IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
JAK	Janus kinase
MFSAF	Myelofibrosis Symptom Assessment Form
PET-MF	post-essential thrombocythaemia myelofibrosis
PMF	primary myelofibrosis
PPV-MF	post-polycythaemia vera myelofibrosis
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
TSS	total symptom score

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 16 May 2014.

Research question

The aim of this report was to assess the added benefit of ruxolitinib in comparison with the appropriate comparator therapy (ACT) in patients with disease-related splenomegaly or symptoms with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis.

The G-BA specified best supportive care (BSC) as ACT. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The company followed the G-BA's specification. For the benefit assessment of ruxolitinib in comparison with the ACT BSC, studies were considered that investigated a comparison of ruxolitinib with or without BSC versus BSC. In the framework of the dossier assessment, the eligibility of the patients for allogeneic stem cell transplantation was also checked for study inclusion.

The assessment was conducted based on patient-relevant outcomes. One direct comparative randomized controlled trial (RCT) was included in the assessment.

Results

One relevant study (COMFORT-I) was available for the benefit assessment. This is a randomized, double-blind, multicentre study comparing ruxolitinib + BSC with placebo + BSC. Adult patients with primary myelofibrosis (PMF), post-essential thrombocythaemia myelofibrosis (PET-MF) or post-polycythaemia vera myelofibrosis (PPV-MF) were enrolled in the study. The patients had to have an intermediate-2 or high-risk profile and, according to the treating doctor, had to be resistant, refractory or intolerant to other available treatment options. A total of 309 patients were randomly assigned in a ratio of 1:1, either to treatment with ruxolitinib + BSC (155 patients) or to treatment with placebo + BSC (154 patients).

The primary analysis was conducted on 2 November 2010, after all patients had been treated for 24 weeks and 50% of the patients had been treated for 36 weeks (or had discontinued treatment prematurely). After the primary analysis, all patients were unblinded and could switch to the ruxolitinib + BSC arm. A 3-year analysis was conducted on 25 January 2013, after all patients had been treated for at least 144 weeks. Following amendment 4 to the study

protocol, the study duration was prolonged to 5 years to be able to record long-term data on safety and effectiveness of ruxolitinib treatment. The study will probably end in June 2015.

The risk of bias of the COMFORT-I study at study level was rated as low so that, in principle, indications of an added benefit could be derived.

For the outcome "overall survival", the risk of bias was rated as high particularly due to the high proportion of patients who switched treatment at the dates of analysis used. For the outcome "Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 (symptoms of myelofibrosis, improvement in total symptom score (TSS) by ≥ 50%)", the risk of bias was also rated as high because considerably more patients were classified as non-responders in the placebo + BSC arm due to missing values. However, sensitivity analyses conducted in the framework of the benefit assessment showed that no important doubts were raised about the magnitude of the resulting effect by the differential proportion of missing values in both groups. The high risk of bias as a whole did therefore not lead to downgrading the reliability of the conclusions. In the remaining outcomes considered, the risk of bias was rated as low in each case.

Mortality (overall survival)

Several dates of analysis were used for the outcome "overall survival". Some of them were not statistically significant, and some of them showed significant results in favour of ruxolitinib. Overall, there was a hint of an added benefit of ruxolitinib + BSC in comparison with the ACT (BSC).

Morbidity

MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)

For the outcome on symptoms of myelofibrosis (MFSAF v2.0, improvement in TSS by ≥ 50%), there was a statistically significant difference between the treatment groups in favour of ruxolitinib + BSC. Based on the COMFORT-I study, there was therefore an indication of an added benefit of ruxolitinib + BSC in comparison with the ACT (BSC).

Leukaemic transformation

For the outcome "leukaemic transformation", there was no statistically significant difference between the treatment groups. An added benefit of ruxolitinib + BSC in comparison with BSC is not proven for this outcome.

EORTC QLQ-C30 (symptoms)

The dossier contained no evaluable data on symptoms recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) symptom scales because the difference of the proportions of patients who were not considered was approximately 20% between the treatment groups and therefore

too high to derive informative results. An added benefit of ruxolitinib + BSC in comparison with BSC is not proven for this outcome.

Health-related quality of life

EORTC QLQ-C30 (health-related quality of life)

The dossier contained no evaluable data on health-related quality of life recorded with the EORTC QLQ-C30 functional scales because the difference of the proportions of patients who were not considered was approximately 20% between the treatment groups and therefore too high to derive informative results. An added benefit of ruxolitinib + BSC in comparison with BSC is not proven for this outcome.

Adverse events

Overall rates of serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events

Overall, the results on the overall rates of adverse events (AEs) were regarded to be not interpretable due to the extensive recording of symptoms of the underlying disease in the recording of the AEs. However, as the absolute differences between the overall rates of AEs was not very large and the recording of symptoms particularly occurred in the placebo + BSC arm, overall greater harm from ruxolitinib can also not be excluded.

Anaemia (serious adverse event)

For the outcome "anaemia (serious AE [SAE])", there was no statistically significant difference between the treatment groups. Greater or lesser harm from ruxolitinib + BSC compared with BSC is not proven for this outcome.

Bleeding (SMQ)

For the outcome "bleeding (Standardized Medical Dictionary for Regulatory Activities Query [SMQ])", there was no statistically significant difference between the treatment groups. Greater or lesser harm from ruxolitinib + BSC compared with BSC is not proven for this outcome.

Nervous system disorders (SOC)

For the outcome "nervous system disorders (System Organ Class [SOC]), there was a statistically significant difference between the treatment groups to the disadvantage of ruxolitinib, the effect size was only marginal, however. Greater or lesser harm from ruxolitinib + BSC compared with BSC is not proven for this outcome.

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, exclusively positive effects remain. In the outcome category "morbidity (MFSAF v2.0 [symptoms of myelofibrosis, improvement in TSS by ≥ 50%])" there is an indication of an added benefit with the extent "considerable". In the outcome category "mortality (overall survival)", there is a hint of a non-quantifiable added benefit.

For the outcomes regarding harm, there is the problem that, overall, the analyses on overall rates of AEs were regarded to be not interpretable due to the extensive recording of symptoms of the underlying disease. Hence no final conclusion can be drawn on harm. Greater harm from ruxolitinib can also not be completely excluded. The available results, however, did not provide signs of harm in a magnitude that would justify downgrading the added benefit. This is particularly due to the size of the effect regarding benefit for the outcome "MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)", which shows the considerable improvement in the burdensome symptoms of the underlying disease.

In summary, for patients with disease-related splenomegaly or symptoms with PMF, PPV-MF or PET-MF, there is an indication of considerable added benefit of ruxolitinib + BSC versus the ACT BSC.

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

Table 2: Ruxolitinib – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Treatment of disease-related splenomegaly or symptoms in adults with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis	BSC[b]	Indication of considerable added benefit
a: Presentation of the ACT specified by the G-BA. b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee		

[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), see [1]. 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), see [2].

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 was to assess the added benefit of ruxolitinib in comparison with the ACT in patients with disease-related splenomegaly or symptoms with PMF, PPV-MF or PET-MF.

The G-BA specified BSC as ACT. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The company followed the G-BA's specification. For the benefit assessment of ruxolitinib in comparison with the ACT BSC, studies were considered that investigated a comparison of ruxolitinib with or without BSC versus BSC. In the framework of the dossier assessment, the eligibility of the patients for allogeneic stem cell transplantation was also checked for study inclusion (see Sections 2.7.1 and 2.7.2.1 of the full dossier assessment).

The assessment was conducted based on patient-relevant outcomes. One direct comparative RCT was included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

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 26 February 2014)
- bibliographical literature search on ruxolitinib (last search on 24 February 2014)
- search in trial registries for studies on ruxolitinib (last search on 24 February 2014)

To check the completeness of the study pool:

- search in trial registries for studies on ruxolitinib (last search on 21 May 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The study listed in Table 3 was included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: ruxolitinib + BSC vs. placebo + BSC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
COMFORT-I	Yes	Yes	No

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of ruxolitinib deviates from that of the company, which, besides the COMFORT-I study, also included the COMFORT-II study in the assessment and used both studies for the derivation of an added benefit.

Contrary to the company's assessment, the COMFORT-II study was not included in the benefit assessment because the ACT (BSC) was not implemented in the comparator arm and because drugs were used outside the approval (for detailed reasons see Section 2.7.2.3.2 of the full dossier assessment).

Section 2.6 contains a reference list for the COMFORT-I study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 4 and Table 5 show the characteristics of the COMFORT-I study and of the interventions investigated in this study.

Table 4: Characteristics of the studies included – RCT, direct comparison: ruxolitinib + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
COMFORT-I	RCT, double-blind, placebo-controlled, multicentre	Adult patients with primary or secondary myelofibrosis (PMF, PPV-MF, PET-MF) with intermediate-2 or high-risk profile[b] who, according to the treating doctor, were resistant, refractory or intolerant to other available treatment options. The patients also had to have a palpable spleen of ≥ 5 cm below the costal margin and a life expectancy of 6 months or longer.	Ruxolitinib + BSC (N = 155) placebo + BSC (N = 154)	Primary analysis after all patients had been treated for 24 weeks and 50% of the patients had been treated for 36 weeks <u>Premature treatment switching:</u> Patients with an increase in spleen volume of ≥ 25% in addition to defined worsening of symptoms[c] could be unblinded before week 24 and change to the ruxolitinib + BSC arm. After the primary analysis, all patients were unblinded and could switch to the ruxolitinib + BSC arm (precondition: adequate laboratory findings[d]). In amendment 4, the study duration was prolonged from 144 weeks to 264 weeks (5 years).	89 centres in Australia, Canada, and United States ongoing study first patient enrolled: 8/2009 cut-off date for primary analysis: 11/2010 end of study probably in June 2015	Primary outcome: proportion of patients with a reduction of ≥ 35% in spleen volume after 24 weeks secondary outcomes: overall survival, modified MFSAF v2.0 (proportion of patients with an improvement in TSS by ≥ 50%), leukaemic transformation, EORTC QLQ-C30 (symptoms and health-related quality of life), adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for the present benefit assessment.
b: Risk classification according to the prognostic score of the International Working Group [3].
c: Worsening of early satiety with accompanying weight loss (≥ 10% compared with baseline) or worsening of (spleen) pain requiring the use of anaesthetics.
d: platelet count ≥ 75,000/µL and absolute neutrophil count ≥ 500/µL.

BSC: best supportive care; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MFSAF: Myelofibrosis Symptom Assessment Form; N: number of randomized patients; PET-MF: post-essential thrombocythaemia myelofibrosis; PMF: primary myelofibrosis; PPV-MF: post-polycythaemia vera myelofibrosis; RCT: randomized controlled trial; TSS: total symptom score; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: ruxolitinib + BSC vs. placebo + BSC

Study	Intervention	Comparison	Concomitant medication
COMFORT-I	Ruxolitinib depending on platelet count (N = 155): > 200,000/µL: starting dose 20 mg (≙ 4 tablets) twice a day; > 100,000 to ≤ 200,000/µL: starting dose 15 mg (≙ 3 tablets) twice a day. Dose adjustments were conducted during the course of the study depending on the platelet count. As soon as the platelet count was below 50,000/µL or the absolute neutrophil count was below 500/µL, ruxolitinib treatment had to be discontinued. Maximum dose: 25 mg twice a day.	Placebo (N = 154): depending on the platelet count 3 or 4 placebo tablets twice a day. To maintain blinding, dose adjustments depending on the platelet count were also conducted in the placebo + BSC arm.	Comprehensive concomitant medication as BSC[a] was allowed in both study arms (e.g. opioids; other analgesics, antihistamines, corticosteroids[b], motility inhibitors, antiemetics, laxatives, antithrombotics, antibiotics, antidepressants, anxiolytics, hypnotics/sedatives, blood transfusions). Simultaneous treatment with the following drugs was not allowed: ▪ other drugs that are still under clinical investigation ▪ potent CYP3A4 inducers (e.g. St. John's Wort) ▪ hydroxycarbamide, interferon, thalidomide, busulfan, lenalidomide or anagrelide ▪ haematopoietic growth factors[c] (e.g. erythropoietin)

a: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
b: According to the study protocol, the use of systemic corticosteroids was limited to a maximum of 10 mg prednisolone (equivalents) [4].
c: According to the study protocol, haematopoietic growth factors were excluded because they can lead to an increase in splenomegaly [4].
BSC: best supportive care; CYP3A4: isoenzyme cytochrome P_{450} 3A4; RCT: randomized controlled trial; vs.: versus

The COMFORT-I study is a randomized, double-blind, multicentre study comparing ruxolitinib + BSC with placebo + BSC. Adult patients with primary myelofibrosis (PMF), post-essential thrombocythaemia myelofibrosis (PET-MF) or post-polycythaemia vera myelofibrosis (PPV-MF) were enrolled in the study. The patients had to have an intermediate-2 or high-risk profile. According to the Summary of Product Characteristics (SPC) however, ruxolitinib is approved for patients of all risk classes who have splenomegaly or disease-related symptoms [5]. Hence the study population did not cover patients with low risk and intermediate-risk 1 who have splenomegaly or disease-related symptoms. It is unclear whether the study results of the COMFORT-I study are transferable to these patients. Moreover, the patients included in the study had to be resistant, refractory or intolerant to

other available treatment options, according to the treating doctor. Although allogeneic stem cell transplantation was not explicitly mentioned in this context, it can be assumed that this can also be regarded as an available treatment option and that the included patients were therefore not eligible for stem cell transplantation. Hence the study population also fulfilled the criterion defined by the G-BA that the patients considered to be the target population for the use of ruxolitinib are not allowed to be eligible for curative stem cell transplantation (see Sections 2.7.1 and 2.7.2.1 of the full dossier assessment).

A total of 309 patients were randomly assigned in a ratio of 1:1, either to treatment with ruxolitinib + BSC (155 patients) or to treatment with placebo + BSC (154 patients).

The primary analysis was conducted on 2 November 2010, after all patients had been treated for 24 weeks and 50% of the patients had been treated for 36 weeks (or had discontinued treatment prematurely). Before the primary analysis, patients with an increase in spleen volume of ≥ 25% could be unblinded and switch to the open-label ruxolitinib treatment; before week 24, defined worsening of symptoms was an additional prerequisite. After the primary analysis, all patients were unblinded and (in case of adequate laboratory findings) could switch to the ruxolitinib + BSC arm. A 3-year analysis was conducted on 25 January 2013, after all patients had been treated for at least 144 weeks. Following amendment 4 to the study protocol, the study duration was prolonged to 5 years to be able to record long-term data on safety and effectiveness of ruxolitinib treatment. The study will probably end in June 2015.

Primary outcome of the study was the proportion of patients with a reduction of ≥ 35% in spleen volume after 24 weeks. As this was an unvalidated surrogate outcome, this outcome was not included in the benefit assessment, however (see Section 2.7.2.9.4 of the full dossier assessment). The outcomes of overall survival, MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%), leukaemic transformation, EORTC QLQ-C30 (symptoms and health-related quality of life) as well as AEs were considered to be patient-relevant and included in the benefit assessment.

In the study, the drug ruxolitinib was used in accordance with its approval [5]: Depending on the platelet count, the starting dose was 15 mg twice a day (corresponding to 3 tablets of 5 mg) or 20 mg (corresponding to 4 tablets of 5 mg), and dose adjustments were allowed after assessment of the effectiveness and tolerability within the approved dosage of 5 mg to 25 mg (in each case twice a day). Patients in the placebo + BSC arm received tablets of identical appearance and “dose adjustments” were also conducted to maintain blinding.

In both study arms, comprehensive concomitant medication in the sense of BSC was allowed to provide patients with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (see Table 5). The only limitation of the concomitant medication was a small number of drugs that were explicitly excluded (e.g. hydroxyurea, CYP3A4 inducers, haematopoietic growth factors). It is to be discussed whether

the exclusion of haematopoietic growth factors raises doubts about the adequate implementation of BSC because burdensome cytopenias can be expected in the framework of the study, which require adequate treatment to relieve their symptoms. However, as blood transfusions for the treatment of cytopenias were allowed in the COMFORT-I study, this limitation as a whole was accepted.

Table 6 shows the characteristics of the patients in the study included.

Table 6: Characteristics of the study populations – RCT, direct comparison: ruxolitinib + BSC vs. placebo + BSC

Study characteristics category	**Ruxolitinib + BSC N[a] = 155**	**Placebo + BSC N[a] = 154**
COMFORT-I		
Age [years]		
Mean (SD)	67 (9)	69 (9)
> 65	85 (55)	102 (66)
≤ 65	70 (45)	52 (34)
Sex: [F/M], %	49/51	42[b]/57[b]
Skin colour, n (%)		
white	138 (89)	139 (90)
other	17 (11)	15 (10)
Myelofibrosis subtype, n (%)		
PMF	70 (45)	84 (55)[b]
PPV-MF	50 (32)	47 (31)[b]
PET-MF	35 (23)	22 (14)[b]
Time since diagnosis [years], mean (SD)	4.9 (6.1)	4.6 (6.2)
Spleen size		
volume (cm^3), mean (SD)	2746 (1247)	2798 (1389)
≤ 10 cm, n (%)[c]	32 (20.6)	27 (17.5)
> 10 cm, n (%)[c]	123 (79.4)	126 (81.8)
ECOG Performance Status		
0	47 (30.3)	38 (24.7)
1	87 (56.1)	82 (53.2)
2	14 (9.0)	25 (16.2)
3	3 (1.9)	4 (2.6)
missing	4 (2.6)	5 (3.2)
Risk group[d], n (%)		
high risk	90 (58.1)	99 (64.3)
intermediate-2 risk	64 (41.3)	54 (35.1)
unknown	1 (0.6)	1 (0.6)
JAK2V617F mutation, n (%)		
yes	113 (72.9)	123 (79.9)
no	40 (25.8)	27 (17.5)
unknown	2 (1.3)	4 (2.6)
Study discontinuations[e], n (%)	21 (13.5)	37 (24.5)

(continued)

Table 6: Characteristics of the study populations – RCT, direct comparison: ruxolitinib + BSC vs. placebo + BSC (continued)

a: Number of randomized patients. Values that are based on other patient data are marked in the respective column if the deviation was identified as relevant (≥ 5%).
b: One patient's data are missing because the documents were lost when the study centre moved.
c: The palpable spleen size below the costal margin is given.
d: Risk classification according to the prognostic score of the International Working Group [3].
e: Referring to the primary data analysis on 2 November 2010.
BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; F: female; JAK: Janus kinase; M: male; n: number of patients in the category; N: number of randomized patients; PET-MF: post-essential thrombocythaemia myelofibrosis; PMF: primary myelofibrosis; PPV-MF: post-polycythaemia vera myelofibrosis; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The characteristics at the start of the study were largely comparable between the 2 treatment arms. However, patients in the placebo + BSC arm were somewhat older and the proportion of patients in the high-risk group was marginally higher in the placebo + BSC arm than in the ruxolitinib + BSC arm (64.3% versus 58.1%). It is unclear, however, whether these differences, which rather favour the ruxolitinib + BSC arm, have a considerable influence on the treatment effects.

Table 7 shows the risk of bias at study level.

Table 7: Risk of bias at study level – RCT, direct comparison: ruxolitinib + BSC vs. placebo + BSC

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

BSC: best supportive care; RCT: randomized controlled trial; vs.: versus

The risk of bias at the study level was rated as low for the COMFORT-I study. This concurs with the company's assessment.

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1 and 4.3.1.2.2, and Appendix 4-F of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were considered in the assessment of the added benefit of ruxolitinib comparison with the ACT (BSC) (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)
  - leukaemic transformation
  - EORTC QLQ-C30 (symptoms); measured with the symptom scales of the EORTC QLQ-C30 instrument
- Health-related quality of life
  - EORTC QLQ-C30 (health-related quality of life); measured with the functional scales of the EORTC QLQ-C30 instrument
- Adverse events
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - anaemia (SAE)
  - bleeding (SMQ)
  - nervous system disorders (SOC)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in its dossier (Module 4). In particular, the outcome “reduction in spleen size” was not used for the present benefit assessment because this outcome was regarded to be an unvalidated surrogate outcome (see Section 2.7.2.9.4 of the full dossier assessment). In addition to the dossier, the outcome “leukaemic transformation” was rated as patient-relevant in the benefit assessment because this is a severe late complication of the disease with very poor prognosis. The specific AEs “anaemia (SAE)”, “bleeding (SMQ) and “nervous system disorders (SOC)” were chosen based on frequency and differences between the treatment groups in the COMFORT-I study and under consideration of the patient relevance.

Further information on the choice of outcomes can be found in Module 4, Section 4.3.1.3 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

Table 8 shows for which outcomes data were available in the studies included.

Table 8: Matrix of outcomes – RCT, direct comparison: ruxolitinib + BSC vs. placebo + BSC

Study	Outcomes										
	Overall survival	MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)	Leukaemic transformation	EORTC QLQ-C30 (symptoms[a])	EORTC QLQ-C30 (health-related quality of life[b])	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Anaemia (SAE)	Bleeding (SMQ)	Nervous system disorders (SOC)
COMFORT-I	Yes	Yes	Yes	No[c]	No[c]	Yes	Yes	Yes	Yes	Yes	Yes

a: Measured with the EORTC QLQ-C30 symptom scales.
b: Measured with the EORTC QLQ-C30 functional scales.
c: No evaluable results available. See Section 2.7.2.4.3 of the full dossier assessment for reasons.
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; MedDRA: Medical Dictionary for Regulatory Activities; MFSAF: Myelofibrosis Symptom Assessment Form; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: MedDRA System Organ Class; TSS: total symptom score; vs.: versus

For all outcomes considered to be relevant for the assessment, data were available in the documents presented. The dates and types of analyses differed depending on the outcome. For the outcomes MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%) and EORTC QLQ-C30 (symptoms and health-related quality of life), data were available for both treatment groups up to week 24. The analyses on the EORTC QLQ-C30 could not be used in the benefit assessment because of the high proportion of patients who remained unconsidered in the analysis. Data up to the first data cut-off on 2 November 2010 (primary analysis[5]) were included in the analyses of AEs (including the outcome "leukaemic transformation"). However, the AEs of the patients who switched from the placebo + BSC arm to the ruxolitinib + BSC arm before reaching the primary analysis were only considered in the analysis up to the time point of the treatment switch. This applied to 36 patients (see Section 2.7.2.4.3 of the full dossier assessment). For the outcomes mentioned, no results at later analysis dates were available, which would have allowed a randomized group comparison. For the outcome "overall survival", additional further results (intention to treat [ITT] analyses) at later analysis dates were available (last available time point: 5 April 2013), which

[5] The primary analysis was conducted after all patients had been treated for 24 weeks and 50% of the patients had been treated for 36 weeks (or had discontinued treatment prematurely).

were considered in the benefit assessment to obtain a comprehensive picture with regard to overall survival (see Section 2.4.3 and Section 2.7.2.4.3 of the full dossier assessment).

2.4.2 Risk of bias at outcome level

Table 9 shows the risk of bias for these outcomes.

Table 9: Risk of bias at study and outcome level – RCT, direct comparison: ruxolitinib + BSC vs. placebo + BSC

Study		Outcomes										
	Study level	Overall survival	MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)	Leukaemic transformation	EORTC QLQ-C30 (symptoms[a])	Health-related quality of life[b]	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Anaemia (SAE)	Bleeding (SMQ)	Nervous system disorders (SOC)
COMFORT-I	L	H[c]	H[d]	L	–[e]	–[e]	L[f]	L[f]	L[f]	L	L	L

a: Measured with the EORTC QLQ-C30 symptom scales.
b: Measured with the EORTC QLQ-C30 functional scales.
c: Overall the results on this outcome were considered to be highly biased because of the high proportion of patients in the placebo + BSC arm who switched to the ruxolitinib + BSC arm (see Section 2.4.3 and Section 2.7.2.4.3 of the full dossier assessment).
d: The results on this outcome were considered to be highly biased because of the different proportion of patients who were regarded as non-responders in the analysis due to missing values. However, this did not lead to a downgrading of the reliability of the conclusions (for reasons, see the following text and Section 2.7.2.4.2 of the full dossier assessment).
e: No evaluable data available.
f: The available analyses on overall AE rates were not evaluable due to the comprehensive consideration of disease symptoms (see Section 2.4.3 and Section 2.7.2.4.3 of the full dossier assessment for explanation).
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; MFSAF: Myelofibrosis Symptom Assessment Form; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: MedDRA System Organ Class; TSS: total symptom score; vs.: versus

The risk of bias for the outcome "overall survival" was rated as high. This deviates from the company's assessment, which assessed the outcome as having a low bias. The high risk of bias for the benefit assessment is mainly due to the high proportion of patients who switched treatment at the (late) analysis dates used. There were no evaluable data for the outcome

"EORTC QLQ-C30 (symptoms and health-related quality of life)". Therefore no outcome-specific assessment of the risk of bias was conducted.

For the outcome "MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%), the risk of bias was assessed as high for the available early analysis date. This deviates from the company's assessment, which assessed the outcome as having a low bias. The high risk of bias was due to the fact that, in the placebo + BSC arm, considerably more patients were classified as non-responders due to missing values (ruxolitinib + BSC arm: 24 patients, placebo + BSC arm: 49 patients). However, sensitivity analyses conducted in the framework of the benefit assessment showed that no important doubts were raised about the magnitude of the resulting effect by the differential proportion of missing values in both groups (see Section 2.7.2.4.2 of the full dossier assessment for detailed reasons). The high risk of bias as a whole did therefore not lead to downgrading the reliability of the conclusions.

The overall rate of AEs was principally considered to have a low risk of bias, which corresponds to the company's assessment. The AEs of patients with treatment switches (from the placebo + BSC to the ruxolitinib + BSC arm) were only considered in the analysis up to the time point of the treatment switch (see Section 2.4.1). However, the median observation times were not considerably different between the treatment arms at the time point of the primary analysis (ruxolitinib + BSC: 236 days, placebo + BSC: 211 days) so that a low risk of bias can still be assumed. Nonetheless, the available analyses were not evaluable for the benefit assessment because in the recording of the AEs, events resulting from the symptoms of the underlying disease (e.g. abdominal pain and night sweats; see Table 21 to Table 24 in Appendix A of the full dossier assessment) were also recorded to a large degree. Hence it was not possible to draw informative conclusions on the actual AEs of the intervention or the control based on the overall rates of AEs (see comment on the recording of AEs in the COMFORT-I study in Section 2.7.2.4.3 of the full dossier assessment for detailed reasons).

The outcomes additionally included in the assessment (leukaemic transformation, anaemia [SAE], bleeding [SMQ] and nervous system disorders [SOC]) were rated as having low bias.

Further information about the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier, and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.4.3 Results

Table 10 and Table 11 summarize the results on the comparison of ruxolitinib + BSC with placebo + BSC for the treatment of disease-related splenomegaly or symptoms in adults with PMF, PPV-MF or PET-MF. Where necessary, the data from the company's dossier were supplemented by the Institute's own calculations.

Table 10: Results (survival time) – RCT, direct comparison: ruxolitinib + BSC versus placebo + BSC

Study outcome analysis	Ruxolitinib + BSC		Placebo + BSC		Ruxolitinib + BSC vs. placebo + BSC	
	N	Median survival time in months [95% CI]	N	Median survival time in months [95% CI]	HR [95% CI]	p-value[a]
COMFORT-I						
Overall survival	155		154			
Primary analysis[b] (2 November 2010)		NA		NA	0.67 [0.30; 1.50]	0.327
3-year analysis[c] (25 January 2013)		NA		NA	0.69 [0.46; 1.03]	0.067

a: Calculation of the p-value using the log-rank test stratified by risk group.
b: Primary data analysis after all patients had been treated for 24 weeks and 50% of the patients had been treated for 36 weeks. In the placebo group, 37 patients had discontinued the study at this time point, and 36 patients had switched to the ruxolitinib + BSC arm.
c: The 3-year analysis was conducted after all patients had been treated for at least 144 weeks. In the placebo group, all patients had either discontinued the study (40 patients) at this time point, or had switched to the ruxolitinib + BSC arm of the study (111 patients). 3 patients are missing in the placebo + BSC arm because they either never received the study medication (2 patients) or because the documents were lost during the move of the study centre (1 patient).
BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Table 11: Results (further outcomes) – RCT, direct comparison: ruxolitinib + BSC versus placebo + BSC

Study outcome category outcome	Ruxolitinib + BSC		Placebo + BSC		Ruxolitinib + BSC vs. placebo + BSC
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
COMFORT-I					
Morbidity					
MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)	148	68 (45.9)	152	8 (5.3)	8.7 [4.3; 17.5]; < 0.001[b]
leukaemic transformation	155	2 (1.3)	151	0 (0)	4.87 [0.24; 100.64]; 0.209[c]
EORTC QLQ-C30 (symptoms)[d]	No evaluable data[e]				
Health-related quality of life					
EORTC QLQ-C30 (health-related quality of life)[f]	No evaluable data[e]				
Adverse events					
AEs	No evaluable data[g]				
SAEs	No evaluable data[g]				
Severe AEs (CTCAE grade ≥ 3)	No evaluable data[g]				
Discontinuation due to AEs	No evaluable data[g]				
Anaemia (SAE)	155	5 (3.2)	151	3 (2.0)	1.62 [0.39; 6.68]; 0.511[c]
Bleeding (SMQ)[h]	155	51 (32.9)	151	38 (25.2)	1.31 [0.92; 1.87]; 0.140[c]
Nervous system disorders (SOC)	155	57 (36.8)	151	36 (23.8)	1.54 [1.08; 2.19]; 0.014[c]

(continued)

Table 11: Results (further outcomes) – RCT, direct comparison: ruxolitinib + BSC versus placebo + BSC (continued)

a: The TSS records the following symptoms typical of myelofibrosis: abdominal discomfort, pain under the ribs on the left side, feeling of fullness, night sweats, itching, muscle and bone pain. It was not clear from the available documents whether the symptoms recorded were mainly severe or serious symptoms. The outcome was therefore assigned to the outcome category "non-serious/non-severe symptoms".
b: P-value calculated with the chi-square test.
c: Institute's calculation, unconditional exact test (CSZ method [6]).
d: Measured with the EORTC QLQ-C30 symptom scales.
e: Only analysis without imputation of missing values available. The data are not presented because the difference of the proportions of patients who were not considered was too large (approximately 20%) between the groups.
f: Measured with the EORTC QLQ-C30 functional scales.
g: The available analyses on overall AE rates were not evaluable due to the comprehensive consideration of disease symptoms (see Section 2.4.2 and Section 2.7.2.4.3 of the full dossier assessment for explanation).
h: Operationalized using the SMQ "bleeding". These were mainly mild AEs. SAEs only occurred in 3.2% (ruxolitinib) and 4.6% (placebo) of the patients.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; MedDRA: Medical Dictionary for Regulatory Activities; MFSAF: Myelofibrosis Symptom Assessment Form; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: MedDRA System Organ Class; TSS: total symptom score; vs.: versus

Only one relevant study was available for the assessment of ruxolitinib. The COMFORT-I study did not meet the particular requirements placed on the derivation of proof of an added benefit from a single study [1]. Hence, at most "indications" could be derived from the data.

Mortality

Overall survival

For the outcome "overall survival", neither the primary analysis nor the 3-year analysis showed a statistically significant effect in favour of ruxolitinib. However, the related Kaplan-Meier curves show a noticeable trend with regard to prolonged overall survival under treatment with ruxolitinib in comparison with the control treatment (see Figure 2 and Figure 3 in Appendix B of the full dossier assessment). Moreover, the p-value for the 3-year analysis clearly shows in the direction of the commonly used significance threshold (two-sided test) of $\alpha = 0.05$.

In both analyses, the survival time of all patients – independent from switching to the other treatment group – was recorded and analysed according to their random allocation (ITT analysis). Because of the high proportion of patients who switched treatment, a possible survival advantage of ruxolitinib is rather underestimated because the effects of the ruxolitinib treatment were also included in the comparator arm of the study (see comment on the course of the study in Section 2.7.2.4.3 for the number of patients who switched treatment).

Besides the analyses mentioned, the available documents also contained further ITT analyses on overall survival. On the one hand, this was an additional analysis on overall survival, which was conducted approximately 4 months after the primary analysis (data cut-off: 1 March 2011 [7]). There was a marginally significant result in favour of ruxolitinib (hazard ratio [HR] 0.50 [0.25; 0.98]; p = 0.040). The second analysis was a sensitivity analysis with the data cut-off on 5 April 2013 (approximately 9 weeks after the 3-year analysis) [8]. In this analysis, 3 additional deaths in the placebo group were included in the analysis. There was also a marginally significant result in favour of ruxolitinib (HR 0.67 [0.45; 0.998]; p = 0.047). Although these two analyses were not planned a priori and the conclusions that can be derived from them are therefore not very robust, they nevertheless support the survival advantage of ruxolitinib + BSC versus placebo + BSC suggested in the 3-year analysis.

An overall interpretation of the analyses on overall survival was conducted. As the analyses with regard to statistical significance showed no clear result, but overall, across all analyses (with a bias to the disadvantage of ruxolitinib in the ITT analysis), suggested a survival advantage of ruxolitinib versus the ACT, overall a hint of an added benefit was derived for this outcome.

Morbidity

MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)

For the outcome on symptoms of myelofibrosis (MFSAF v2.0, improvement in TSS by ≥ 50%), there was a statistically significant difference between the treatment groups in favour of ruxolitinib + BSC. Based on the COMFORT-I study, there was therefore an indication of an added benefit of ruxolitinib + BSC in comparison with the ACT (BSC).

This concurs with the company's assessment, which also derived an added benefit based on this outcome. However, the company itself did not make any statements on the probability of the added benefit.

Leukaemic transformation

For the outcome "leukaemic transformation", there was no statistically significant difference between the treatment groups. An added benefit of ruxolitinib + BSC in comparison with BSC is not proven for this outcome.

The company did not present this outcome in Module 4 of its dossier.

EORTC QLQ-C30 (symptoms)

The dossier contained no evaluable data on symptoms recorded with the EORTC QLQ-C30 symptom scales because the difference of the proportions of patients who were not considered was approximately 20% between the treatment groups and therefore too high to derive informative results (see Section 2.7.2.4.3 of the full dossier assessment). An added benefit of ruxolitinib + BSC in comparison with BSC is not proven for this outcome.

This deviates from the company's assessment, which derived an added benefit on the basis of the data recorded with the EORTC QLQ-C30 instrument.

Health-related quality of life

EORTC QLQ-C30 (health-related quality of life)

The dossier contained no evaluable data on health-related quality of life recorded with the EORTC QLQ-C30 functional scales because the difference of the proportions of patients who were not considered was approximately 20% between the treatment groups and therefore too high to derive informative results (see Section 2.7.2.4.3 of the full dossier assessment). An added benefit of ruxolitinib + BSC in comparison with BSC is not proven for this outcome.

This deviates from the company's assessment, which derived an added benefit on the basis of the data recorded with the EORTC QLQ-C30 instrument.

Adverse events

Overall rates of serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events

The respective overall AE rates and the SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuations due to AEs that most commonly occurred in the studies are presented in Appendix C (Table 22, Table 23 and Table 24) of the full dossier assessment.

Overall, the results on the overall AE rates were regarded to be not interpretable due to the extensive recording of symptoms of the underlying disease in the overall recording of the AEs (see Section 2.4.2 and comment on the recording of AEs in the COMFORT-I study in Section 2.7.2.4.3 of the full dossier assessment). However, as the absolute differences between the overall rates of AEs were not very large (see Table 22, Table 23 and Table 24 of the full dossier assessment) and the symptoms of the underlying disease particularly occurred in the placebo + BSC arm, overall greater harm from ruxolitinib can also not be excluded.

This deviates from the company's assessment, which considered the AEs between the study arms to be comparable and overall derived good tolerability of ruxolitinib from this.

Anaemia (SAE)

For the outcome "anaemia (SAE)", there was no statistically significant difference between the treatment groups. Greater or lesser harm from ruxolitinib + BSC compared with BSC is not proven for this outcome.

The company did not present this outcome in Module 4 of its dossier.

Bleeding (SMQ)

For the outcome "bleeding (SMQ)", there was no statistically significant difference between the treatment groups. Greater or lesser harm from ruxolitinib + BSC compared with BSC is not proven for this outcome.

The company did not present this outcome in Module 4 of its dossier.

Nervous system disorders (SOC)

For the outcome "nervous system disorders (SOC)", there was a statistically significant difference between the treatment groups to the disadvantage of ruxolitinib, but the effect size was only marginal (the upper confidence interval was above the threshold of 0.9; outcome category "non-severe/non-serious AEs" [1], see Table 13). Greater harm from ruxolitinib + BSC compared with BSC is therefore not proven.

The company did not present this outcome in Module 4 of its dossier.

Further information on the results of outcomes can be found in Module 4, Section 4.3.1.3 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

2.4.4 Subgroup analyses

Selected subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifications. In Module 4, Section 4.3.1.3.2, the company presented subgroup analyses including an interaction test on the COMFORT-I study only for the primary outcome "reduction of ≥ 35% in spleen volume" and for the outcome "MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)". As "reduction of ≥ 35% in spleen volume" is an unvalidated surrogate outcome (see Section 2.7.2.9.4 of the full dossier assessment), only the analyses on the outcome "improvement in TSS by ≥ 50%" were relevant for the benefit assessment. Subgroup analyses for the outcomes additionally rated as relevant were therefore missing and could also not be subsequently calculated from the available documents (see Section 2.7.2.2 of the full dossier assessment).

The effect modifiers described in Section 2.7.2.2 of the full dossier assessment were considered.

Below, only the results on subgroups are presented, in which there was at least an indication of an interaction between treatment effect and subgroup characteristic. The prerequisite for proof of differing effects is a statistically significant interaction test ($p < 0.05$). A p-value between 0.05 and 0.2 provides an indication of differing effects.

Table 12 shows the subgroups for the outcome "MFSAF v2.0 (improvement in TSS by ≥ 50%)" for which there was at least an indication of an effect modification or which are relevant for the interpretation of the result.

Table 12: Relevant subgroup results for the outcome "MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)", RCT, direct comparison: ruxolitinib + BSC vs. placebo + BSC

Study characteristic subgroup	Ruxolitinib + BSC		Placebo + BSC		Ruxolitinib + BSC vs. placebo + BSC	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]	p-value
COMFORT-I						
Spleen volume at baseline						
≤ median	73	30 (41.1)	76	4 (5.3)	7.81 [2.89; 21.07]	< 0.001[a]
> median	75	38 (50.7)	76	4 (5.3)	9.63 [3.61; 25.64]	< 0.001[a]
					interaction:	0.768
Palpable spleen length at baseline						
≤ 10 cm	30	11 (36.7)	26	4 (15.4)	2.38 [0.86; 6.59]	0.088[a]
> 10 cm	118	57 (48.3)	125	4 (3.2)	15.10 [5.65; 40.30]	< 0.001[a]
					interaction:	0.007

a: Institute's calculation, unconditional exact test (CSZ method [6]).

BSC. best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z score; MFSAF: Myelofibrosis Symptom Assessment Form; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; TSS: total symptom score; vs.: versus

For the outcome "MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)", there was proof of an effect modification by the subgroup characteristic "palpable spleen length at baseline" (interaction test: p = 0.007). Whereas for patients with a palpable spleen length of > 10 cm at baseline, there was a statistically significant effect in favour of ruxolitinib, this positive effect was no longer statistically significant in patients with a palpable spleen length of ≤ 10 cm. However, no corresponding interaction occurred for the subgroup characteristic "spleen volume at baseline", which also is a characteristic to record splenomegaly and for which therefore similar results as for palpable spleen length could have been expected. Overall, these results were not considered further in the benefit assessment because of the inconsistent picture they provide.

The company also considered there to be an indication of an effect modification for the characteristic "Janus kinase (JAK) V617F mutation" (interaction test by the company: p = 0.134 [Module 4, Section 4.3.1.3.2, Table 4–45]). The interaction test was recalculated for the benefit assessment on the basis of the effect measure "relative risk" (see Section 2.7.2.2 of the full dossier assessment for reasons) and showed no indication of an interaction (p = 0.220) so that this result also had no consequences for the benefit assessment.

In summary, the results of the subgroup analyses for the outcome "MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)" did not influence the derivation of the

added benefit of ruxolitinib. However, it should be noted again that no comprehensive assessment of potential effect modifiers could be conducted because the company presented no subgroup analyses on further outcomes. This deficiency was all the more critical because the European Public Assessment Report (EPAR) indicates that, for example, individual AEs differed from each other depending on age (≤/> 65 years) and sex [9].

Further information on the subgroup results can be found in Module 4, Section 4.3.1.3.2 of the dossier, and in Section 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of the Institute [1].

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 an indication of an added benefit for the outcome "MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)" and in a hint of an added benefit for the outcome "overall survival". Overall, the results on the overall AE rates were regarded to be not interpretable due to the frequent occurrence of symptoms of the underlying disease in the recording of the AEs (see Section 2.4.2 and Section 2.7.2.4.3 of the full dossier assessment). However, due to the extensive recording of symptoms particularly in the placebo + BSC arm, greater harm from ruxolitinib cannot be excluded.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 13).

Table 13: Extent of added benefit at outcome level: ruxolitinib + BSC vs. placebo + BSC

Outcome category **outcome**	**Ruxolitinib + BSC vs. placebo + BSC**[a] **quantile of time to event or proportion of events/** **effect estimate [95% CI]** **p-value** **probability**[b]	**Derivation of extent**[c]
Mortality		
Overall survival	**Primary analysis (2 November 2010)** median: NA vs. NA HR 0.67 [0.30; 1.50] p = 0.327 **3-year analysis (25 January 2013)** median: NA vs. NA HR 0.69 [0.46; 1.03] p = 0.067 probability: "hint"[d]	Outcome category "mortality" added benefit, extent "non-quantifiable"
Morbidity		
MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)	45.9% vs. 5.3% RR: 8.7 [4.3; 17.5] RR[e]: 0.11 [0.06; 0.23] p < 0.001[f] probability: "indication"	Outcome category: non-serious/non-severe symptoms CI_u < 0.8 added benefit, extent "considerable"
Leukaemic transformation	1.3% vs. 0% RR: 4.87 [0.24; 100.64] p = 0.209[f]	Added benefit not proven
EORTC QLQ-C30 (symptoms)	No evaluable data	
Health-related quality of life		
EORTC QLQ-C30 (health-related quality of life)	No evaluable data	
Adverse events		
SAEs	No evaluable data	
Severe AEs (CTCAE grade ≥ 3)	No evaluable data	
Discontinuation due to AEs	No evaluable data	

(continued)

Table 13: Extent of added benefit at outcome level: ruxolitinib + BSC vs. placebo + BSC (continued)

Outcome category **outcome**	**Ruxolitinib + BSC vs. placebo + BSC[a]** **quantile of time to event or proportion of events/** **effect estimate [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Anaemia (SAE)	3.2% vs. 2.0% RR: 1.62 [0.39; 6.68]; p = 0.511[f]	Greater/lesser harm not proven
Bleeding (SMQ)	32.9% vs. 25.2% RR: 1.31 [0.92; 1.87] p = 0.140[f]	Greater/lesser harm not proven
Nervous system disorders (SOC)	36.8% vs. 23.8% RR: 1.54 [1.08; 2.19] RR[e]: 0.65 [0.46; 0.93] p = 0.014[f]	Outcome category: non-serious/severe AEs $CI_u > 0.9$ greater/lesser harm not proven

a: According to the inclusion criteria, patients with intermediate-2 or high-risk profile were included in the study. According to the SPC however, ruxolitinib is approved for patients of all risk classes who have splenomegaly or disease-related symptoms [5]. Hence the study population did not cover patients with low risk and intermediate-risk 1 who have splenomegaly or disease-related symptoms. It is unclear whether the study results of the COMFORT-I study are transferable to these patients.
b: Probability given, if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: In this outcome, 2 further ITT analyses were considered to derive conclusions on the added benefit. Data cut-off 1 March 2011: HR 0.50 [0.25; 0.98]; p = 0.040; data cut-off 5 April 2013: HR 0.67 [0.45; 0.998]; p = 0.047 (see description of the results on overall survival in Section 2.4.3).
e: Institute's calculation: reversed direction of effect to enable direct use of limits to derive added benefit.
f: Institute's calculation, unconditional exact test (CSZ method [6]).

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of the CI; CTCAE: Common Terminology Criteria for Adverse Events; CSZ: convexity, symmetry, z score; EORTC QLQC30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; HR: hazard ratio; ITT: intention to treat; MedDRA: Medical Dictionary for Regulatory Activities; MFSAF: Myelofibrosis Symptom Assessment Form; NA: not achieved; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: MedDRA System Organ Class; SPC: Summary of Product Characteristics; TSS: total symptom score; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 14 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of ruxolitinib + BSC compared with BSC

Positive effects	Negative effects
Hint of an added benefit – extent: "non-quantifiable" (mortality: overall survival)	–[a]
Hint of an added benefit – extent: "considerable" (morbidity: MFSAF v2.0 [symptoms of myelofibrosis, improvement in TSS by ≥ 50%])	
a: The available analyses on overall AE rates were not evaluable due to the comprehensive consideration of disease symptoms. AE: adverse events; BSC: best supportive care; MFSAF: Myelofibrosis Symptom Assessment Form; TSS: total symptom score	

Overall, only positive effects remain. In the outcome category "morbidity (MFSAF v2.0 [symptoms of myelofibrosis, improvement in TSS by ≥ 50%])", there is an indication of an added benefit with the extent "considerable". In the outcome category "mortality (overall survival)", there is a hint of a non-quantifiable added benefit.

For the outcomes regarding harm, there is the problem that, overall, the analyses on overall rates of AEs were regarded to be not interpretable due to the extensive recording of symptoms of the underlying disease. Hence no final conclusion can be drawn on harm. Greater harm from ruxolitinib can also not be completely excluded. The available results, however, did not provide signs of harm in a magnitude that would justify downgrading the added benefit. This is particularly due to the size of the effect regarding benefit for the outcome "MFSAF v2.0 (symptoms of myelofibrosis, improvement in TSS by ≥ 50%)", which shows the considerable improvement in the burdensome symptoms of the underlying disease.

In summary, for patients with disease-related splenomegaly or symptoms with PMF, PPV-MF or PET-MF, there is an indication of considerable added benefit of ruxolitinib + BSC versus the ACT BSC.

The result of the assessment of the added benefit of ruxolitinib in comparison with the ACT is summarized in Table 15.

Table 15: Ruxolitinib – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Treatment of disease-related splenomegaly or symptoms in adults with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis	BSC[b]	Indication of considerable added benefit
a: Presentation of the ACT specified by the G-BA. b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee		

This approach partially deviates from that of the company. The company also claimed considerable added benefit of ruxolitinib versus the ACT. However, it additionally included the COMFORT-II study in its deliberations on the added benefit, and considered further outcomes, some of which were not included in the assessment (e.g. splenomegaly) or for which no evaluable data were available (e.g. health-related quality of life). Moreover, the company did not make any concrete statements on the probability of the added benefit.

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

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

COMFORT-I

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Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF et al. Efficacy, safety and survival with ruxolitinib in patients with myelofibrosis: results of a median 2-year follow-up of COMFORT-I. Haematologica 2013; 98(12): 1865-1871.

References for English extract

Please see full dossier assessment for full reference list.

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