IQWiG Reports – Commission No. A21-31

Avatrombopag (thrombocytopenia and chronic liver disease) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Avatrombopag (Thrombozytopenie und chronische Lebererkrankung) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2021). 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.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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[2] 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
CLD	chronic liver disease
CTP	Child-Turcotte-Pugh
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MELD	Model for End-Stage Liver Disease
NASH	nonalcoholic steatohepatitis
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SPC	Summary of Product Characteristics
WHO	World Health Organization

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 avatrombopag. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 22 March 2021.

Research question

The aim of the present report is the assessment of the added benefit of avatrombopag in comparison with watchful waiting as appropriate comparator therapy (ACT) for the treatment of severe thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo an invasive procedure.

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of avatrombopag

Therapeutic indication	ACT[a]
Adult patients with severe thrombocytopenia and chronic liver disease (CLD) who are scheduled to undergo an invasive procedure	Watchful waiting[b]
a. Presentation of the respective ACT specified by the G-BA. b. It is assumed that platelet transfusions, if indicated, are performed in both arms of the study. The reasons have to be documented. Furthermore, it is assumed that the patients in the therapeutic indication undergo an invasive medical procedure. ACT: appropriate comparator therapy; CLD: chronic liver disease; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. The included studies had to provide for the possibility of prophylactic and/or acute platelet transfusion at the physician's discretion.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Study pool and study design

Studies ADAPT-1 and ADAPT-2

The studies ADAPT-1 and ADAPT-2 were included in the benefit assessment. These studies are 2 identical, double-blind, multinational, randomized clinical studies comparing avatrombopag with placebo.

The studies included adult patients with CLD of diverse aetiology and severe thrombocytopenia ($< 50\times10^9$/L) who were scheduled to undergo an invasive procedure and who, in the opinion of the physician, would have required a platelet transfusion to address a risk of bleeding associated with the procedure unless there was a clinically significant increase in platelet count from baseline.

In both studies, patients were randomized in a 2:1 ratio to the treatment arms with avatrombopag (ADAPT-1: N = 149; ADAPT-2: N = 128) or with placebo (ADAPT-1: N = 82; ADAPT-2: N = 76). Randomization was stratified by lower ($< 40\times10^9$/L) or higher baseline platelet count (≥ 40 to $< 50\times10^9$/L), hepatocellular carcinoma (HCC) status, and risk of bleeding associated with the elective procedure (low, moderate or high). In the studies, the cohorts of patients with lower ($< 40\times10^9$/L) and with higher baseline platelet counts (≥ 40 to $< 50\times10^9$/L) were considered separately.

Treatment of the patients with avatrombopag was in compliance with the description in the Summary of Product Characteristics (SPC). Platelet transfusions were available from randomization as prophylaxis and for the treatment of bleeding events for all patients.

Invasive procedures took place 5 to 8 days after completion of the 5-day treatment with the study drug.

The primary outcome of the studies was the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. Patient-relevant outcomes on all-cause mortality, morbidity, and adverse events (AEs) were additionally recorded.

Risk of bias

The risk of bias across outcomes was rated as low for the studies ADAPT-1 and ADAPT-2.

The risk of bias for the results of the category of all-cause mortality and for all outcomes of the category of side effects was rated as low.

The risk of bias for the outcome “patients without transfusion” was rated as high. There is no information on how missing values were distributed among patients with low, moderate or high risk of bleeding associated with the procedure. Therefore, the proportion of missing values is unclear in the subpopulation of interest, i.e. patients who have procedures with a moderate or high risk of bleeding. However, the certainty of results for this outcome was not downgraded for the ADAPT-2 study because the influence of the missing values on the large observed effect was estimated to be minor.

The risk of bias for the results of the morbidity outcome “World Health Organization (WHO) grade ≥ 2 bleeding events” was rated as high. The reason for this was an unclear proportion of patients with missing values.

Results

Mortality

All-cause mortality

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of avatrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Patients without transfusion

For the outcome "patients without transfusion", the meta-analysis of the studies showed a statistically significant difference in favour of avatrombopag in patients who were scheduled to undergo an invasive procedure associated with moderate or high risk of bleeding. This resulted in proof of an added benefit of avatrombopag in comparison with watchful waiting.

WHO grade ≥ 2 bleeding events

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome "WHO grade ≥ 2 bleeding events". This resulted in no hint of an added benefit of avatrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

No data are available for the outcome "health-related quality of life", as this outcome was not recorded in the studies ADAPT-1 and ADAPT-2. This resulted in no hint of an added benefit of avatrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

The meta-analysis of the studies showed no statistically significant differences between the treatment groups for the outcomes "serious adverse events (SAEs)" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm of avatrombopag in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Thromboembolic events (Standardized Medical Dictionary for Regulatory Activities Query [SMQ], AEs)

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome "thromboembolic events". This resulted in no hint of greater or lesser harm of avatrombopag in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug avatrombopag in comparison with the ACT are assessed as follows:

In the overall picture, there is exclusively a positive effect of avatrombopag in comparison with watchful waiting for patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure with moderate or high risk of bleeding. This positive effect is not accompanied by negative effects.

In summary, there is proof of considerable added benefit of avatrombopag in comparison with the ACT of watchful waiting for the treatment of severe thrombocytopenia in adult patients with CLD who are scheduled to undergo an invasive procedure with moderate or high risk of bleeding.

There is no hint of an added benefit of avatrombopag in comparison with watchful waiting for adult patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure with low risk of bleeding; an added benefit is therefore not proven.

Table 3 shows a summary of probability and extent of the added benefit of avatrombopag.

Table 3: Avatrombopag – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure[c]	Watchful waiting[b]	Moderate or high risk of bleeding from the invasive procedure: ▪ Proof of considerable added benefit
		Low risk of bleeding from the invasive procedure: ▪ Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. b. It is assumed that platelet transfusions, if indicated, are performed in both arms of the study. The reasons have to be documented. Furthermore, it is assumed that the patients in the therapeutic indication undergo an invasive medical procedure. c. No data are available for patients with a MELD score > 24. ACT: appropriate comparator therapy; CLD: chronic liver disease; G-BA: Federal Joint Committee; MELD: Model for End-Stage Liver Disease		

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of avatrombopag in comparison with watchful waiting as ACT for the treatment of severe thrombocytopenia in adult patients with CLD who are scheduled to undergo an invasive procedure.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of avatrombopag

Therapeutic indication	ACT[a]
Adult patients with severe thrombocytopenia and chronic liver disease (CLD) who are scheduled to undergo an invasive procedure	Watchful waiting[b]

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed that platelet transfusions, if indicated, are performed in both arms of the study. The reasons have to be documented. Furthermore, it is assumed that the patients in the therapeutic indication undergo an invasive medical procedure.

ACT: appropriate comparator therapy; CLD: chronic liver disease; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT. The included studies had to provide for the possibility of prophylactic and/or acute platelet transfusion at the physician's discretion.

The assessment was conducted by means of patient-relevant outcomes on the basis of 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 avatrombopag (status: 4 January 2021)
- bibliographical literature search on avatrombopag (last search on 23 February 2021)
- search in trial registries/trial results databases for studies on avatrombopag (last search on 11 March 2021)
- search on the G-BA website for avatrombopag (last search on 4 January 2021)

The completeness of the study pool was checked by:

- search in trial registries for studies on avatrombopag (last search on 30 March 2021); for search strategies, see Appendix C of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: avatrombopag vs. placebo

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
E5501-G000-310 (ADAPT-1[c])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6-8]
E5501-G000-311 (ADAPT-2[c])	Yes	Yes	No	Yes [9]	Yes [10-12]	Yes [6-8]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool of the benefit assessment of avatrombopag in comparison with the ACT comprises the randomized controlled trials (RCTs) ADAPT-1 and ADAPT-2 and concurs with the study pool of the company.

2.3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: avatrombopag vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ADAPT-1	RCT, double-blind, parallel	Adults (≥ 18 years) with CLD[b] ▪ with a mean baseline platelet count of < 50×10^9/L[c] ▪ who were scheduled to undergo an invasive procedure and who, in the opinion of the investigator, would have required a platelet transfusion to address a risk of bleeding associated with the procedure[d] ▪ MELD score ≤ 24 at screening	Avatrombopag (N = 149) placebo (N = 82) ▪ Cohort with lower baseline platelet count (< 40×10^9/L) avatrombopag 60 mg (N = 90) placebo (N = 48) ▪ Cohort with higher baseline platelet count (≥ 40 to < 50×10^9/L): avatrombopag 40 mg (N = 59) placebo (N = 34)	Screening: ≤ 14 days Treatment: day 1–5 Elective procedure: day 10–13 Observation: 30 days after completion of treatment	75 centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, France, Germany, Hungary, Italy, Poland, Portugal, South Korea, Spain, Taiwan, Thailand, United Kingdom, USA 2/2014–1/2017	Primary: proportion of study participants who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure Secondary: outcomes of the categories of mortality, morbidity, AEs
ADAPT-2	RCT, double-blind, parallel	See ADAPT-1	Avatrombopag (N = 128) placebo (N = 76) ▪ Cohort with lower baseline platelet count (< 40×10^9/L) avatrombopag 60 mg (N = 70) placebo (N = 43) ▪ Cohort with higher baseline platelet count (≥ 40 to < 50×10^9/L): avatrombopag 40 mg (N = 58) placebo (N = 33)	See ADAPT-1	74 centres in Argentina, Australia, Belgium, Brazil, China, Czech Republic, France, Germany, Israel, Italy, Japan, Mexico, Romania, Russia, Spain, USA 12/2013–1/2017	See ADAPT-1

Table 6: Characteristics of the studies included – RCT, direct comparison: avatrombopag vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Patients with HCC with Barcelona Clinic Liver Cancer (BCLC) staging classification C or D, as well as with evidence or history of thrombosis, genetic prothrombotic syndrome, primary haematologic disorder or liver transplantation were excluded.
c. Mean of 2 measurements at screening and randomization; neither platelet count was allowed to be above 60×10^9/L.
d. Unless there was a clinically significant increase in platelet count from baseline.

AE: adverse event; CLD: chronic liver disease; HCC: hepatocellular carcinoma; MELD: Model for End-Stage Liver Disease; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: avatrombopag vs. placebo

Study	Intervention	Comparison
ADAPT-1	Cohort with lower baseline platelet count (< 40×10^9/L): avatrombopag orally 60 mg/day	Cohort with lower baseline platelet count (< 40×10^9/L): placebo
	Cohort with higher baseline platelet count (≥ 40 to < 50×10^9/L): avatrombopag orally 40 mg/day	Cohort with higher baseline platelet count (≥ 40 to < 50×10^9/L): placebo
	Treatment duration: 5 days each	
	Pretreatment Not allowed: ▪ platelet transfusion or transfusion of another blood product containing platelets ≤ 7 days before screening (packed red blood cells were allowed) ▪ heparin, warfarin, NSAIDs ≤ 7 days before screening **Concomitant treatment** Allowed: With the exception of the prohibited concomitant treatments, all treatments are permitted, including in particular: ▪ prophylactic administration of platelet concentrates ▪ rescue therapy[a] for bleeding Not allowed: ▪ erythropoiesis-stimulating agents ≤ 7 days before screening and during the study ▪ interferon ≤ 14 days before screening until the day of the procedure ▪ oestrogen-containing treatments ≤ 30 days before screening and during the study ▪ eltrombopag, romiplostim, heparin, warfarin, NSAIDs ▪ acetylsalicylic acid[b], verapamil, and platelet aggregation inhibitor therapy with ticlopidine or glycoprotein IIb/IIIa antagonists (e.g. tirofiban) ≤ 7 days before screening	
ADAPT-2	See ADAPT-1	

a. Platelet transfusions, fresh frozen plasma, cryoprecipitate, vitamin K (phytonadione), desmopressin, recombinant activated factor VII, aminocaproic acid, tranexanic acid, whole blood transfusion, packed red cell transfusion, surgical intervention or interventional radiology.
b. Acetylsalicylic acid (or, if contraindicated, an alternative therapy with ADP receptor inhibitors such as clopidogrel) can be administered at the discretion of the investigator if the platelet count rises and the risk of thrombosis is increased.

ADP: adenosine diphosphate; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial

Study design

The studies ADAPT-1 and ADAPT-2 are 2 identical, double-blind, multinational RCTs comparing avatrombopag with placebo.

The studies included adult patients with CLD of diverse aetiology and severe thrombocytopenia (platelet count < 50×10^9/L) who were scheduled to undergo an invasive procedure and who, in the opinion of the physician, would have required a platelet transfusion to address a risk of

bleeding associated with the procedure unless there was a clinically significant increase in platelet count from baseline.

In addition, the severity of liver disease as measured by the Model for End-Stage Liver Disease (MELD) score was not allowed to exceed 24 out of a maximum of 40 points. Therefore, no conclusions can be drawn from the studies ADAPT-1 and ADAPT-2 for patients with a MELD score > 24.

In both studies, patients were randomized in a 2:1 ratio to the treatment arms with avatrombopag (ADAPT-1: N = 149; ADAPT-2: N = 128) or with placebo (ADAPT-1: N = 82; ADAPT-2: N = 76). Randomization was stratified by lower (< 40×10^9/L) or higher baseline platelet count (≥ 40 to < 50×10^9/L), HCC status, and risk of bleeding associated with the elective procedure (low, moderate or high). In the studies, the cohorts of patients with lower (< 40×10^9/L) and with higher baseline platelet counts (≥ 40 to < 50×10^9/L) were considered separately.

Treatment of the patients with avatrombopag was in compliance with the requirements of the SPC [13].

Platelet transfusions were available from randomization as prophylaxis and for the treatment of bleeding events for all patients. Other concomitant treatments were allowed under restrictions. These included rescue procedures (including platelet transfusion) for bleeding, although rescue procedures other than platelet transfusions were only used in a total of 2 patients in the ADAPT-2 study.

Invasive procedures took place 5 to 8 days after completion of the 5-day treatment with the study drug. The assessment of the platelet count scheduled for this visit had to be available to the physician. The subsequent follow-up phase comprised 2 visits and ended a maximum of 35 days after randomization.

The primary outcome of the studies was the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. Patient-relevant outcomes on all-cause mortality, morbidity, and AEs were additionally recorded.

Operationalization and implementation of the appropriate comparator therapy

The G-BA determined watchful waiting as the ACT, assuming that platelet transfusions, if indicated, was performed in both arms of the study. The reasons have to be documented. Furthermore, it is assumed that the patients in the therapeutic indication undergo an invasive medical procedure.

In the studies conducted by the company, the patients in the comparator arm received treatment with placebo. Both study arms provided for the possibility of prophylactic and/or acute platelet transfusion at the physician's discretion. According to the study protocols, platelet counts were assessed at each visit and information on the number and timing of platelet transfusions was

documented. Thus, the design of the studies ADPAT-1 and ADAPT-2 allows an adequate implementation of the ACT.

Prophylactic platelet transfusion before invasive procedures

The information in Module 4 A shows that administration of platelet transfusions in the studies ADAPT-1 and ADAPT-2 was almost exclusively prophylactic.

According to guidelines, the therapeutic indication for platelet transfusion depends on a sum of various factors including platelet count and function, bleeding risk, bleeding symptoms (according to the WHO, other reasons for abnormal blood coagulation, bleeding history and underlying disease [14,15]. Recommended threshold values are often based on the consideration of the risk of bleeding associated with the procedure and platelet counts. The corresponding recommendations on the critical platelet count for invasive procedures vary in national and international guidelines [14-17]. According to general clinical experience, there is no increased risk of bleeding with a platelet count > 50×10^9/L and normal platelet function.

In patients with CLD and severe thrombocytopenia, other factors such as portal hypertension or an accompanying coagulation disorder must be considered when assessing the risk of bleeding [15]. A patient-specific assessment of the risk of bleeding associated with the procedure and other patient-specific factors is recommended for the therapeutic indication of a platelet transfusion [15]. In invasive procedures that tend to have a higher risk of bleeding, there is a general consensus that there is a therapeutic indication for prophylactic platelet administration with a platelet count < 50×10^9/L. For procedures with a low risk of bleeding, platelet thresholds tend to be set lower or it is recommended to conduct no prophylactic platelet transfusion [15,18,19].

Patients included in the studies were scheduled to undergo invasive procedures with low, moderate or high risk of bleeding. The assessment of the risk of bleeding was based on the consensus guideline by Malloy [20] and the opinions of clinical experts. Table 8 shows the invasive procedures allowed in the studies with the associated risk of bleeding.

Table 8: Risk of bleeding of invasive procedures in the studies ADAPT-1 and ADAPT-2

Risk of bleeding associated with procedure	Permitted invasive procedure
Low risk of bleeding	▪ Paracentesis ▪ Thoracentesis (pleural tap) ▪ Gastrointestinal endoscopy with or without plans for biopsy, colonoscopy, polypectomy, or variceal banding
Moderate risk of bleeding	▪ Liver biopsy ▪ Bronchoscopy with or without plans for biopsy ▪ Ethanol ablation therapy or chemoembolization for HCC
High risk of bleeding	▪ Vascular catheterization (including right side procedures in patients with pulmonary hypertension) ▪ Transjugular intrahepatic portosystemic shunt ▪ Dental procedures ▪ Renal biopsy ▪ Biliary interventions ▪ Nephrostomy tube placement ▪ Radiofrequency ablation ▪ Laparoscopic interventions

A maximum proportion of 60% procedures with a low risk of bleeding was scheduled. In this patient group, the threshold value for prophylactic platelet transfusion recommended in German guidelines is rather $< 20\times10^9$/L [14,16]. According to the study protocol, it was planned to enrol the patients into 2 cohorts of similar size according to mean baseline platelet count, one lower baseline platelet count cohort ($< 40\times10^9$/L) and one higher baseline platelet count cohort (≥ 40 to $< 50\times10^9$/L). This means that about half of the patients had a baseline platelet count in a range bordering on the threshold value for severe thrombocytopenia.

It is not clear from the patient characteristics alone (median platelet count about 38×10^9/L) and the type of elective procedures (about 50–60% procedures with a low risk of bleeding) that prophylactic platelet transfusion was indicated in the patients included in the studies. Based on the information in Module 4, it can be estimated that about 50% of the patients treated with placebo and 18% of the patients treated with avatrombopag received prophylactic platelet transfusions. Contrary to the note by G-BA, the company did not provide any information on the reasons for the platelet transfusions in Module 4. It is therefore not possible to assess whether prophylactic platelet transfusion was necessary, particularly in the patients undergoing an invasive procedure with a low risk of bleeding. This is addressed in the interpretation of the outcome “patients without transfusion” (see Section 2.4.1).

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study populations – RCT, direct comparison: avatrombopag vs. placebo (multipage table)

Study Characteristic Category	ADAPT-1		ADAPT-2	
	Avatrombopag	Placebo	Avatrombopag	Placebo
	N[a] = 149	N[a] = 82	N[a] = 128	N[a] = 76
Age [years], mean (SD)	56 (10)	56 (11)	58 (13)	58 (11)
Sex [F/M], %	32/68	32/68	35/65	42/58
Region, n (%)				
North America	31 (21)	16 (20)	27 (21)	15 (20)
Europe	55 (37)	30 (37)	36 (28)	24 (32)
East Asia	54 (36)	32 (39)	35 (27)	18 (24)
Rest of the world	9 (6)	4 (5)	30 (23)	19 (25)
Baseline platelet count [$\times 10^9$/L]				
Mean (SD)	36.3 (8.8)	36.6 (9.1)	38.0 (7.4)	37.7 (7.8)
Median [min; max]	38.0 [10; 49.5]	37.5 [11.5; 50.5]	38.8 [18; 50]	39.0 [12; 49]
Baseline platelet count [$\times 10^9$/L], n (%)				
< 40	88 (59[b])	47 (57)	72 (56)	44 (58)
≥ 40 to < 50	59 (40[b])	34 (41)	55 (43)	32 (42)
≥ 50	0 (0)	1 (1)	1 (1)	0 (0)
Missing values	2 (1[b])	0 (0)	0 (0)	0 (0)
MELD score				
< 10	50 (34[b])	34 (42)	50 (39[b])	28 (37)
≥ 10 to ≤ 14	72 (48[b])	36 (44)	55 (43[b])	37 (49)
> 14	25 (17[b])	12 (15)	22 (17[b])	11 (14)
Missing values	2 (1[b])	0 (0)	1 (1[b])	0 (0)
CTP stage				
A	80 (54[b])	50 (61[b])	76 (59[b])	37 (49)
B	60 (40[b])	29 (35[b])	42 (33[b])	33 (43)
C	7 (5[b])	2 (2[b])	9 (7[b])	6 (8)
Missing values	2 (1[b])	1 (1[b])	1 (1[b])	0 (0)
Baseline INR[c], n (%)				
≤ 1.6	133 (89[b])	76 (93[b])	121 (95[b])	74 (97[b])
> 1.6	7 (5[b])	1 (1[b])	5 (4[b])	1 (1[b])
Missing values	9 (6[b])	5 (6[b])	2 (2[b])	1 (1[b])
Disease aetiology				
Alcoholic liver disease	24 (16[b])	9 (11)	18 (14)	12 (16)
Chronic viral hepatitis	86 (58[b])	57 (70)	63 (49)	44 (58)
Chronic hepatitis B	28 (19[b])	18 (22)	6 (5)	9 (12)
Chronic hepatitis C	57 (38[b])	39 (48)	55 (43)	34 (45)
Chronic hepatitis B and C	1 (1[b])	0 (0)	2 (2)	1 (1)

Table 9: Characteristics of the study populations – RCT, direct comparison: avatrombopag vs. placebo (multipage table)

Study Characteristic Category	ADAPT-1		ADAPT-2	
	Avatrombopag	Placebo	Avatrombopag	Placebo
	N[a] = 149	N[a] = 82	N[a] = 128	N[a] = 76
NASH	10 (7[b])	4 (5)	16 (13)	10 (13)
Other	26 (17[b])	12 (15)	31 (24)	10 (13)
Missing values	3 (2[b])	0 (0)	0 (0)	0 (0)
Invasive procedures by bleeding risk, n (%)				
Low	89 (60[b])	48 (59[b])	73 (57[b])	38 (50[b])
Moderate	21 (14[b])	11 (13[b])	20 (16[b])	18 (24[b])
High	30 (20[b])	13 (16[b])	31 (24[b])	16 (21[b])
Unknown	9 (6[b])	10 (12[b])	4 (3[b])	4 (5[b])
Treatment discontinuation, n (%)	9 (6)[d]	4 (5)[d]	5 (4)	8 (11[b])
Study discontinuation, n (%)	ND	ND	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Percentages: Institute's calculation, in relation to all randomized patients.
c. INR for the prothrombin time.
d. 2 patients did not receive treatment.

CTP: Child-Turcotte-Pugh; F: female; INR: international normalized ratio; M: male; MELD: Model for End-Stage Liver Disease; n: number of patients in the category; N: number of randomized patients; NASH: nonalcoholic steatohepatitis; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics are balanced between the studies and between the study arms. The mean age of the patients was 56 to 58 years, and about 1 third were female. About 1 third of the patients came from Europe. The chronic liver disease was mainly due to chronic viral hepatitis or was caused by alcoholic liver disease or nonalcoholic steatohepatitis (NASH). The severity of the liver disease corresponded to a rather less severe state characterized by a Child-Turcotte-Pugh (CTP) stage A in just over half of the included patients and a MELD score ≤ 14 in just over 80% of the included patients. The patients had severe thrombocytopenia with a mean platelet count of about 37×10^9/L (median about 38×10^9/L). In both studies combined, the scheduled invasive procedures had a low risk of bleeding in a total of 248 patients (57%), a moderate risk of bleeding in 70 patients (16%) and a high risk of bleeding in 90 patients (21%). The cohort of patients with low baseline platelet count comprised approximately 58% of both study populations and the cohort with high baseline platelet count comprised 42%.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: avatrombopag vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ADAPT-1	Yes	Yes	Yes	Yes	Yes	Yes	Low
ADAPT-2	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies. This concurs with the company's assessment.

Transferability of the study results to the German health care context

In the opinion of the company, the results of the studies ADAPT-1 and ADAPT-2 are transferable to the German health care context for the following reasons.

According to the company, the study comparator placebo in connection with the possibility to perform prophylactic platelet transfusions as well as rescue procedures for bleeding in both study arms if required is not only in accordance with international but also with German guidelines and with common German practice.

In addition, about half of the included patients were treated in study centres in Europe and North America, and the majority of the study population was of "white" family origin. Furthermore, the reported underlying diseases alcoholic liver disease, chronic viral hepatitis and NASH are the main causes of CLD in Germany.

The company concluded that therefore neither the study design nor the patient characteristics indicated that the results of the studies ADAPT-1 and ADAPT-2 could not be transferred to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - patients without transfusion
  - WHO grade ≥ 2 bleeding events
- Side effects
  - SAEs
  - discontinuation due to AEs
  - thromboembolic events (SMQ, AE)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes of the categories of morbidity and side effects in the dossier (Module 4 A).

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

Table 11: Matrix of outcomes – RCT, direct comparison: avatrombopag vs. placebo

Study	Outcomes							
	All-cause mortality	Patients without transfusion[a]	WHO grade ≥ 2 bleeding events[b, c]	Health-related quality of life	SAEs[d]	Discontinuation due to AEs	Thromboembolic events (SMQ[e], AE)	Further specific AEs
ADAPT-1	Yes	Yes	Yes	No[f]	Yes	Yes	Yes	No[g]
ADAPT-2	Yes	Yes	Yes	No[f]	Yes	Yes	Yes	No[g]

a. Proportion of study participants who did not require a platelet transfusion after randomization and up to 7 days following an elective procedure.
b. Bleeding events were recorded from randomization over the entire study period (35 days).
c. Grade 2: mild blood loss (clinically significant), grade 3: gross blood loss, requires transfusion (severe).
d. Excluding the following haemorrhage-specific PTs: anal haemorrhage, blood urine present, conjunctiva haemorrhage, ecchymosis, epistaxis, gastric haemorrhage, gastrointestinal haemorrhage, gingival bleeding, haemarthrosis, haematemesis, haematuria, haemorrhoidal haemorrhage, oesophageal haemorrhage, oesophageal varices with bleeding, petechiae, post procedural haemorrhage, procedural haemorrhage, puncture site haemorrhage, purpura, rectal haemorrhage, tooth socket haemorrhage, vessel puncture site haemorrhage, and platelet count decreased.
e. SMQ "embolic and thrombotic events".
f. Outcome not recorded.
g. No further specific AEs were identified based on the information provided in Module 4 of the dossier.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; WHO: World Health Organization

Analyses presented by the company

In Module 4, the company presented results of the studies ADAPT-1 and ADAPT-2 only separately for the cohorts with low and high baseline platelet counts and summarized them in a meta-analysis.

For the dossier assessment, the results of the total populations of the studies ADAPT-1 and ADAPT-2 are considered in each case, regardless of cohort assignment. If possible, the studies are summarized in a meta-analysis.

Outcome "patients without transfusion"

It is unclear whether prophylactic platelet transfusions were required in the patients with a low risk of bleeding (see Section 2.3.2). Contrary to the note by G-BA, the company did not provide any information on the reasons for the platelet transfusions in Module 4. For the benefit assessment, only patients with an invasive procedure with a moderate and high risk of bleeding are therefore considered for the outcome "patients without transfusion".

2.4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: avatrombopag vs. placebo

Study	Study level	Outcomes							
		All-cause mortality	Patients without transfusion[a]	WHO grade ≥ 2 bleeding events[b]	Health-related quality of life	SAEs[c]	Discontinuation due to AEs	Thromboembolic events (SMQ[d], AE)	Further specific AEs
ADAPT-1	L	L	H[e]	H[f]	–[g]	L	L	L	–
ADAPT-2	L	L	H[e]	H[f]	–[g]	L	L	L	–

a. Proportion of study participants who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure.
b. Grade 2: mild blood loss (clinically significant), grade 3: gross blood loss, requires transfusion (severe).
c. Excluding Haemorrhage-specific PTs.
d. SMQ "embolic and thrombotic events".
e. Distribution of missing values among the subgroups of invasive procedures with different risks of bleeding (low, moderate, high) is unclear.
f: Unclear proportion of missing values.
g. Outcome not recorded.

AE: adverse event; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; WHO: World Health Organization

In accordance with the company, the risk of bias for the results of the category of all-cause mortality and for all outcomes of the category of side effects was rated as low.

Deviating from the company, the risk of bias for the outcome "patients without transfusion" was rated as high. There is no information on how missing values were distributed among patients with low, moderate or high risk of bleeding associated with the procedure. Therefore, the proportion of missing values is unclear in the subpopulation of interest, i.e. patients who have procedures with a moderate or high risk of bleeding. Assuming that all missing values are attributable to this subpopulation, there is a difference of 13.5 percentage points in the proportion of missing values between the avatrombopag arm (15.7%) and the placebo arm (29.9%) in the ADAPT-1 study. In addition, the proportion of missing values is 20% overall. For the ADAPT-2 study, there was a difference of 5.9 percentage points in the proportion of missing values between the avatrombopag arm (5.9%) and the placebo arm (11.8%). However,

the certainty of results for this outcome was not downgraded for the ADAPT-2 study because the influence of the missing values on the large observed effect was estimated to be minor.

Deviating from the company's assessment, the risk of bias for the results of the morbidity outcome "WHO grade ≥ 2 bleeding events" was rated as high. The reason for this was an unclear proportion of patients with missing values.

2.4.3 Results

Table 13 summarizes the results of the comparison of avatrombopag with placebo for the treatment of severe thrombocytopenia in patients with CLD who are scheduled to undergo an invasive procedure. The forest plots of the meta-analyses calculated by the Institute can be found in Appendix A of the full dossier assessment.

Tables with common AEs, SAEs and discontinuations due to AEs can be found in Appendix B of the full dossier assessment. The presentation is provided separately for the patients with low and high baseline platelet count.

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 13: Results (mortality, morbidity, side effects) – RCT, direct comparison: avatrombopag vs. placebo (multipage table)

Outcome category Outcome Study	Avatrombopag N	Avatrombopag Patients with event n (%)[a]	Placebo N	Placebo Patients with event n (%)[a]	Avatrombopag vs. placebo RR [95% CI]; p-value
Mortality					
All-cause mortality					
ADAPT-1	147	2 (1.4)	80	0 (0)	2.74 [0.13; 56.31]; 0.407[b]
ADAPT-2	127	0 (0)	76	1 (1.3)	0.20 [0.01; 4.86]; 0.235[b]
Total					0.85 [0.14; 5.18]; 0.861[c]
Morbidity					
Patients without transfusion[d]					
Invasive procedures with a low risk of bleeding					
ADAPT-1	89	79 (88.8)	48	17 (35.4)	–[e]
ADAPT-2	73	57 (78.1)	38	18 (47.4)	–[e]
Invasive procedures with moderate or high risk of bleeding					
ADAPT-1	51	32 (62.7)	24	7 (29.2)	2.15 [1.11; 4.16]; 0.007[b]
ADAPT-2	51	42 (82.4)	34	8 (23.5)	3.50 [1.88; 6.50]; < 0.001[b]
Total					2.83 [1.81; 4.43]; < 0.001[c]
WHO grade ≥ 2 bleeding events[f]					
ADAPT-1	149	9 (6.0)	82	4 (4.9)	1.24 [0.39; 3.90]; 0.797[b]
ADAPT-2	128	2 (1.6)	76	2 (2.6)	0.59 [0.09; 4.13]; 0.616[b]
Total					1.03 [0.39; 2.72]; 0.957[c]
Side effects					
AEs (supplementary information)[g]					
ADAPT-1	147	81 (55.1)	80	47 (58.8)	–
ADAPT-2	127	59 (46.5)	76	34 (44.7)	–
SAEs[g]					
ADAPT-1	147	16 (10.9)	80	9 (11.3)	0.97 [0.45; 2.09]; 0.966[b]
ADAPT-2	127	1 (0.8)	76	2 (2.6)	0.30 [0.03; 3.24]; 0.421[b]
Total					0.85 [0.41; 1.75]; 0.657[c]
Discontinuation due to AEs					
ADAPT-1	147	2 (1.4)	80	0 (0)	2.74 [0.13; 56.31]; 0.407[b]
ADAPT-2	127	0 (0)	76	0 (0)	–
Total					_[h]
Thromboembolic events (SMQ[i], AEs)					
ADAPT-1	147	0 (0)	80	0 (0)	–
ADAPT-2	127	1 (0.8)	76	2 (2.6)	0.30 [0.03; 3.24]; 0.421[b]
Total					_[h]

Table 13: Results (mortality, morbidity, side effects) – RCT, direct comparison: avatrombopag vs. placebo (multipage table)

Outcome category Outcome Study	Avatrombopag N	Avatrombopag Patients with event n (%)[a]	Placebo N	Placebo Patients with event n (%)[a]	Avatrombopag vs. placebo RR [95% CI]; p-value
a. Institute's calculation from separate data per cohort with lower or higher baseline platelet count. b. Institute's calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [21]). c. Institute's calculation from meta-analysis with fixed effect (Mantel-Haenszel). d. Proportion of study participants who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. e. Patients with an invasive procedure with a low risk of bleeding are not considered for the benefit assessment, see Section 2.4.1. f. Grade 2: mild blood loss (clinically significant), grade 3: gross blood loss, requires transfusion (severe). Only 2 severe bleeding events (grade 3) occurred overall, each in the avatrombopag arm of the ADAPT-1 study. g. Excluding haemorrhage-specific PTs. h. A meta-analysis was not performed because no event occurred in one of 2 studies. i. SMQ "embolic and thrombotic events". AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; WHO: World Health Organization					

Based on the available information, at most proof, e.g. of an added benefit, can be determined for the outcomes "all-cause mortality" and "patients without transfusion" as well as for the outcomes of the category of side effects, and at most an indication can be determined for the outcome "WHO grade ≥ 2 bleeding events" due to the high risk of bias.

Mortality

All-cause mortality

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of avatrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

This deviates from the approach of the company, which recorded deaths as part of side effects, but did not use this outcome for the derivation of the added benefit.

Morbidity

Patients without transfusion

For the outcome "patients without transfusion", the meta-analysis of the studies showed a statistically significant difference in favour of avatrombopag in patients who were scheduled to undergo an invasive procedure associated with moderate or high risk of bleeding. This resulted in proof of an added benefit of avatrombopag in comparison with watchful waiting.

This deviates from the approach of the company insofar as the company derived proof of an added benefit of avatrombopag for the total population of all patients, regardless of the risk of bleeding of the scheduled invasive procedure.

WHO grade ≥ 2 bleeding events

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome "WHO grade ≥ 2 bleeding events". This resulted in no hint of an added benefit of avatrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

No data are available for the outcome "health-related quality of life", as this outcome was not recorded in the studies ADAPT-1 and ADAPT-2. This resulted in no hint of an added benefit of avatrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

The company did not use the outcome.

Side effects

SAEs, discontinuation due to AEs

The meta-analysis of the studies showed no statistically significant differences between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm of avatrombopag in comparison with watchful waiting; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Thromboembolic events (SMQ, AEs)

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome "thromboembolic events". This resulted in no hint of greater or lesser harm of avatrombopag in comparison with watchful waiting; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- age (< 65 years/≥ 65 years)
- sex (male/female)
- risk of bleeding associated with the invasive procedure (low/moderate/high)

These characteristics were predefined for the outcome “patients without transfusion”.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

There was no relevant effect modification with a statistically significant and relevant effect for any of the available subgroup analyses of the considered effect modifiers on patient-relevant outcomes.

2.5 Probability and extent of added benefit

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

The approach for deriving an overall conclusion on the 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 the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 14).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier for the following outcome whether it is serious/severe or non-serious/non-severe. The classification for this outcome is justified.

Patients without transfusion

It is not clear from the information provided in Module 4 A that the avoidance of transfusions is to be assigned to serious/severe symptoms or late complications. Therefore, the outcome “patients without transfusion” was assigned to the category of non-serious/non-severe symptoms or late complications.

Table 14: Extent of added benefit at outcome level: avatrombopag vs. placebo

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Avatrombopag vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0–1.4% vs. 0–1.3%[c] RR: 0.85 [0.14; 5.18] p = 0.861	Lesser benefit/added benefit not proven
Morbidity		
Patients without transfusion Invasive procedure with moderate or high risk of bleeding	62.7–82.4% vs. 23.5–29.2%[c] RR: 2.83 [1.81; 4.43] RR[d]: 0.35 [0.23; 0.55] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: "considerable"
WHO grade ≥ 2 bleeding events	1.6–6.0% vs. 2.6–4.9%[c] RR: 1.03 [0.39; 2.72] p = 0.957	Lesser benefit/added benefit not proven
Health-related quality of life		
Not recorded		
Side effects		
SAEs	0.8–10.9% vs. 2.6–11.3%[c] RR: 0.85 [0.41; 1.75] p = 0.657	Greater/lesser harm not proven
Discontinuation due to AEs	0–1.4% vs. 0%[c] RR: NC	Greater/lesser harm not proven
Thromboembolic events	0–0.8% vs. 0–2.6%[c] RR: NC	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Minimum and maximum proportions of events in each treatment arm in the studies included.
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; NC: not calculable; RR: relative risk; SAE: serious adverse event; WHO: World Health Organization

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of avatrombopag in comparison with watchful waiting

Positive effects	Negative effects
Morbidity ▪ Patients without transfusion ▫ Invasive procedure with moderate or high risk of bleeding: proof of added benefit – extent: "considerable"	–

In the overall picture, there is exclusively a positive effect of avatrombopag in comparison with watchful waiting for patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure with moderate or high risk of bleeding. This positive effect is not accompanied by negative effects.

In summary, there is proof of considerable added benefit of avatrombopag in comparison with the ACT of watchful waiting for the treatment of severe thrombocytopenia in adult patients with CLD who are scheduled to undergo an invasive procedure with moderate or high risk of bleeding.

There is no hint of an added benefit of avatrombopag in comparison with watchful waiting for adult patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure with low risk of bleeding; an added benefit is therefore not proven.

Table 16 summarizes the result of the assessment of the added benefit of avatrombopag in comparison with the ACT.

Table 16: Avatrombopag – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure[c]	Watchful waiting[b]	Moderate or high risk of bleeding from the invasive procedure: ▪ proof of considerable added benefit
		Low risk of bleeding from the invasive procedure: ▪ added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed that platelet transfusions, if indicated, are performed in both arms of the study. The reasons have to be documented. Furthermore, it is assumed that the patients in the therapeutic indication undergo an invasive medical procedure.
c. No data are available for patients with a MELD score > 24.

ACT: appropriate comparator therapy; CLD: chronic liver disease; G-BA: Federal Joint Committee; MELD: Model for End-Stage Liver Disease

The assessment described above deviates from that of the company, which derived proof of considerable added benefit for all patients, irrespective of the bleeding risk of the scheduled invasive procedure.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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