IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A15-13

# Ruxolitinib – Benefit assessment according to §35a Social Code Book V[1]

## Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ruxolitinib – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 July 2015). 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.

# Publishing details

**Publisher:**
Institute for Quality and Efficiency in Health Care

**Topic:**
Ruxolitinib – Benefit assessment according to §35a Social Code Book V

**Commissioning agency:**
Federal Joint Committee

**Commission awarded on:**
8 April 2015

**Internal Commission No.:**
A15-13

**Address of publisher:**
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[2] Due to legal data protection regulations, employees have the right not to be named.

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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| BAT | best available therapy |
| CI | confidence interval |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECOG | Eastern Cooperative Oncology Group |
| 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) |
| PGIC | Patients Global Impression of Change |
| QLQ C-30 | Quality of Life Questionnaire - Core 30 |
| SAE | serious adverse event |
| 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 ruxolitinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 8 April 2015.

### Research question

The aim of this report is to assess the added benefit of ruxolitinib in comparison with the appropriate comparator therapy (ACT) in patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

For patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea, the G-BA specified individual treatment at the physician's discretion, generally under consideration of the approval status in drug treatments, if appropriate also dose reduction of or retreatment with hydroxyurea, as ACT. The company initially concurred with the ACT specified by the G-BA, but considered the ACT to also include off-label treatment options. The ACT specified by the G-BA was used for the present benefit assessment.

### Results

One relevant study (RESPONSE) was available for the benefit assessment. This is a multicentre, open-label, randomized controlled parallel group trial. Adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea were included in the study. A total of 222 patients were randomly assigned in a ratio of 1:1, 110 patients to the ruxolitinib group, and 112 to the control group (best available therapy [BAT]). Patients in the control group received BAT as monotherapy at the physician's discretion, which the physician specified individually for each patient after randomization to the control group. In the BAT arm, 83 of 112 patients (about 75%) received approval-compliant treatment with hydroxyurea or were observed. 28 of 112 patients (about 25%) received off-label treatment. Besides the analyses of the total population, the company also presented analyses that considered only the patients in the control arm with approval-compliant treatment or only the patients in the control arm with off-label treatment. The assessment was based on the results of the total population with supplementary observation of the results of patients with approval-compliant treatment. The result in the group of patients who received approval-compliant treatment was in line with the qualitative conclusion on the basis of the total population (hint and no hint of an added benefit or greater harm). The analysis for the benefit assessment was conducted at treatment week 32. At this time point, the observation period under the allocated treatment in the 2 study arms was still comparable.

Starting from treatment week 32, it was allowed to cross over from the control to the intervention group if the primary outcome of the study was not achieved. Patients in the intervention group were not allowed to cross over to the control group, but they were allowed to discontinue their ruxolitinib treatment. Besides the primary outcome, disease-related symptoms, health-related quality of life and adverse events (AEs) were investigated in the study.

For the patients in the control group, the study was completed after 80 weeks. In contrast, the patients in the intervention group and the patients in the control group who had crossed over to the ruxolitinib group continued their treatment until week 256. The study will probably be completed in January 2019.

The risk of bias of the RESPONSE study at study level was rated as low for the data cut-off after 32 weeks. The risk of bias was rated as high for the following outcomes: symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 [EORTC QLQ-C30]), health status (Patient Global Impression of Change [PGIC]), health-related quality of life (EORTC QLQ-C30), pruritus, muscle spasms, and dyspnoea. In the remaining outcomes considered, the risk of bias was rated as low. Irrespective of this, 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.

***Mortality***

*Overall survival*

No deaths occurred in the RESPONSE study up to treatment week 32. This resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

***Morbidity***

*Thromboembolic events*

There was no statistically significant difference between the intervention and the control group for the outcome "thromboembolic events". This resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

*Disease transformation*

There was no statistically significant difference between the intervention and the control group for the outcome "disease transformation". This resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

*Disease-related symptoms (EORTC QLQ-C30)*

For the outcome **"fatigue"**, there was a statistically significant effect in favour of ruxolitinib. The 95% confidence interval (CI) of Hedges' g was completely below the irrelevance

threshold of −0.2. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of ruxolitinib in comparison with the BAT.

For each of the outcomes **"pain", "dyspnoea", "sleep disorder"** and **"appetite loss"**, there was a statistically significant effect in favour of ruxolitinib. In each case, however, the 95% CI of Hedges' g was not completely below the irrelevance threshold of −0.2. It can therefore not be inferred that the effects are relevant. Overall, this resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

There was no statistically significant difference between the intervention and the control group for the outcomes **"nausea/vomiting", "constipation"** and **"diarrhoea"**. This resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

*Health status (PGIC)*

For the outcome "health status (PGIC)" there was a statistically significant effect in favour of ruxolitinib. This resulted in a hint of an added benefit of ruxolitinib in comparison with the BAT.

***Health-related quality of life***

*Health-related quality of life (EORTC QLQ-C30)*

For each of the outcomes **"general health status/quality of life"** and **"physical functioning"**, there was a statistically significant effect in favour of ruxolitinib. In each case, the 95% CI of Hedges' g was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect in each case. This resulted in hints of an added benefit of ruxolitinib in comparison with the BAT.

For each of the outcomes **"emotional functioning", "cognitive functioning"** and **"social functioning"**, there was a statistically significant effect in favour of ruxolitinib. In each case, however, the 95% CI of Hedges' g was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effects are relevant. Overall, this resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

There was no statistically significant difference between the intervention and the control group for the outcome **"role functioning"**. This resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

***Adverse events***

There was no statistically significant difference between the intervention and the control group for the outcomes **"serious adverse events (SAEs)"** and **"severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3/4)"**. This resulted in no hint

of greater or lesser harm from ruxolitinib in comparison with the BAT. Greater or lesser harm is not proven for these outcomes.

There were no interpretable data for the outcome **"discontinuation due to AEs"**. This resulted in no hint of greater or lesser harm from ruxolitinib in comparison with the BAT. Greater or lesser harm is not proven for this outcome.

There was no statistically significant difference between the intervention and the control group for the outcome **"pruritus"**. This resulted in no hint of greater or lesser harm from ruxolitinib in comparison with the BAT. Greater or lesser harm is not proven for this outcome.

For each of the outcomes **"muscle spasms"** and **"dyspnoea"**, there was a statistically significant difference to the disadvantage of ruxolitinib. Overall, this resulted in a hint of greater harm from ruxolitinib in comparison with the BAT.

**Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]**

On the basis of the results presented, the extent and probability of the added benefit of the drug ruxolitinib compared with the ACT is assessed as follows:

On the basis of the available results, there were hints of an added benefit of ruxolitinib in comparison with the BAT for the following outcomes: fatigue (EORTC QLQ-C30 symptom scale), health status (PGIC), general health status/quality of life (EORTC QLQ-C30), and physical functioning (EORTC QLQ-C30 functional scale). For the AEs "dyspnoea" and "muscle spasms", there were hints of greater harm from ruxolitinib in comparison with the BAT.

Due to the large proportion of patients who were not treated in compliance with the approval, only non-quantifiable effects can be derived from the RESPONSE study.

In summary, there is a hint of a non-quantifiable added benefit for patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

Table 2 presents a summary of the extent and probability of the added benefit of ruxolitinib.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Table 2: Ruxolitinib – extent and probability of added benefit

| **Therapeutic indication** | **ACT**[a] | **Extent and probability of added benefit** |
|---|---|---|
| Treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxycarbamide (hydroxyurea) | Individual treatment at the physician's discretion, generally under consideration of the approval status in drug treatments; if appropriate dose reduction of or retreatment with hydroxyurea also possible | Hint of a non-quantifiable added benefit |
| a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | | |

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

## 2.2 Research question

The aim of this report is to assess the added benefit of ruxolitinib in comparison with the ACT in patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

For patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea, the G-BA specified individual treatment at the physician's discretion, generally under consideration of the approval status in drug treatments, if appropriate also dose reduction of or retreatment with hydroxyurea, as ACT. The company initially accepted the ACT specified by the G-BA. However, it considered the ACT to also include off-label treatment options. The ACT specified by the G-BA was used for the present benefit assessment.

The assessment was conducted based on patient-relevant outcomes and on 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 ruxolitinib (studies completed up to 3 March 2015)
- bibliographical literature search on ruxolitinib (last search on 1 April 2015)
- search in trial registries for studies on ruxolitinib (last search on 4 February 2015)

To check the completeness of the study pool:

- search in trial registries for studies on ruxolitinib (last search on 22 April 2015)

No additional relevant study was identified from the check.

### 2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: ruxolitinib vs. BAT

| Study | Study category | | |
|---|---|---|---|
| | Study for approval of the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) |
| RESPONSE | Yes | Yes | Yes |
| a: Study for which the company was sponsor, or in which the company was otherwise financially involved.<br>RCT: randomized controlled trial; vs.: versus | | | |

The study pool of the benefit assessment concurred with the one of the company and contained the RESPONSE study. In the study, ruxolitinib was compared with the BAT. About 75% of the patients in the control arm of the study received approval-compliant treatment with hydroxyurea or were observed without receiving cytoreductive treatment. The remaining approximately 25% of the patients in the control arm received off-label treatment. However, besides the analyses of the total population, the company also presented analyses that considered only the patients in the control arm with approval-compliant treatment or only the patients in the control arm with off-label treatment. The direction of effect between the total population and the population with approval-compliant treatment was in each case identical for the outcomes relevant for the decision. The assessment was therefore based on the results of the total population with supplementary observation of the results of patients with approval-compliant treatment. In the following Sections 2.3 and 2.4, only the characteristics and results of the total population are presented. Detailed reasons for the approach can be found in Sections 2.7.2.2 and 2.7.2.3.2 of the full dossier assessment.

Section 2.6 contains a reference list for the study included.

### 2.3.2 Study characteristics

Table 4 and Table 5 describe the study used for the benefit assessment.

Table 4: Characteristics of the study included – RCT, direct comparison: ruxolitinib vs. BAT

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| RESPONSE | RCT, open-label, parallel | Adults with polycythaemia vera who are resistant to or intolerant of hydroxyurea | ▪ Ruxolitinib (N = 110)<br>▪ BAT (N = 112)<br><br>Treatment in the control group:<br>▪ approval-compliant treatment[b] (n = 83)<br>▪ off-label treatment (n = 28)<br>▪ no treatment (n = 1)[e] | ▪ Screening: up to 3 weeks<br>▪ Prerandomization phase: up to 4 weeks<br>▪ Treatment phase: day 1 to week 80, patients from the control arm could cross over to the ruxolitinib arm after week 32<br>▪ Extended treatment phase[c]: week 80 to week 256 | Worldwide in 92 study centres: Argentina, Australia, Belgium, Canada, China, France, Germany, Hungary, Italy, Japan, Korea, Netherlands, Russia, Spain, Thailand, Turkey, United Kingdom, United States<br><br>since 10/2010 until probably 1/2019<br><br>Data cut-off of the primary analysis after at least 48 weeks of treatment: 15 January 2014 | ▪ Primary: haematocrit control with absence of phlebotomy eligibility[d] and ≥ 35% reduction in spleen volume after 32 weeks<br>▪ Secondary: survival, morbidity, health-related quality of life, AEs |

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Besides ruxolitinib, hydroxyurea is the only approved drug in this therapeutic indication. Patients who were treated with hydroxyurea or who were observed are considered to have received approval-compliant treatment.
c: Only for patients in the intervention group and patients in the control group who crossed over to the intervention group after week 32.
d: Absence of phlebotomy eligibility starting from week 8 up to and including week 32 and no more than one phlebotomy between randomization and week 8.
e: One patient in the control group withdrew his informed consent for participation in the study after randomization. He was therefore not treated and not included in the analysis.
AE: adverse event; BAT: best available therapy; N: number of randomized patients; n: number of patients; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: ruxolitinib vs. BAT

| Study | Intervention | Comparison |
|---|---|---|
| RESPONSE | Ruxolitinib, starting dose: 2x 10 mg/day, orally<br>▪ Dose adjustments and treatment discontinuations due to lack of efficacy or intolerance were allowed:<br>▫ minimum dosage: 5 mg/day, orally<br>▫ maximum dosage: 2x 25 mg/day, orally<br>▪ ASA 75–150 mg/day or other antithrombotics if ASA contraindicated | BAT:<br>▪ treatment as monotherapy[a]<br>▪ dosage and administration as specified by the respective manufacturer (according to the SPC)<br>▪ dose adjustment at the physician's discretion possible at any time<br>▪ Crossover only allowed if the criteria[b] specified in the protocol were met<br>▪ ASA 75–150 mg/day or other antithrombotics if ASA contraindicated<br><br>The following individual treatments were used:<br>approval-compliant:<br>▪ hydroxyurea<br>▪ observation<br>off-label:<br>▪ interferon<br>▪ pegylated interferon<br>▪ anagrelide<br>▪ pipobroman<br>▪ immunomodulators (thalidomide or lenalidomide) |
| | **Concomitant medication/treatment**<br>▪ Concomitant medication prohibited:<br>▫ other JAK inhibitors<br>▫ investigational drugs without approval for any therapeutic indication<br>▫ strong CYP3A4 inducers (e.g. rifampicin or St. John's Wort)<br>▫ peginterferon alfa-2a (5 weeks before screening until day -1)<br>▫ phosphorus 32 radionuclide<br>▫ busulfan<br>▫ chlorambucil<br>▪ Concomitant treatment allowed:<br>▫ phlebotomy when HCT > 45% and ≥ 3% increase in comparison with baseline value or HCT of > 48% | |

a: Crossover was allowed if the criteria for disease progression or treatment discontinuation due to intolerance specified in the protocol were met.

b: Crossover (day 1 to week 80) to ruxolitinib treatment was allowed under the following conditions:
- ▫ after 32 weeks: if the primary outcome was not achieved
- ▫ at later time points: in case of continued phlebotomy requirement or increase in spleen volume by ≥ 25% from Nadir

ASA: acetylsalicylic acid; BAT: best available therapy; CYP3A4: cytochrome P450 3A4; HCT: haematocrit; JAK: Janus kinase; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

The RESPONSE study was a multicentre, open-label, randomized controlled parallel group study. It was conducted in countries in North and South America, Australia, Europe and East

Asia. Adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea were included in the study. Ruxolitinib is approved for the patients included [3].

In the study, ruxolitinib was compared with the BAT. A total of 222 patients were randomly assigned in a ratio of 1:1, 110 patients to the ruxolitinib group, and 112 to the control group (BAT). For randomization, the company stratified the patients by resistance or intolerance to hydroxyurea.

The patients in the intervention group received a starting dosage of 10 mg ruxolitinib twice daily. Dose adjustments were possible in the course of the study: The minimum daily dosage was 5 mg, and the maximum dosage was twice 25 mg. The treatment regimen of the intervention group concurs with the description in the Summary of Product Characteristics (SPC) [3]. Patients in the control group received BAT as monotherapy at the physician's discretion. The physician specified the BAT individually for each patient after randomization to the control group.

In the BAT arm of the RESPONSE study, 83 of 112 patients (about 75%) received approval-compliant treatment with hydroxyurea or were observed without receiving cytoreductive treatment. The dosage of hydroxyurea in the RESPONSE study was adapted to the individual patient. Hence an adequate operationalization of the ACT, individual treatment at the physician's discretion, can be assumed for these 83 patients.

28 patients in the control arm (about 25%) received off-label treatment with interferon or pegylated interferon, anagrelide, pipobroman or immunomodulating agents, e.g. lenalidomide. These agents are not approved in Germany for the treatment of polycythaemia vera.

One of 112 patients in the control group was randomized, but not treated because he had withdrawn his informed consent to participation in the study.

Crossover was allowed in the control group only after criteria defined a priori in case of disease progression or treatment discontinuation due to intolerance.

Besides the study medication, about 88% of the patients in both treatment groups received a platelet aggregation inhibitor, in most cases low dosage acetylsalicylic acid or an alternative antithrombotic drug (in each case about 14% of the patients in the intervention and control group who received an antithrombotic drug). Phlebotomy was possible in both treatment groups when haematocrit was higher than the predefined value of 45% or increased by more than 3% compared with baseline.

Starting from treatment week 32, it was allowed to cross over from the control to the intervention group if the primary outcome of the study (haematocrit control with absence of phlebotomy eligibility and $\geq$ 35% reduction in spleen volume compared with baseline) was not achieved. Patients in the intervention group were not allowed to cross over to the control group, but they were allowed to discontinue their ruxolitinib treatment. Besides the primary

outcome, disease-related symptoms, health-related quality of life and AEs were investigated in the study.

For the patients in the control group, the study was completed after 80 weeks. In contrast, the patients in the intervention group and the patients in the control group who had crossed over to the ruxolitinib group continued their treatment until week 256. Figure 1 provides an overview of the course of the study, which will probably be completed in January 2019. Table 6 shows the planned duration of follow-up of the patients for the individual outcomes.

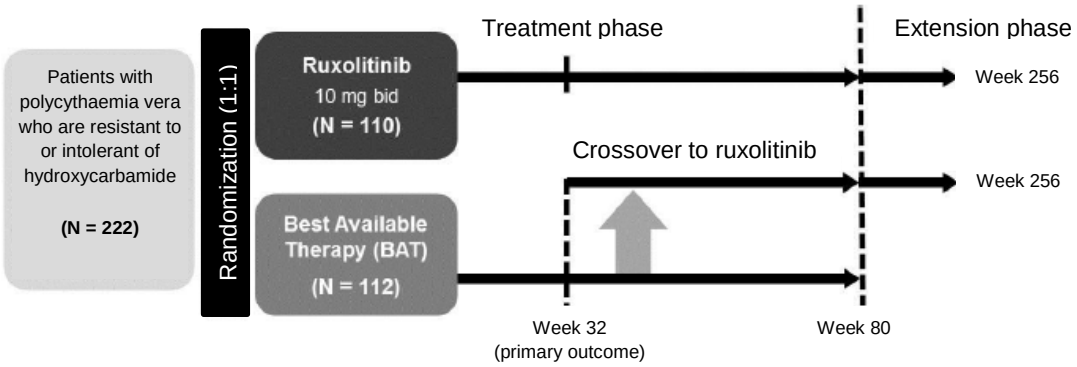


Figure 1: Time course of the RESPONSE study

Table 6: Planned duration of follow-up – RCT, direct comparison: ruxolitinib vs. BAT

| **Study**<br>**Outcome category** | **Planned follow-up** |
|---|---|
| RESPONSE | |
| Overall survival | continuously until the last patient has completed the study |
| Morbidity | ▪ thromboembolic events/disease transformation: continuously up to and including 35 ± 5 days after the last study medication or premature discontinuation<br>▪ EORTC QLQ-C30 (symptoms), PGIC: every 4 weeks until week 32 |
| Health-related quality of life | EORTC QLQ-C30: every 4 weeks until week 32 |
| Adverse events | continuously up to and including 35 ± 5 days after the last study medication or premature discontinuation |
| BAT: best available therapy; EORTC: European Organisation for Research and Treatment of Cancer; PGIC: Patient Global Impression of Change; QLQ-C30: Quality of Life Questionnaire-C30; RCT: randomized controlled trial; vs.: versus | |

Overall survival is observed until the last patient has completed the study. Symptoms of the disease and health-related quality of life were recorded with the EORTC QLQ-C30 up to treatment week 32. All other outcomes including AEs are recorded up to 35 ± 5 days after the last study medication or after premature discontinuation.

Table 7 and Table 8 show the characteristics of the patients in the study included.

Table 7: Characteristics of the study population – RCT, direct comparison: ruxolitinib vs. BAT (demographic characteristics)

| **Study**<br>**Characteristics**<br>**Category** | **Ruxolitinib**<br>**N = 110** | **BAT**<br>**N = 112** |
|---|---|---|
| **RESPONSE** | | |
| Age [years], mean (SD) | 61 (10) | 59 (10) |
| Sex [F/M], % | 40/60 | 29/71 |
| Skin colour [white/other], n (%) | 98 (89.1)/12 (10.9) | 96 (85.7)/16 (14.3) |
| Treatment discontinuations week 32, n (%) | 12 (10.9) | 12 (10.7) |
| BAT: best available therapy; F: female; M: male; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; vs.: versus | | |

Table 8: Characteristics of the study population – RCT, direct comparison: ruxolitinib vs. BAT (disease severity)

| **Study**<br>**Characteristics**<br>**Category** | **Ruxolitinib**<br>**N = 110** | **BAT**<br>**N = 112** |
|---|---|---|
| **RESPONSE** | | |
| ECOG performance status, n (%) | | |
| 0 | 76 (69.1) | 77 (68.8) |
| 1 | 31 (28.2) | 34 (30.4) |
| 2 | 3 (2.7) | 1 (0.9) |
| 3 or 4 | 0 (0) | 0 (0) |
| Disease duration: time between first diagnosis and randomization [months], mean (SD) | 106.8 (74.84) | 114.9 (68.52) |
| Hydroxyurea status, n (%) | | |
| Resistance | 51 (46.4) | 51 (45.5) |
| Intolerance | 59 (53.6) | 61 (54.5) |
| Duration of treatment with hydroxyurea [weeks], mean (SD) | 262.8 (268.34) | 244.8 (253.92) |
| History of thromboembolic events, n (%) | | |
| Yes | 39 (35.5) | 33 (29.5) |
| No | 71 (64.5) | 79 (70.5) |
| Haematocrit [%], mean (SD) | 43.6 (2.20) | 43.9 (2.17) |
| Leucocytes [$10^9$/L], mean (SD) | 17.6 (9.65) | 19.0 (12.16) |
| Platelets [$10^9$/L], mean (SD) | 484.5 (323.33) | 499.4 (318.60) |
| Spleen size [cm below the costal margin], mean (SD) | 7.8 (5.10) | 8.2 (5.61) |
| JAK2 mutation, n (%) | | |
| Yes | 104 (94.5) | 107 (95.5) |
| No | 3 (2.7) | 1 (0.9) |
| No data | 3 (2.7) | 4 (3.6) |

BAT: best available therapy; ECOG: Eastern Cooperative Oncology Group; JAK: Janus kinase; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patients in the intervention and control group were largely comparable with regard to the characteristics presented in Table 7 and Table 8. There were more men than women in both groups, and more than 85% of the patients in both groups were white. The mean disease duration at the start of the study was more than 106 months in both groups. Somewhat more than half of the patients in both groups were intolerant to hydroxyurea, whereas the other patients had resistance to hydroxyurea. Most patients in both groups were in good general condition (Eastern Cooperative Oncology Group [ECOG] 0/1).

Table 9 shows the median treatment duration of the patients and the follow-up period for individual outcomes.

Table 9: Information on the course of the study – RCT, direct comparison: ruxolitinib vs. BAT

| **Study**<br>**Duration of the study phase**<br>**Outcome category** | **Ruxolitinib**<br>**N = 110** | **BAT**<br>**N = 112** |
|---|---|---|
| **RESPONSE** | | |
| Median treatment duration up to the visit in week 32 [weeks], M [min; max] | 34.1 [1.1; 34.1] | 34.0 [2.1; 34.1] |
| Median treatment duration up to the data cut-off on 15 January 2014 [weeks], M [min; max] | 81 [1.1; 156.3] | 34 [2.1; 74.1] |
| Mean observation period [days], mean (SD) | | |
| Adverse events | ND | ND |
| Outcomes | ND | ND |

BAT: best available therapy; M: median; max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The primary data analysis was conducted on 15 January 2014; all patients had been treated for at least 48 weeks by then. At this time point, 84.5% of the patients in the intervention group and 2.7% in the control group were being treated with the treatments they had been originally allocated to. Most patients in the control arm (86%) crossed over to the ruxolitinib arm after treatment week 32. The median treatment duration up to week 32 was about 34 weeks in both groups. At the data cut-off in January 2014, the median treatment duration was 81 weeks in the intervention group, and 34 weeks in the control group. The data at the data cut-off on 15 January 2014 are therefore not interpretable. For this reason, post-hoc analyses were conducted after 32 weeks of treatment. The present benefit assessment was also based on the analyses at week 32.

Table 10 shows the risk of bias at study level regarding the data cut-off after a treatment duration of 32 weeks.

Table 10: Risk of bias at study level – RCT, direct comparison: ruxolitinib vs. BAT

| **Study** | | | **Blinding** | | | | |
|---|---|---|---|---|---|---|---|
| | **Adequate random sequence generation** | **Allocation concealment** | **Patient** | **Treating staff** | **Reporting independent of the results** | **No additional aspects** | **Risk of bias at study level** |
| RESPONSE | Yes | Yes | No | No | Yes | Yes | Low |

BAT: best available therapy; RCT: randomized controlled trial; vs.: versus

The risk of bias at the study level was rated as low for the study. This concurs with the company's assessment. Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias. Irrespective of this, 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.

## 2.4 Results on added benefit

### 2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - thromboembolic events
  - disease transformation
  - disease-related symptoms (EORTC QLQ-C30)
  - health status (PGIC)
- Health-related quality of life
  - health-related quality of life (EORTC QLQ-C30)
- Adverse events
  - SAEs
  - severe AEs (CTCAE grade 3/4)
  - discontinuation due to AEs
  - pruritus
  - muscle spasms
  - dyspnoea

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 11 shows for which outcomes data were available in the study included.

Table 11: Matrix of outcomes – RCT, direct comparison: ruxolitinib vs. BAT

| Study | Outcomes | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **All-cause mortality** | **Thromboembolic events** | **Disease transformation** | **Symptoms (EORTC QLQ-C30[a])** | **Health status (PGIC)** | **Health-related quality of life (EORTC QLQ-C30[b])** | **SAEs** | **Severe AEs (CTCAE grade 3/4)** | **Discontinuation due to AEs** | **Pruritus** | **Muscle spasms** | **Dyspnoea** |
| RESPONSE | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No[c] | Yes | Yes | Yes |

a: Measured with the EORTC QLQ-C30 symptom scales.
b: Measured with the EORTC QLQ-C30 functional scales.
c: No evaluable data; for reasons, see Section 2.7.2.4.3 of the full dossier assessment.
AE: adverse event; BAT: best available therapy; CTCAE: Common Terminology Criteria for Adverse Events, EORTC: European Organisation for Research and Treatment of Cancer; PGIC: Patient Global Impression of Change; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

### 2.4.2 Risk of bias

Table 12 shows the risk of bias for the relevant outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: ruxolitinib vs. BAT

| Study | | Outcomes | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study level | All-cause mortality | Thromboembolic events | Disease transformation | Symptoms (EORTC QLQ-C30[a]) | Health status (PGIC) | Health-related quality of life (EORTC QLQ-C30[b]) | SAEs | Severe AEs (CTCAE grade 3/4) | Discontinuation due to AEs | Pruritus | Muscle spasms | Dyspnoea |
| RESPONSE | L | L | L | L | H[c] | H[c] | H[c] | L | L | –[d] | H[e] | H[e] | H[e] |

a: Measured with the EORTC QLQ-C30 symptom scales.
b: Measured with the EORTC QLQ-C30 functional scales.
c: Due to the lack of blinding in subjective recording of outcomes and a relevant high proportion of patients who were not included in the analysis or because this proportion differed between the treatment groups to a relevant degree.
d: No evaluable data; for reasons, see Section 2.7.2.4.3 of the full dossier assessment.
e: Due to lack of blinding in subjective recording of outcomes.
AE: adverse event; BAT: best available therapy; CTCAE: Common Terminology Criteria for Adverse Events, EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; PGIC: Patient Global Impression of Change; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias for the outcome “overall survival” was rated as low. The company presented no analysis for overall survival and hence did not assess the risk of bias.

The risk of bias was also rated as low for the following outcomes: thromboembolic events, disease transformation, SAEs and severe AEs (CTCAE grade 3/4). This concurs with the company’s assessment.

No interpretable data were available for the outcome “discontinuation due to AEs” so that no outcome-specific rating of the risk of bias was conducted. This deviates from the company’s assessment, which assessed the risk of bias as low.

The risk of bias of the outcomes “symptoms (EORTC QLQ-C30)”, “health status (PGIC)” and “health-related quality of life (EORTC QLQ-C30)” was rated as high. This concurs with the company’s assessment. The outcomes “pruritus” “muscle spasms” and “dyspnoea” were assessed as having a high risk of bias. The company did not use these outcomes and hence did not assess the risk of bias.

### 2.4.3 Results

Table 13, Table 14 and Table 15 summarize the results of the comparison of ruxolitinib with the BAT in patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

The assessment was based on the total populations of both study arms with supplementary observation of the results of patients with approval-compliant treatment. The result in the group of patients who received approval-compliant treatment was in line with the qualitative conclusion on the basis of the total population (hint and no hint of an added benefit or greater harm). The results of the subpopulations of patients in the control group with approval-compliant and non-approval-compliant treatment are presented in Table 28, Table 29 and Table 30 in Appendix B of the full dossier assessment.

Table 13: Results (dichotomous outcomes) – RCT, direct comparison: ruxolitinib vs. BAT

| Study<br>Outcome category<br>Outcome | Ruxolitinib | | BAT | | Ruxolitinib vs. BAT |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | RR [95% CI]; p-value |
| **RESPONSE** | | | | | |
| **Mortality** | | | | | |
| All-cause mortality | 110 | 0 (0) | 111 | 0 (0) | |
| **Morbidity** | | | | | |
| Thromboembolic events | 110 | 1 (0.9) | 111 | 6 (5.4) | 0.17 [0.02; 1.37]; 0.120 |
| Disease transformation[a] | 110 | 3 (2.7)[b] | 111 | 1 (0.9)[b] | 3.03 [0.32; 28.66][c]; 0.326[d] |
| **Adverse events** | | | | | |
| AEs | 110 | 105 (95.5) | 111 | 104 (93.7) | |
| SAEs | 110 | 15 (13.6) | 111 | 10 (9.0) | 1.51 [0.71; 3.22]; 0.290[d] |
| Severe AEs (CTCAE grade 3/4) | 110 | 36 (32.7) | 111 | 32 (28.8) | 1.14 [0.76; 1.69]; 0.560[d] |
| Discontinuation due to AEs | No evaluable data | | | | |
| Pruritus | 110 | 15 (13.6) | 111 | 25 (22.5) | 0.61 [0.34; 1.08][c]; 0.096[d] |
| Muscle spasms | 110 | 13 (11.8) | 111 | 5 (4.5) | 2.62 [0.97; 7.11][c]; 0.049[d, e] |
| Dyspnoea | 110 | 11 (10.0) | 111 | 2 (1.8) | 5.55 [1.26; 24.46][c]; 0.010[d] |

a: Transformation to acute leukaemia or myelofibrosis.
b: Institute's calculation.
c: Institute's calculation of effect estimate and CI (asymptotic).
d: Institute's calculation; unconditional exact test (CSZ method according to [4]).
e: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
AE: adverse event; BAT: best available therapy; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 14: Results (categorical outcomes) – RCT, direct comparison: ruxolitinib vs. BAT

| **Study** | **Patients with one event n (%[a])** | | |
|---|---|---|---|
| **Outcome category**<br>**Outcome**<br>**Category** | **Ruxolitinib**<br>**N = 94** | **BAT**<br>**N = 103** | **p-value[b]** |
| **RESPONSE** | | | |
| **Morbidity** | | | |
| Health status (PGIC) | | | < 0.001 |
| Very much improved | 35 (37.2) | 4 (3.9) | |
| Much improved | 39 (41.5) | 10 (9.7) | |
| Minimally improved | 12 (12.8) | 23 (22.3) | |
| No change | 7 (7.4) | 47 (45.6) | |
| Minimally worse | 1 (1.1) | 15 (14.6) | |
| Much worse | 0 (0) | 4 (3.9) | |
| Very much worse | 0 (0) | 0 (0) | |

a: Institute's calculation.
b: Institute's calculation, Fisher exact test.
BAT: best available therapy; N: number of patients in the analysis; n: number of patients with event; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; vs.: versus

Table 15: Results (continuous outcomes) – RCT, direct comparison: ruxolitinib vs. BAT

| Study<br>Outcome category<br>Instrument<br>Scales | Ruxolitinib | | | BAT | | | Ruxolitinib vs. BAT |
|---|---|---|---|---|---|---|---|
| | N[a] | Baseline values mean (SD) | Change at week 32 mean (SD) | N[a] | Baseline values mean (SD) | Change at week 32 mean (SD) | Mean difference[b] [95% CI]; p-value |
| **RESPONSE** | | | | | | | |
| **Morbidity** | | | | | | | |
| Symptoms (EORTC QLQ-C30) | | | | | | | |
| Fatigue[c] | 89 | 37.70 (25.98) | -12.17 (23.40) | 81 | 36.76 (26.33) | 0.82 (18.74) | -12.60 [-18.17; -7.04]; < 0.001<br>Hedges' g: -0.61 [-0.91; -0.30][d] |
| Nausea/ vomiting[c] | 89 | 5.24 (12.71) | -1.50 (13.91) | 80 | 4.79 (10.34) | 0.21 (11.40) | -1.49 [-4.98; 2.01]; 0.402 |
| Pain[c] | 86 | 25.39 (25.79) | -11.05 (25.13) | 80 | 24.38 (25.84) | 0.21 (23.34) | -10.74 [-17.00; -4.47]; < 0.001<br>Hedges' g: -0.46 [-0.77; -0.15][d] |
| Dyspnoea[c] | 89 | 22.47 (28.33) | -5.99 (27.32) | 80 | 19.58 (26.88) | 2.50 (21.07) | -7.22 [-13.73; -0.71]; 0.030<br>Hedges' g: -0.34 [-0.65; -0.04][d] |
| Sleep disorder[c] | 89 | 26.97 (30.52) | -11.99 (32.66) | 81 | 37.04 (32.91) | -7.82 (22.53) | -9.41 [-16.49; -2.33]; 0.010<br>Hedges' g: -0.15 [-0.45; 0.15][d] |
| Appetite loss[c] | 88 | 12.50 (23.87) | -10.23 (21.06) | 81 | 15.64 (23.62) | -0.82 (20.40) | -11.40 [-15.74; -7.06]; < 0.001<br>Hedges' g: -0.45 [-0.76; -0.15][d] |
| Constipation[c] | 88 | 14.39 (25.17) | -2.65 (24.35) | 80 | 13.33 (22.87) | 1.67 (23.66) | -3.74 [-9.88; 2.40]; 0.231 |
| Diarrhoea[c] | 87 | 12.64 (23.43) | -3.83 (21.22) | 80 | 9.58 (17.75) | 2.92 (19.27) | -5.04 [-10.15; 0.07]; 0.053 |

(continued)

Table 15: Results (continuous outcomes) – RCT, direct comparison: ruxolitinib vs. BAT (continued)

| Study | Ruxolitinib | | | BAT | | | Ruxolitinib vs. BAT |
|---|---|---|---|---|---|---|---|
| Outcome category<br>Instrument<br>Scales | N[a] | Baseline values mean (SD) | Change at week 32 mean (SD) | N[a] | Baseline values mean (SD) | Change at week 32 mean (SD) | Mean difference[b] [95% CI]; p-value |
| **RESPONSE** | | | | | | | |
| **Health-related quality of life** | | | | | | | |
| EORTC QLQ-C30 | | | | | | | |
| General health status/quality of life[e] | 89 | 59.64 (22.08) | 10.86 (20.51) | 83 | 64.56 (22.00) | -4.82 (16.00) | 13.77 [8.80; 18.74]; < 0.001<br>Hedges' g: 0.85 [0.53; 1.16][d] |
| Physical functioning[e] | 90 | 80.00 (18.70) | 6.44 (15.43) | 84 | 83.17 (18.93) | -1.51 (12.98) | 6.90 [3.02; 10.79]; < 0.001<br>Hedges' g: 0.55 [0.25; 0.86][d] |
| Role functioning[e] | 88 | 78.41 (27.58) | 5.30 (26.57) | 81 | 78.19 (29.54) | -0.41 (22.20) | 5.82 [-0.30; 11.94]; 0.062 |
| Emotional functioning[e] | 88 | 75.88 (21.44) | 7.92 (17.78) | 80 | 77.40 (22.70) | 1.04 (15.43) | 6.40 [1.76; 11.05]; 0.007<br>Hedges' g: 0.41 [0.10; 0.72][d] |
| Cognitive functioning[e] | 88 | 76.70 (23.37) | 4.17 (21.03) | 80 | 77.92 (23.08) | -3.33 (19.74) | 6.92 [1.67; 12.18]; 0.010<br>Hedges' g: 0.37 [0.06; 0.67][d] |
| Social functioning[e] | 87 | 81.42 (26.10) | 7.66 (20.46) | 80 | 81.25 (24.93) | -0.42 (20.37) | 8.15 [2.91; 13.39]; 0.003<br>Hedges' g: 0.39 [0.09; 0.70][d] |

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Effect estimate; CI and p-value from an ANCOVA adjusted for baseline value.
c: Negative changes in comparison with start of study indicate improvement on a scale of 0 to 100.
d: Institute's calculation.
e: Positive changes in comparison with start of study indicate improvement on a scale of 0 to 100.
ANCOVA: analysis of covariance; BAT: best available therapy; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-C30; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

**Mortality**

***Overall survival***

No deaths occurred in the RESPONSE study up to treatment week 32. This resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

The company did not use this outcome in its assessment.

**Morbidity**

***Thromboembolic events***

There was no statistically significant difference between the intervention and the control group for the outcome "thromboembolic events". This resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived an added benefit for this outcome. It rated the probability as "high". However, for its assessment, it used the incidence density ratio at the data cut-off on 15 January 2014, which is not interpretable (see Section 2.3.2).

***Disease transformation***

There was no statistically significant difference between the intervention and the control group for the outcome "disease transformation". This resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

This concurs with the company's assessment.

***Disease-related symptoms (EORTC QLQ-C30)***

For the outcome **"fatigue"**, there was a statistically significant effect in favour of ruxolitinib. The 95% CI of Hedges' g was completely below the irrelevance threshold of −0.2. This was interpreted to be a relevant effect. This resulted in a hint of an added benefit of ruxolitinib in comparison with the BAT.

For each of the outcomes **"pain", "dyspnoea", "sleep disorder"** and **"appetite loss"**, there was a statistically significant effect in favour of ruxolitinib. In each case, however, the 95% CI of Hedges' g was not completely below the irrelevance threshold of −0.2. It can therefore not be inferred that the effects are relevant. Overall, this resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

There was no statistically significant difference between the intervention and the control group for the outcomes **"nausea/vomiting", "constipation"** and **"diarrhoea"**. This resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived an added benefit for these outcomes. It rated the probability as "high". The company based its assessment on a joint consideration of all outcomes recorded with the EORTC QLQ-C30 symptom scales.

***Health status (PGIC)***

For the outcome "health status (PGIC)" there was a statistically significant effect in favour of ruxolitinib. This resulted in a hint of an added benefit of ruxolitinib in comparison with the BAT.

The company presented this outcome as additional information.

**Health-related quality of life**

***Health-related quality of life (EORTC QLQ-C30)***

For each of the outcomes **"general health status/quality of life"** and **"physical functioning"**, there was a statistically significant effect in favour of ruxolitinib. In each case, the 95% CI of Hedges' g was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect in each case. This resulted in hints of an added benefit of ruxolitinib in comparison with the BAT.

For each of the outcomes **"emotional functioning", "cognitive functioning"** and **"social functioning"**, there was a statistically significant effect in favour of ruxolitinib. In each case, however, the 95% CI of Hedges' g was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that the effects are relevant. Overall, this resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

There was no statistically significant difference between the intervention and the control group for the outcome **"role functioning"**. This resulted in no hint of an added benefit of ruxolitinib in comparison with the BAT; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived an added benefit for these outcomes. It rated the probability as "high". The company based its assessment on a joint consideration of all outcomes recorded with the EORTC QLQ-C30 functional scales.

**Adverse events**

The AEs, SAEs and severe AEs (CTCAE grade 3/4) that most commonly occurred in the study are presented in Appendix A of the full dossier assessment.

There was no statistically significant difference between the intervention and the control group for the outcomes **"SAEs"** and **"severe AEs (CTCAE grade 3/4)"**. This resulted in no hint of greater or lesser harm from ruxolitinib in comparison with the BAT. Greater or lesser harm is not proven for these outcomes.

This concurs with the company's assessment.

There were no interpretable data for the outcome **"discontinuation due to AEs"** (see Section 2.7.2.4.3 of the full dossier assessment). This resulted in no hint of greater or lesser harm from ruxolitinib in comparison with the BAT. Greater or lesser harm is not proven for this outcome.

This concurs with the company's assessment.

There was no statistically significant difference between the intervention and the control group for the outcome **"pruritus"**. This resulted in no hint of greater or lesser harm from ruxolitinib in comparison with the BAT. Greater or lesser harm is not proven for this outcome.

The company did not use this outcome in its assessment.

For each of the outcomes **"muscle spasms"** and **"dyspnoea"**, there was a statistically significant difference to the disadvantage of ruxolitinib. Overall, this resulted in hints of greater harm from ruxolitinib in comparison with the BAT.

The company did not use these outcomes in its assessment.

### 2.4.4 Subgroups and other effect modifiers

Selected subgroups were to be investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifications. The company's dossier contained no subgroup analyses for the outcomes included in the present benefit assessment (see Section 2.7.2.4.3 of the full dossier assessment). Hence no subgroup results are presented.

## 2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level. Due to the large proportion of patients who were not treated in compliance with the approval, only non-quantifiable effects can be derived from the RESPONSE study.

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

### 2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in hints of an added benefit of ruxolitinib in comparison with the BAT for the following outcomes: fatigue (EORTC QLQ-C30 symptom scale), health status (PGIC), general health status/quality of life (EORTC QLQ-C30), and physical functioning (EORTC QLQ-C30 functional scale). For each of the AEs "muscle

spasms" and "dyspnoea", there was a hint of greater harm from ruxolitinib in comparison with the BAT.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 16).

Table 16: Extent of added benefit at outcome level: ruxolitinib vs. BAT

| **Outcome category**<br>**Outcome**<br>**Scale** | **Ruxolitinib vs. BAT**<br>**Proportion of events/mean change**<br>**Effect estimate [95% CI]**<br>**p-value**<br>**probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Mortality** | | |
| Overall survival | 0% vs. 0% | Added benefit not proven |
| **Morbidity** | | |
| Thromboembolic events | 0.9% vs. 5.4%<br>RR: 0.17 [0.02; 1.37]<br>p = 0.120 | Added benefit not proven |
| Disease transformation[c] | 2.7%[d] vs. 0.9%[d]<br>RR: 3.03 [0.32; 28.66][e]<br>p = 0.326[f] | Added benefit not proven |
| Symptoms (EORTC QLQ-C30) | | |
| Fatigue | -12.17 vs. 0.82<br>MD: -12.60 [-18.17; -7.04]<br>p < 0.001<br>Hedges' g: -0.61 [-0.91; -0.30][d]<br>probability: "hint" | Outcome category: non-serious/non-severe symptoms<br>added benefit, extent: "non-quantifiable" |
| Nausea/vomiting | -1.50 vs. 0.21<br>MD: -1.49 [-4.98; 2.01]<br>p = 0.402 | Added benefit not proven |
| Pain | -11.05 vs. 0.21<br>MD: -10.74 [-17.00; -4.47]<br>p < 0.001<br>Hedges' g: -0.46 [-0.77; -0.15][d]<br>No relevant effect can be derived | Added benefit not proven |
| Dyspnoea | -5.99 vs. 2.50<br>MD: -7.22 [-13.73; -0.71]<br>p = 0.030<br>Hedges' g: -0.34 [-0.65; -0.04][d]<br>No relevant effect can be derived | Added benefit not proven |
| Sleep disorder | -11.99 vs. -7.82<br>MD: -9.41 [-16.49; -2.33]<br>p = 0.010<br>Hedges' g: -0.15 [-0.45; 0.15][d]<br>No relevant effect can be derived | Added benefit not proven |

(continued)

Table 16: Extent of added benefit at outcome level: ruxolitinib vs. BAT (continued)

| **Outcome category**<br>**Outcome**<br>**Scale** | **Ruxolitinib vs. BAT**<br>**Proportion of events/mean change**<br>**Effect estimate [95% CI]**<br>**p-value**<br>**probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Morbidity** | | |
| Symptoms (EORTC QLQ-C30) | | |
| Appetite loss | -10.23 vs. -0.82<br>MD: -11.40 [-15.74; -7.06]<br>p < 0.001<br>Hedges' g: -0.45 [-0.76; -0.15][d]<br>No relevant effect can be derived | Added benefit not proven |
| Constipation | -2.65 vs. 1.67<br>MD: -3.74 [-9.88; 2.40]<br>p = 0.231 | Added benefit not proven |
| Diarrhoea | -3.83 vs. 2.92<br>MD: -5.04 [-10.15; 0.07]<br>p = 0.053 | Added benefit not proven |
| Health status (PGIC) | Very much improved: 37.2 vs. 3.9<br>Much improved: 41.5 vs. 9.7<br>Minimally improved: 12.8 vs. 22.3<br>No change: 7.4 vs. 45.6<br>Minimally worse: 1.1 vs. 14.6<br>Much worse: 0 vs. 3.9<br>Very much worse: 0 vs. 0<br>p < 0.001[g]<br>probability: "hint" | Outcome category: non-serious/non-severe symptoms<br>added benefit, extent: "non-quantifiable" |
| **Health-related quality of life** | | |
| EORTC QLQ-C30 | | |
| General health status/quality of life | 10.86 vs. -4.82<br>MD: 13.77 [8.80; 18.74]<br>p < 0.001<br>Hedges' g: 0.85 [0.53; 1.16][d]<br>probability: "hint" | Outcome category: health-related quality of life<br>added benefit, extent: "non-quantifiable" |
| Physical functioning | 6.44 vs. -1.51<br>MD: 6.90 [3.02; 10.79]<br>p < 0.001<br>Hedges' g: 0.55 [0.25; 0.86][d]<br>probability: "hint" | Outcome category: health-related quality of life<br>added benefit, extent: "non-quantifiable" |
| Role functioning | 5.30 vs. -0.41<br>MD: 5.82 [-0.30; 11.94]<br>p = 0.062 | Added benefit not proven |

(continued)

Table 16: Extent of added benefit at outcome level: ruxolitinib vs. BAT (continued)

| **Outcome category**<br>**Outcome**<br>**Scale** | **Ruxolitinib vs. BAT**<br>**Proportion of events/mean change**<br>**Effect estimate [95% CI]**<br>**p-value**<br>**probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Health-related quality of life** | | |
| EORTC QLQ-C30 | | |
| Emotional functioning | 7.92 vs. 1.04<br>MD: 6.40 [1.76; 11.05]<br>p = 0.007<br>Hedges' g: 0.41 [0.10; 0.72][d]<br>No relevant effect can be derived | Added benefit not proven |
| Cognitive functioning | 4.17 vs. -3.33<br>MD: 6.92 [1.67; 12.18]<br>p = 0.010<br>Hedges' g: 0.37 [0.06; 0.67][d]<br>No relevant effect can be derived | Added benefit not proven |
| Social functioning | 7.66 vs. -0.42<br>MD: 8.15 [2.91; 13.39]<br>p = 0.003<br>Hedges' g: 0.39 [0.09; 0.70][d]<br>No relevant effect can be derived | Added benefit not proven |
| **Adverse events** | | |
| SAEs | 13.6% vs. 9.0%<br>RR: 1.51 [0.71; 3.22]<br>p = 0.290[f] | Greater/lesser harm not proven |
| Severe AEs<br>(CTCAE grade 3/4) | 32.7% vs. 28.8%<br>RR: 1.14 [0.76; 1.69]<br>p = 0.560[f] | Greater/lesser harm not proven |
| Discontinuation due to AEs | No evaluable data | |
| Pruritus | 13.6% vs. 22.5%<br>RR: 0.61 [0.34; 1.08][e]<br>p = 0.096[f] | Greater/lesser harm not proven |
| Muscle spasms | 11.8% vs. 4.5%<br>RR: 2.62 [0.97; 7.11][e, h]<br>p = 0.049[f]<br>probability: "hint" | Outcome category: non-serious/non-severe AEs<br>greater harm, extent: "non-quantifiable" |
| Dyspnoea | 10.0% vs. 1.8%<br>RR: 5.55 [1.26; 24.46][e]<br>p = 0.010[f]<br>probability: "hint" | Outcome category: non-serious/non-severe AEs<br>greater harm, extent: "non-quantifiable" |

(continued)

Table 16: Extent of added benefit at outcome level: ruxolitinib vs. BAT (continued)

| |
|---|
| a: Probability provided if statistically significant differences were present.<br>b: In large effects, estimations of effect size are made depending on the outcome category with different limits based on the $CI_u$.<br>c: Transformation to acute leukaemia or myelofibrosis<br>d: Institute's calculation.<br>e: Institute's calculation of effect estimate and CI (asymptotic).<br>f: Institute's calculation, unconditional exact test (CSZ method according to [4]).<br>g: Institute's calculation, Fisher exact test.<br>h: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.<br>AE: adverse event; BAT: best available therapy; CI: confidence interval, $CI_u$: upper limit of CI;<br>CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events;<br>EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; RR: relative risk; SAE: serious adverse event; vs.: versus |

### 2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of ruxolitinib in comparison with the BAT

| **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" (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) | |
| BAT: best available therapy | |

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 and health status) 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 AEs (muscle spasms and dyspnoea), also with the extent "non-quantifiable". It should be noted in the interpretation of this greater harm that the EORTC QLQ-C30 produced opposing results in the recording of dyspnoea. Hence overall, the greater harm does not outweigh the positive effects regarding benefit, and a hint of an added benefit with the extent "non-quantifiable" remains.

The result of the assessment of the added benefit of ruxolitinib in comparison with the ACT is summarized in Table 18.

Table 18: Ruxolitinib – extent and probability of added benefit

| **Therapeutic indication** | **ACT**[a] | **Extent and probability of added benefit** |
|---|---|---|
| Treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxycarbamide (hydroxyurea) | Individual treatment at the physician's discretion, generally under consideration of the approval status in drug treatments; if appropriate dose reduction of or retreatment with hydroxyurea also possible | Hint of a non-quantifiable added benefit |
| a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | | |

This deviates from the company's approach, which derived considerable added benefit of ruxolitinib.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

## 2.6 List of included studies

**RESPONSE**

Incyte Corporation. Study of efficacy and safety in polycythemia vera subjects who are resistant to or intolerant of hydroxyurea: JAK inhibitor INC424 (INCB018424) tablets versus best available care; the RESPONSE trial; study results [online]. In: ClinicalTrials.gov. 19 February 2015 [accessed: 28 April 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01243944.

Incyte Corporation. Study of efficacy and safety in polycythemia vera subjects who are resistant to or intolerant of hydroxyurea: JAK inhibitor INC424 (INCB018424) tablets versus best available care: the RESPONSE trial; full text view [online]. In: ClinicalTrials.gov. 8 April 2015 [accessed: 10 July 2015]. URL: http://clinicaltrials.gov/show/NCT01243944.

Novartis. Randomized, open label, multicenter phase III study of efficacy and safety in polycythemia vera subjects who are resistant to or intolerant of hydroxyurea: JAK inhibitor INC424 tablets versus best available care (the RESPONSE Trial); protocol (Italy) [online]. In: EU Clinical Trials Register. [Accessed: 1 December 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-020807-57/IT.

Novartis. Randomized, open label, multicenter phase III study of efficacy and safety in polycythemia vera subjects who are resistant to or intolerant of hydroxyurea: JAK inhibitor INC424 tablets versus best available care (The RESPONSE Trial): study CINC424B2301; clinical study report (primary analysis) [unpublished]. 2014.

Vannucchi AM, Kiladjian JJ, Griesshammer M, Masszi T, Durrant S, Passamonti F et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med 2015; 372(5): 426-435.

**References for English extract**

Please see full dossier assessment for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden: Version 4.2. Köln: IQWiG; 2015. URL: https://www.iqwig.de/download/IQWiG_Methoden_Version_4-2.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2 July 2015 [Epub ahead of print].

3. Novartis. Jakavi Tabletten: Fachinformation [online]. March 2015 [accessed: 14 April 2015]. URL: http://www.fachinfo.de.

4. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

*The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-13-ruxolitinib-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6678.html.*