IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ruxolitinib (Addendum to Commission A15-13)[1]

Addendum

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Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
BAT	best available therapy
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference

1 Background

On 26 August 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-13 (Ruxolitinib – Benefit assessment according to §35a Social Code Book [SGB] V).

In its dossier [1], the pharmaceutical company (hereinafter referred to as "the company") presented results from the RESPONSE study on symptoms and health-related quality of life on the basis of symptom and functional scales of the questionnaire developed by the European Organisation for Research and Treatment of Cancer (EORTC). These analyses were presented in the benefit assessment of ruxolitinib [2]. Since the company had presented only continuous data and no responder analyses, a general statistical measure in the form of standardized mean differences (SMDs in the form of Hedges' g) had to be used for evaluating relevance.

With its written comments, the company subsequently submitted responder analyses on the EORTC scales [3]. After the oral hearing on ruxolitinib, the company submitted responder analyses on the EORTC that had been changed again [4]. The G-BA commissioned IQWiG to assess the responder analyses on the EORTC. Furthermore, the G-BA commissioned IQWiG to analyse the primary outcome of the RESPONSE study (haematocrit control with absence of phlebotomy eligibility and reduction in spleen volume, as well as its individual components).

The responsibility for the present assessment and the results of the assessment 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 submitted with the comment

2.1 Responder analyses on the EORTC

Evaluation of the validity of the responder analyses presented by the company

In the framework of the commenting procedure on the early benefit assessment of ruxolitinib, the company presented data from the RESPONSE study on symptoms and health-related quality of life on the basis of the symptom and functional scales of the EORTC. These were responder analyses based on a validated response criterion (change by 10 points) [5].

With its written comments, the company had initially presented analyses in which all those patients who had achieved a mean improvement in score by at least 10 points versus the baseline score at all time points at which they had completed the questionnaire were considered responders. It was notable in this analysis that only in the comparator arm (best available therapy [BAT]), but not in the ruxolitinib arm, considerably more patients were included in the analysis than in the analysis based on continuous data. Moreover, an early study effect might have had a major influence on these analyses, and in such a case patients can be rated as responders also if there was no sustained improvement of symptoms under the treatment.

After the oral hearing, the company therefore presented corrected responder analyses, in which those patients were considered responders who had achieved an improvement in score by at least 10 points at the end of the observation period (week 32) or at the time point of their last observation (analysis using the last observation carried forward [LOCF]) in comparison with the start of the observation. However, the company had also included patients for whom no baseline value or no subsequent value had been determined in this analysis, apparently considering them as non-responders. This handling of missing values is comprehensible in the present case. Since more patients were rated as non-responders due to missing values in the ruxolitinib arm than in the intervention arm (between 6% and 8%, depending on the scale), and statistically significant effects in individual scales were only observed in favour of ruxolitinib, it is not assumed that the observed effects were only caused by the imputation strategy. The responder analyses after week 32 using LOCF presented by the company can therefore be considered to be sufficiently valid in the present case.

Results

The following Tables show the results of both responder analyses. (Table 1: Responders at the time point 32 weeks after the start of treatment; Table 2: responder analysis as mean value over the total observation period). Table 3 shows a comparison of the results of the 2 different responder analyses and of the analyses of continuous data included in the benefit assessment of ruxolitinib [2]. The results of the total populations in both study arms are presented in each case. The overall certainty of conclusions was low because of the large number of patients not treated in compliance with the approval. In principle, only hints, e.g. of an added benefit, with the extent “non-quantifiable” can therefore be derived (see also benefit assessment of

ruxolitinib [2]). The results of the patients treated in compliance with the approval are presented in Appendix A, Table 6 and Table 7.

Table 1: Results (EORTC – responder analyses at week 32, LOCF) – RCT, direct comparison: ruxolitinib vs. BAT

Study Outcome category Instrument Scales	Ruxolitinib		BAT		Ruxolitinib vs. BAT
	N	Patients with event[a] n (%)	N	Patients with event[a] n (%)	RR [95% CI]; p-value
RESPONSE					
Morbidity					
Symptoms (EORTC QLQ-C30)					
Fatigue	110	63 (57.3)	112	45 (40.2)	1.42 [1.08; 1.88]; 0.011
Nausea/vomiting	110	20 (18.2)	112	17 (15.2)	1.19 [0.66; 2.16]; 0.592
Pain	110	52 (47.3)	112	40 (35.7)	1.33 [0.97; 1.82]; 0.079
Dyspnoea	110	35 (31.8)	112	18 (16.1)	1.98 [1.20; 3.27]; 0.006
Sleep disorder	110	40 (36.4)	112	31 (27.7)	1.32 [0.89; 1.94]; 0.161
Appetite loss	110	31 (28.2)	112	17 (15.2)	1.86 [1.09; 3.16]; 0.023
Constipation	110	24 (21.8)	112	20 (17.9)	1.23 [0.72; 2.08]; 0.500
Diarrhoea	110	23 (20.9)	112	17 (15.2)	1.38 [0.78; 2.44]; 0.299
Health-related quality of life					
EORTC QLQ-C30					
General health status/quality of life	110	52 (47.3)	112	15 (13.4)	3.53 [2.12; 5.88]; < 0.001
Physical functioning	110	33 (30.0)	112	10 (8.9)	3.36 [1.74; 6.48]; < 0.001
Role functioning	110	35 (31.8)	112	24 (21.4)	1.48 [0.95; 2.32]; 0.082
Emotional functioning	110	34 (30.9)	112	24 (21.4)	1.44 [0.92; 2.26]; 0.110
Cognitive functioning	110	29 (26.4)	112	23 (20.5)	1.28 [0.80; 2.08]; 0.306
Social functioning	110	32 (29.1)	112	25 (22.3)	1.30 [0.82; 2.06]; 0.249

a: Responder analysis: patients who achieved an improvement in score by at least 10 points after 32 weeks in comparison with the baseline score using the LOCF method.

BAT: best available therapy; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; LOCF: last observation carried forward; N: number of randomized patients; n: number of patients with event; QLQ-C30: Quality of Life Questionnaire-C30; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 2: Results (EORTC – responder analyses across all time points until week 32) – RCT, direct comparison: ruxolitinib vs. BAT

Study Outcome category Instrument Scales	Ruxolitinib		BAT		Ruxolitinib vs. BAT
	N[a]	Patients with event[b] n (%)	N[a]	Patients with event[b] n (%)	RR [95% CI]; p-value
RESPONSE					
Morbidity					
Symptoms (EORTC QLQ-C30)					
Fatigue	90	39 (43.3)	98	21 (21.4)	2.04 [1.30; 3.18]; 0.001
Nausea/vomiting	90	10 (11.1)	97	12 (12.4)	0.91 [0.42; 2.00]; > 0.999
Pain	88	39 (44.3)	97	27 (27.8)	1.59 [1.07; 2.38]; 0.020
Dyspnoea	90	29 (32.2)	98	20 (20.4)	1.61 [0.97; 2.65]; 0.068
Sleep disorder	90	32 (35.6)	98	31 (31.6)	1.11 [0.74; 1.65]; 0.621
Appetite loss	89	22 (24.7)	98	16 (16.3)	1.52 [0.85; 2.73]; 0.203
Constipation	90	19 (21.1)	97	16 (16.5)	1.26 [0.69; 2.30]; 0.460
Diarrhoea	90	18 (20.0)	97	10 (10.3)	1.99 [0.97; 4.10]; 0.065
Health-related quality of life					
EORTC QLQ-C30					
General health status/quality of life	91	43 (47.3)	98	17 (17.3)	2.78 [1.70; 4.55]; < 0.001
Physical functioning	91	26 (28.6)	99	13 (13.1)	2.19 [1.19; 4.05]; 0.012
Role functioning	89	32 (36.0)	98	23 (23.5)	1.56 [1.00; 2.44]; 0.051
Emotional functioning	90	29 (32.2)	97	20 (20.6)	1.57 [0.96; 2.57]; 0.072
Cognitive functioning	90	28 (31.1)	97	19 (19.6)	1.58 [0.95; 2.62]; 0.092
Social functioning	89	30 (33.7)	96	23 (24.0)	1.41 [0.88; 2.24]; 0.146

a: Consideration of all patients with baseline value and at least one post-baseline value.
b: Responder analysis: Patients who achieved an average improvement in score of at least 10 points versus the baseline score at all time points at which they filled in the questionnaire are considered responders.

BAT: best available therapy; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; N: number of analysed patients; n: number of patients with event; QLQ-C30: Quality of Life Questionnaire-C30; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 3: Results on the EORTC (symptoms and health-related quality of life) on the basis of responder analyses and continuous values

Study Outcome category Instrument Scales	Types of analysis		
	Continuous data: SMD (Hedges' g) at week 32	Responder analysis at week 32, LOCF[a]	Responder analysis across all time points until week 32[b, c]
RESPONSE			
Morbidity			
Symptoms (EORTC QLQ-C30)			
Fatigue	+	+	+
Nausea/vomiting	O	O	O
Pain	O	O	+
Dyspnoea	O	+	O
Sleep disorder	O	O	O
Appetite loss	O	+	O
Constipation	O	O	O
Diarrhoea	O	O	O
Health-related quality of life			
EORTC QLQ-C30			
General health status/quality of life	+	+	+
Physical functioning	+	+	+
Role functioning	O	O	O
Emotional functioning	O	O	O
Cognitive functioning	O	O	O
Social functioning	O	O	O

a: Responder analysis: patients who achieved an improvement in score by at least 10 points after 32 weeks in comparison with the baseline score using the LOCF method.
b: Responder analysis: Patients who achieved an average improvement in score of at least 10 points versus the baseline score at all time points at which they filled in the questionnaire are considered responders.
c: Consideration of all patients with baseline value and at least one post-baseline value.
+: Result statistically significant in favour of ruxolitinib (in continuous data: relevant effect can be derived)
O: Result not statistically significant or no relevant effect can be derived
EORTC: European Organisation for Research and Treatment of Cancer; LOCF: last observation carried forward; QLQ-C30: Quality of Life Questionnaire-C30; SMD: standardized mean difference

The comparison of the results of the different analyses shows that for those scales for which, on the basis of the analysis of the continuous data, a relevant effect was already derived in the original dossier assessment, the responder analyses presented by the company also showed a statistically significant result in favour of ruxolitinib. The responder analyses presented by the company also showed no statistically significant result for most symptom scales as well as for all quality of life scales for which, on the basis of continuous data, no relevant effect was derived in the original dossier assessment.

In contrast to the analysis on the basis of continuous data, the responder analysis at week 32 using LOCF showed a statistically significant result in favour of ruxolitinib for 2 symptom scales (dyspnoea and appetite loss). Deviating from the dossier assessment A15-13 [2], this resulted in a hint of a non-quantifiable added benefit for these symptoms in each case.

For the symptom scale "pain", only the responder analysis across all time points showed a statistically significant result, but not the responder analysis at week 32 using LOCF. Due to the limited evaluability of the responder analyses across all time points presented by the company (see above), as in the original dossier assessment A15-13 [2], this resulted in no hint of an added benefit for this outcome.

Summary

The overall assessment of the original dossier assessment A15-13 [2] and the analysis of the responder analyses on the EORTC produced the positive and negative effects of ruxolitinib in comparison with the appropriate comparator presented in the following Table 4:

Table 4: Positive and negative effects from the assessment of ruxolitinib in comparison with the best available therapy

Positive effects	**Negative effects**
Hint of added benefit – extent: "non-quantifiable" (non-serious/non-severe symptoms: health status)	Hint of greater harm – extent: "non-quantifiable" (non-serious/non-severe adverse events: muscle spasms)
Hint of added benefit – extent: "non-quantifiable" (non-serious/non-severe symptoms: fatigue)	Hint of greater harm – extent: "non-quantifiable" (non-serious/non-severe adverse events: dyspnoea)
Hint of added benefit – extent: "non-quantifiable" (non-serious/non-severe symptoms: dyspnoea)	
Hint of added benefit – extent: "non-quantifiable" (non-serious/non-severe symptoms: appetite loss)	
Hint of added benefit – extent: "non-quantifiable" (health-related quality of life: general health status/quality of life)	
Hint of added benefit – extent: "non-quantifiable" (health-related quality of life: physical functioning)	

Overall, positive and negative effects remain. There were hints of an added benefit with the extent "non-quantifiable" in the outcome category "non-serious/non-severe symptoms" (fatigue, health status, dyspnoea, appetite loss) and "health-related quality of life" (general health status/quality of life; physical functioning). On the other hand, there were hints of greater harm in non-serious/non-severe adverse events (muscle spasms and dyspnoea), also with the extent "non-quantifiable". It should be noted in the interpretation of the greater harm regarding dyspnoea that this is offset by the opposing result in favour of ruxolitinib in the recording of dyspnoea with the EORTC QLQ-C30. The remaining greater harm regarding muscle spasms does not raise doubts about the result of the overall assessment. Overall, a hint of an added benefit with the extent "non-quantifiable" remains.

2.2 Outcome additionally presented: absence of phlebotomy eligibility and reduction in spleen volume

In its dossier [1], the company had presented data on the composite outcome "absence of phlebotomy eligibility and reduction in spleen volume" and its individual components. Phlebotomy eligibility was defined as a haematocrit > 45% and > 3 percentage points higher than previous measurement or a haematocrit > 48%. The composite outcome was operationalized as proportion of patients without phlebotomy eligibility from week 8 to week 32, with no more than one phlebotomy since randomization and before week 8 and a reduction in spleen volume by ≥ 35% after 32 weeks. Table 5 presents the results of the composite outcome, its individual components and the number of actually performed phlebotomies as additional information (separately for the time periods week 1 up to and including week 7 as well as week 8 up to and including week 32 because no analyses were available for the total observation period). The results of the subpopulations of patients in the control group with approval-compliant and non-approval-compliant treatment are presented in Appendix A, Table 8.

Table 5: Results (dichotomous outcomes) – RCT, direct comparison: ruxolitinib vs. BAT

Study Outcome	Ruxolitinib		BAT		Ruxolitinib vs. BAT
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
RESPONSE					
Additional information: absence of phlebotomy eligibility and reduction in spleen volume by ≥ 35%	110	23 (20.9)	112	1 (0.9)	23.42 [3.22; 170.42]; < 0.001
Additional information: absence of phlebotomy eligibility	110	66 (60.0)	112	22 (19.6)	2.7 [1.87; 3.9]; < 0.001
Additional information: phlebotomy in week 1-7	110	18 (16.4)[a]	112	24 (21.4)[a]	0.76 [0.44; 1.33]; 0.517[b]
Additional information: phlebotomy in week 8-32	106	21 (19.8)[a]	109	68 (62.4)[a]	0.32 [0.21; 0.48]; < 0.001[b]
Additional information: spleen volume reduction by ≥ 35%	110	42 (38.2)	112	1 (0.9)	42.76 [5.99; 305.31]; < 0.001

a: Institute's calculation.
b: Institute's calculation of RR. CI (asymptotic) and p-value (unconditional exact test (CSZ method according to [6])).
BAT: best available therapy; CI: confidence interval; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; vs.: versus

2.3 Summary

The data subsequently submitted by the company changed the assessment of individual symptoms (appetite loss and dyspnoea), but not the overall conclusion of the benefit assessment A15-13 [2]. In summary, there is still a hint of a non-quantifiable added benefit for patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

3 References

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Appendix A – Presentation of the results on patients treated in compliance with the approval and patients not treated in compliance with the approval

Table 6: Results (EORTC – responder analyses at week 32; LOCF) – RCT, direct comparison: ruxolitinib vs. BAT

Study Outcome category Instrument Scales Population	Ruxolitinib		BAT		Ruxolitinib vs. BAT
	N	Patients with event[a] n (%)	N	Patients with event[a] n (%)	RR
RESPONSE					
Morbidity					
Symptoms (EORTC QLQ-C30)					
Fatigue	110	63 (57.3)	112	45 (40.2)	1.42
BAT (approval-compliant)	110	63 (57.3)	83	33 (39.8)	1.46
BAT (not approval-compliant)	110	63 (57.3)	28	12 (42.9)	1.31
Nausea/vomiting	110	20 (18.2)	112	17 (15.2)	1.19
BAT (approval-compliant)	110	20 (18.2)	83	12 (14.5)	1.28
BAT (not approval-compliant)	110	20 (18.2)	28	5 (17.9)	0.95
Pain	110	52 (47.3)	112	40 (35.7)	1.33
BAT (approval-compliant)	110	52 (47.3)	83	31 (37.3)	1.25
BAT (not approval-compliant)	110	52 (47.3)	28	9 (32.1)	1.51
Dyspnoea	110	35 (31.8)	112	18 (16.1)	1.98
BAT (approval-compliant)	110	35 (31.8)	83	15 (18.1)	1.77
BAT (not approval-compliant)	110	35 (31.8)	28	3 (10.7)	2.91
Sleep disorder	110	40 (36.4)	112	31 (27.7)	1.32
BAT (approval-compliant)	110	40 (36.4)	83	22 (26.5)	1.35
BAT (not approval-compliant)	110	40 (36.4)	28	9 (32.1)	1.15
Appetite loss	110	31 (28.2)	112	17 (15.2)	1.86
BAT (approval-compliant)	110	31 (28.2)	83	11 (13.3)	2.13
BAT (not approval-compliant)	110	31 (28.2)	28	6 (21.4)	1.35

(continued)

Table 6: Results (EORTC – responder analyses at week 32; LOCF) – RCT, direct comparison: ruxolitinib vs. BAT (continued)

Study Outcome category Instrument Scales Population	Ruxolitinib		BAT		Ruxolitinib vs. BAT
	N	Patients with event[a] n (%)	N	Patients with event[a] n (%)	RR
RESPONSE					
Morbidity					
Symptoms (EORTC QLQ-C30)					
Constipation	110	24 (21.8)	112	20 (17.9)	1.23
BAT (approval-compliant)	110	24 (21.8)	83	10 (12.0)	1.79
BAT (not approval-compliant)	110	24 (21.8)	28	10 (35.7)	0.67
Diarrhoea	110	23 (20.9)	112	17 (15.2)	1.38
BAT (approval-compliant)	110	23 (20.9)	83	10 (12.0)	1.75
BAT (not approval-compliant)	110	23 (20.9)	28	7 (25.0)	0.80
Health-related quality of life					
EORTC QLQ-C30					
General health status/quality of life	110	52 (47.3)	112	15 (13.4)	3.53
BAT (approval-compliant)	110	52 (47.3)	83	11 (13.3)	3.59
BAT (not approval-compliant)	110	52 (47.3)	28	4 (14.3)	3.37
Physical functioning	110	33 (30.0)	112	10 (8.9)	3.36
BAT (approval-compliant)	110	33 (30.0)	83	10 (12)	2.48
BAT (not approval-compliant)	110	33 (30.0)	28	0 (0.0)	ND
Role functioning	110	35 (31.8)	112	24 (21.4)	1.48
BAT (approval-compliant)	110	35 (31.8)	83	20 (24.1)	1.33
BAT (not approval-compliant)	110	35 (31.8)	28	4 (14.3)	2.13
Emotional functioning	110	34 (30.9)	112	24 (21.4)	1.44
BAT (approval-compliant)	110	34 (30.9)	83	18 (21.7)	1.44
BAT (not approval-compliant)	110	34 (30.9)	28	6 (21.4)	1.48

(continued)

Table 6: Results (EORTC – responder analyses at week 32; LOCF) – RCT, direct comparison: ruxolitinib vs. BAT (continued)

Study	Ruxolitinib		BAT		Ruxolitinib vs. BAT
Outcome category Instrument Scales Population	N	Patients with event[a] n (%)	N	Patients with event[a] n (%)	RR
RESPONSE					
Morbidity					
Symptoms (EORTC QLQ-C30)					
Cognitive functioning	110	29 (26.4)	112	23 (20.5)	1.28
BAT (approval-compliant)	110	29 (26.4)	83	16 (19.3)	1.38
BAT (not approval-compliant)	110	29 (26.4)	28	7 (25.0)	1.11
Social functioning	110	32 (29.1)	112	25 (22.3)	1.30
BAT (approval-compliant)	110	32 (29.1)	83	19 (22.9)	1.27
BAT (not approval-compliant)	110	32 (29.1)	28	6 (21.4)	1.47

a: Responder analysis: patients who achieved an improvement in score by at least 10 points after 32 weeks in comparison with the baseline score using the LOCF method.

BAT: best available therapy; EORTC: European Organisation for Research and Treatment of Cancer; LOCF: last observation carried forward; N: number of randomized patients; n: number of patients with event; ND: no data; QLQ-C30: Quality of Life Questionnaire-C30; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 7: Results (EORTC – responder analyses across all time points until week 32) – RCT, direct comparison: ruxolitinib vs. BAT

Study Outcome category Instrument Scales Population	Ruxolitinib		BAT		Ruxolitinib vs. BAT
	N[a]	Patients with event[b] n (%)	N[a]	Patients with event[b] n (%)	RR
RESPONSE					
Morbidity					
Symptoms (EORTC QLQ-C30)					
Fatigue	90	39 (43.3)	98	21 (21.4)	2.04
BAT (approval-compliant)	90	39 (43.3)	77	15 (19.5)	2.28
BAT (not approval-compliant)	90	39 (43.3)	21	6 (28.6)	1.50
Nausea/vomiting	90	10 (11.1)	97	12 (12.4)	0.91
BAT (approval-compliant)	90	10 (11.1)	77	10 (13.0)	0.90
BAT (not approval-compliant)	90	10 (11.1)	20	2 (10.0)	1.06
Pain	88	39 (44.3)	97	27 (27.8)	1.59
BAT (approval-compliant)	88	39 (44.3)	77	22 (28.6)	1.55
BAT (not approval-compliant)	88	39 (44.3)	20	5 (25.0)	1.79
Dyspnoea	90	29 (32.2)	98	20 (20.4)	1.61
BAT (approval-compliant)	90	29 (32.2)	77	19 (24.7)	1.33
BAT (not approval-compliant)	90	29 (32.2)	21	1 (4.8)	6.48
Sleep disorder	90	32 (35.6)	98	31 (31.6)	1.11
BAT (approval-compliant)	90	32 (35.6)	77	21 (27.3)	1.26
BAT (not approval-compliant)	90	32 (35.6)	21	10 (47.6)	0.76
Appetite loss	89	22 (24.7)	98	16 (16.3)	1.52
BAT (approval-compliant)	89	22 (24.7)	77	11 (14.3)	1.76
BAT (not approval-compliant)	89	22 (24.7)	21	5 (23.8)	1.04

(continued)

Table 7: Results (EORTC – responder analyses across all time points until week 32) – RCT, direct comparison: ruxolitinib vs. BAT (continued)

Study Outcome category Instrument Scales Population	Ruxolitinib		BAT		Ruxolitinib vs. BAT
	N[a]	Patients with event[b] n (%)	N[a]	Patients with event[b] n (%)	RR
RESPONSE					
Morbidity					
Symptoms (EORTC QLQ-C30)					
Constipation	90	19 (21.1)	97	16 (16.5)	1.26
BAT (approval-compliant)	90	19 (21.1)	77	11 (14.3)	1.46
BAT (not approval-compliant)	90	19 (21.1)	20	5 (25.0)	0.93
Diarrhoea	90	18 (20.0)	97	10 (10.3)	1.99
BAT (approval-compliant)	90	18 (20.0)	77	9 (11.7)	1.81
BAT (not approval-compliant)	90	18 (20.0)	20	1 (5.0)	3.98
Health-related quality of life					
EORTC QLQ-C30					
General health status/quality of life	91	43 (47.3)	98	17 (17.3)	2.78
BAT (approval-compliant)	91	43 (47.3)	77	13 (16.9)	2.93
BAT (not approval-compliant)	91	43 (47.3)	21	4 (19.0)	2.43
Physical functioning	91	26 (28.6)	99	13 (13.1)	2.19
BAT (approval-compliant)	91	26 (28.6)	77	11 (14.3)	2.05
BAT (not approval-compliant)	91	26 (28.6)	22	2 (9.1)	3.30
Role functioning	89	32 (36.0)	98	23 (23.5)	1.51
BAT (approval-compliant)	89	32 (36.0)	77	20 (26.0)	1.41
BAT (not approval-compliant)	89	32 (36.0)	21	3 (14.3)	2.38
Emotional functioning	90	29 (32.2)	97	20 (20.6)	1.57
BAT (approval-compliant)	90	29 (32.2)	77	16 (20.8)	1.56
BAT (not approval-compliant)	90	29 (32.2)	20	4 (2.0)	1.62

(continued)

Table 7: Results (EORTC – responder analyses across all time points until week 32) – RCT, direct comparison: ruxolitinib vs. BAT (continued)

Study Outcome category Instrument Scales Population	Ruxolitinib		BAT		Ruxolitinib vs. BAT
	N[a]	Patients with event[b] n (%)	N[a]	Patients with event[b] n (%)	RR
RESPONSE					
Morbidity					
Symptoms (EORTC QLQ-C30)					
Cognitive functioning	90	28 (31.1)	97	19 (19.6)	1.58
BAT (approval-compliant)	90	28 (31.1)	77	14 (18.2)	1.72
BAT (not approval-compliant)	90	28 (31.1)	20	5 (25.0)	1.26
Social functioning	89	30 (33.7)	96	23 (24.0)	1.41
BAT (approval-compliant)	89	30 (33.7)	76	16 (21.1)	1.61
BAT (not approval-compliant)	89	30 (33.7)	20	7 (35)	0.99

a: Consideration of all patients with baseline value and at least one post-baseline value.
b: Responder analysis: Patients who achieved an average improvement in score of at least 10 points versus the baseline score at all time points at which they filled in the questionnaire.
BAT: best available therapy; EORTC: European Organisation for Research and Treatment of Cancer; N: number of analysed patients; n: number of patients with event; QLQ-C30: Quality of Life Questionnaire-C30; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 8: Results (dichotomous outcomes) – RCT, direct comparison: ruxolitinib vs. BAT

Study Outcome category Outcome Population	Ruxolitinib N	Ruxolitinib Patients with event n (%)	BAT N	BAT Patients with event n (%)	Ruxolitinib vs. BAT RR
RESPONSE					
Additional information: absence of phlebotomy eligibility and reduction in spleen volume by ≥ 35%	110	23 (20.9)	112	1 (0.9)	23.42
BAT (approval-compliant)	110	23 (20.9)	83	1 (1.2)	17.95
BAT (not approval-compliant)	110	23 (20.9)	28	0 (0)	12.28
Additional information: absence of phlebotomy eligibility	110	66 (60.0)	112	22 (19.6)	2.7
BAT (approval-compliant)	110	66 (60.0)	83	16 (19.3)	3.11
BAT (not approval-compliant)	110	66 (60.0)	28	6 (21.4)	2.66
Additional information: phlebotomy in week 1-7	110	18 (16.4)[a]	112	24 (21.4)[a]	0.76[a]
BAT (approval-compliant)		ND		ND	
BAT (not approval-compliant)		ND		ND	
Additional information: phlebotomy in week 8-32	106	21 (19.8)[a]	109	68 (62.4)[a]	0.32[a]
BAT (approval-compliant)		ND		ND	
BAT (not approval-compliant)		ND		ND	
Additional information: spleen volume reduction by ≥ 35%	110	42 (38.2)	112	1 (0.9)	42.76
BAT (approval-compliant)	110	42 (38.2)	83	1 (1.2)	32.69
BAT (not approval-compliant)	110	42 (38.2)	28	0 (0)	22.21

a: Institute's calculation.

BAT: best available therapy; CI: confidence interval; N: number of analysed patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; RR: relative risk; vs.: versus