EORTC QLQ-C30 and QLQ-LC13 refer to symptoms of a minor degree and the mean values observed were continuously below or only slightly above this value (see Table 2), symptoms in Study PROFILE 1007 were assessed as being non-severe.

The company did not provide data in the commenting procedure for adult patients with previously treated ALK-positive advanced NSCLC in whom chemotherapy is not indicated (BSC population).

Table 5: Crizotinib versus chemotherapy – Extent of added benefit at outcome level, chemotherapy population

Outcome	Effect estimates [95% CI]/ proportion of events crizotinib versus chemotherapy / p-value probability ^a	Derivation of extent ^b
Morbidity		
EORTC QLQ C30: Improvement of symptoms		
Fatigue	RR ^f : 2.26 [1.58; 3.22] RR ^g : 0.44 [0.31; 0.63] 46.3% vs. 20.5% p < 0.001	Outcome category: non-serious / non-severe symptoms Added benefit; extent: “considerable” (for the symptoms “fatigue”, “pain”, “dyspnoea”)
Nausea and vomiting	RR ^f : 0.83 [0.51; 1.36] 15.4% vs. 18.5% p = 0.463	
Pain	RR ^f : 2.13 [1.49; 3.06] RR ^g : 0.47 [0.33; 0.67] 43.8% vs. 20.5% p < 0.001	
Dyspnoea	RR ^f : 1.98 [1.38; 2.86] RR ^g : 0.50 [0.35; 0.73] 40.7% vs. 20.5% p < 0.001	
Insomnia	RR ^f : 1.27 [0.90; 1.81] 32.9% vs. 25.8% p = 0.170	
Appetite loss	RR ^f : 1.59 [1.09; 2.34] RR ^g : 0.63 [0.43; 0.92] 32.7% vs. 20.5% p = 0.015	
Constipation	RR ^f : 0.66 [0.40; 1.09] 13.7% vs. 20.7% p = 0.101	
Diarrhoea	RR ^f : 0.89 [0.52; 1.52] 13.6% vs. 15.3%] p = 0.660 Probability: “hint”	

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Table 5: Crizotinib versus chemotherapy – Extent of added benefit at outcome level, chemotherapy population (continued)

Outcome	Effect estimates [95% CI]/ proportion of events crizotinib versus chemotherapy / p-value probability ^a	Derivation of extent ^b
Morbidity		
EORTC QLQ LC13: Improvement of symptoms		
Dyspnoea	RR ^f : 2.26 [1.51; 3.36] RR ^g : 0.44 [0.30; 0.66] 39.1% vs. 17.3% p < 0.001	Outcome category: non-serious / non-severe symptoms Added benefit; extent: “considerable” (for the symptoms “dyspnoea”, “pain”, “cough”).
Pain (chest)	RR ^f : 1.79 [1.26; 2.56] RR ^g : 0.56 [0.39; 0.80] ^e 40.0% vs. 22.3% p = 0.001	
Pain (arm or shoulder)	RR ^f : 1.72 [1.16; 2.55] RR ^g : 0.58 [0.39; 0.86] 33.5% vs. 19.5% p = 0.005	
Pain (other)	RR ^f : 1.22 [0.90; 1.66] 38.8% vs. 31.7% p = 0.200	
Cough	RR ^f : 1.66 [1.27; 2.16] RR ^g : 0.60 [0.46; 0.79] 55.3% vs. 33.3% p < 0.001	
Oral pain	RR ^f : 1.02 [0.46; 2.23]; 7.5% vs. 7.3% p = 0.968	
Dysphagia	RR ^f : 1.71 [0.88; 3.33]; 13.7% vs. 8.0% p = 0.110	
Peripheral neuropathy	RR ^f : 0.97 [0.58; 1.62]; 15.5% vs. 16.0% p = 0.909	
Alopecia	RR ^f : 1.45 [0.97; 2.19]; 28.1% vs. 19.3% p = 0.070	
Haemoptysis	RR ^f : 0.93 [0.38; 2.28]; 5.6% vs. 6.0% p = 0.877 Probability: “hint”	

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Table 5: Crizotinib versus chemotherapy – Extent of added benefit at outcome level, chemotherapy population (continued)

Outcome	Effect estimates [95% CI]/ proportion of events crizotinib versus chemotherapy / p-value probability ^a	Derivation of extent ^b
Morbidity		
EORTC QLQ LC 13: Deterioration of symptoms		
Combined outcome of pain (chest), cough or dyspnoea	HR: 0.54 [0.40; 0.71] 56.2% vs. 73.5% p < 0.001 Probability: “hint”	Outcome category: non-serious / non-severe symptoms Added benefit; extent: “considerable” (for the symptoms “pain”, “cough”, “dyspnoea”).
Health-related quality of life		
Disease-specific instrument (EORTC QLQ-C30)		
Global health status / health-related quality of life	RR ^f : 2.06 [1.44; 3.00] RR ^g : 0.49 [0.34; 0.70] 42.6% vs. 20.7% p < 0.001	Outcome category: health-related quality of life Added benefit; extent: “considerable”
Physical function	RR ^f : 2.28 [1.38; 3.76] RR ^g : 0.44 [0.27; 0.72] 27.2% vs. 11.9% p = 0.001	
Role function	RR ^f : 2.12 [1.35; 3.32] RR ^g : 0.47 [0.30; 0.74] 30.9% vs. 14.6% p = 0.001	
Emotional function	RR ^f : 1.54 [1.09; 2.19] RR ^g : 0.65 [0.46; 0.92] 37.0% vs. 24.0% p = 0.013	
Cognitive function	RR ^f : 1.03 [0.65; 1.62] 19.1% vs. 18.7% p = 0.916	
Social function	RR ^f : 1.55 [1.12; 2.13] RR ^g : 0.64 [0.47; 0.89] 41.4% vs. 26.7% p = 0.006 Probability: “hint”	
Generic instrument (EQ-5D)	No evaluable results available	Lesser benefit / added benefit not proven

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Table 5: Crizotinib versus chemotherapy – Extent of added benefit at outcome level, chemotherapy population (continued)

a: Probability of added benefit provided, if statistically significant differences are available.
b: Estimations of the effect size are made depending on the outcome category with different limits by means of the upper limit of the CI (CI_u).
c: Proportion of patients with an improvement of the score by an average of at least 10 points during the treatment period (time to progression or up to the end of study or data cut-off point).
d: Time to first occurrence of a deterioration of at least 10 points in at least one of the corresponding scales of EORTC QLQ-LC13 for pain, cough or dyspnoea.
e: Upper limit of the 95% CI: 0.795.
f: Institute's calculation (asymptotic), proportion of events crizotinib vs. chemotherapy.
g: Institute's calculation (asymptotic), proportion of events chemotherapy versus crizotinib (reversed direction of effects for derivation of the extent of added benefit).
CI: confidence interval; CI_l : lower limit confidence interval; CI_u : upper limit confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C 30; EQ-5D: EuroQol-5D; HR: hazard ratio; RR: relative risk

In the category “morbidity” there is an added benefit of crizotinib with the probability “hint” and the extent “considerable”. This added benefit refers to the symptoms with the characteristics dyspnoea, pain and cough. The company also assesses the added benefit with regard to symptoms as being considerable, but assumes an “indication” instead of a “hint”.

In the category HRQoL, there is an added benefit of crizotinib with the probability “hint”. With the exception of cognitive function, in the single scales a minor to major extent was achieved. In summary the extent of added benefit for HRQoL is rated as “considerable”. This assessment concurs with that of the company, which determined a considerable added benefit (though with the probability “indication”) for the single scales, with the exception of cognitive function.

The added benefit of crizotinib described above applies in each case to adult patients with previously treated ALK-positive advanced NSCLC **in whom chemotherapy is indicated (chemotherapy population)**.

In adult patients with previously treated ALK-positive advanced NSCLC **in whom chemotherapy is not indicated (BSC population)**, no data were available in the comment for a comparison of crizotinib with BSC concerning morbidity (symptoms) or HRQoL. In the BSC population the added benefit of crizotinib is thus not proven with regard to symptoms and health-related quality of life.

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