IQWiG Reports – Commission No. A21-157

# Lusutrombopag (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 *Lusutrombopag (Thrombozytopenie und chronische Lebererkrankung) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2022). Please note: This document was translated by an external translator and 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.

**Patient and family involvement**

No feedback was received in the framework of the present dossier assessment.

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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 |
| CTCAE | Common Terminology Criteria for Adverse Events |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| HCC | hepatocellular carcinoma |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PT | Preferred Term |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SMQ | Standardized MedDRA Query |
| SOC | System Organ Class |
| 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 lusutrombopag. 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 29 November 2021.

### Research question

The aim of the present report is to assess the added benefit of lusutrombopag in comparison with watchful waiting as the 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 G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of lusutrombopag

| Therapeutic indication | ACT[a] |
|---|---|
| Adult patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure | Watchful waiting[b] |

a. Presented is the respective ACT specified by the G-BA.
b. It was assumed that, where indicated, platelet transfusions were administered in both study arms. The reasons must be documented.

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 were to offer the option of platelet transfusions, where indicated.

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

#### *L-PLUS 2, L-PLUS 1, and M0626 studies*

The L-PLUS 2, L-PLUS 1, and M06261 studies were included in the benefit assessment. The studies are double-blind randomized controlled trials (RCTs) comparing lusutrombopag with placebo. L-PLUS 2 is a multinational study, whereas L-PLUS 1 and M0626 were conducted only in Japan.

The studies included adult patients with CLD of different aetiologies and severe thrombocytopenia (platelet count < $50x10^9$/L) who were scheduled to undergo an invasive procedure.

The studies randomly allocated patients to the treatment arms of lusutrombopag (L-PLUS 2: N = 108; L-PLUS 1: N = 49; M0626: N = 16) and placebo (L-PLUS 2: N = 107; L-PLUS 1: N = 48; M0626: N = 15).

In all 3 studies, lusutrombopag treatment was administered largely in line with the specifications of the Summary of Product Characteristics (SPC).

Prophylactic platelet transfusions were allowed in all 3 studies, with specifications differing between studies. Platelet transfusions due to bleeding were also allowed as part of rescue therapy.

The primary outcome of the L-PLUS 2 study was the percentage of patients who required no platelet transfusion prior to the invasive procedure and no rescue therapy for bleeding from randomization through 7 days after a planned procedure. The primary outcome of the L-PLUS 1 and M0626 studies was the percentage of participants who received no platelet transfusion prior to the invasive procedure. Patient-relevant outcomes on all-cause mortality, morbidity, and adverse events (AEs) were additionally recorded.

In the studies, the administration of prophylactic platelet transfusion was directly based on the platelet count prior to the invasive procedure. This approach is inadequate. There is no way to determine whether prophylactic platelet transfusions administered to L-PLUS 2, L-PLUS 1, and M0626 participants were required in each case because no information on further reasons is available. Therefore, the presented studies on lusutrombopag implemented the ACT only with limitations. In the present situation, this means, in particular, that the outcome of patients without transfusion cannot be interpreted.

Invasive procedures were performed after completion of treatment with the study drug, on Days 9 through 14.

**Risk of bias**

The risk of bias across outcomes was rated as low for the L-PLUS 2, L-PLUS 1, and M0626 studies.

In all 3 studies, the risk of bias is rated as low for the available data from the employed outcome operationalizations.

**Results**

***Mortality***

*All-cause mortality*

For the outcome of all-cause mortality, the L-PLUS 2 study shows no statistically significant difference between treatment groups. No patients died in the L-PLUS 1 and M0626 studies. Consequently, there is no hint of added benefit of lusutrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

***Morbidity***

*Patients without transfusion*

For the outcome of patients without transfusion, no usable data are available. Consequently, there is no hint of added benefit of lusutrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

*World Health Organization (WHO grade) ≥ 2 bleeding events*

For the outcome of WHO grade ≥ 2 bleeding events, the L-PLUS 2 study shows no statistically significant difference between treatment groups. No data are available for the L-PLUS 1 and M0626 studies. Consequently, there is no hint of added benefit of lusutrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

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

No data are available for the outcome of health-related quality of life because the L-PLUS 2, L-PLUS 1, and M0626 studies did not survey this outcome. Consequently, there is no hint of added benefit of lusutrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

***Side effects***

*Serious adverse events (SAEs)*

For the outcome of SAEs, the metaanalysis of the studies does not show a statistically significant difference between treatment groups. Consequently, there is no hint of greater or lesser harm from lusutrombopag in comparison with watchful waiting; greater or lesser harm is therefore not proven.

*Discontinuation due to AEs*

For the outcome of discontinuation due to AEs, the L-PLUS 2 study shows no statistically significant difference between treatment groups. Only 1 patient in the comparator arm discontinued treatment due to adverse events. In the L-PLUS 1 and M0626 studies, there were no patients with event. Consequently, there is no hint of greater or lesser harm from lusutrombopag in comparison with watchful waiting; greater or lesser harm is therefore not proven.

*Thromboembolic events (Standardized MedDRA Query [SMQ], AEs)*

The metaanalysis of the studies showed no statistically significant difference between treatment groups for the outcome of thromboembolic events. Consequently, there is no hint of greater or lesser harm from lusutrombopag 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, the probability and extent of added benefit of the drug lusutrombopag in comparison with the ACT are assessed as follows:

Overall, there is no favourable or unfavourable effect of lusutrombopag in comparison with watchful waiting for patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure.

In summary, for the treatment of patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure, there is no hint of added benefit of lusutrombopag in comparison with the ACT of watchful waiting; added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of added benefit of lusutrombopag.

Table 3: Lusutrombopag – 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] | Added benefit not proven |

a. Presented is the respective ACT specified by the G-BA.
b. It was assumed that, where indicated, platelet transfusions were administered in both study arms. The reasons must be documented.
c. The L-PLUS 2, L-PLUS 1, and M0626 studies were to include only patients in Child-Pugh stage A or B. It remains unclear whether the observed effects can be extrapolated to patients in Child-Pugh stage C.

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

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

[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].

## 2.2 Research question

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

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of lusutrombopag

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| Adult patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure | Watchful waiting[b] |
| a. Presented is the respective ACT specified by the G-BA.<br>b. It was assumed that, where indicated, platelet transfusions were administered in both study arms. The reasons must be documented.<br>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 were to offer the option of platelet transfusions, where indicated.

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 lusutrombopag (status: 24 September 2021)
- bibliographical literature search on lusutrombopag (last search on 24 September 2021)
- search in trial registries / trial results databases for studies on lusutrombopag (last search on 24 September 2021)
- search on the G-BA website for lusutrombopag (last search on 24 September 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on lusutrombopag (last search on 10 December 2021); see Appendix A of the full dossier assessment for search strategies.

The check did not identify any additional relevant studies.

### 2.3.1 Studies included

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

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

| Study | Study category | | | Available sources | | |
|---|---|---|---|---|---|---|
| | Approval study for the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) | Clinical study report (CSR) (yes/no [citation]) | Registry entries[b] (yes/no [citation]) | Publication (yes/no [citation]) |
| L-PLUS 2[c] (1423M0634) | Yes | Yes | No | Yes [3] | Yes [4,5] | Yes [6,7] |
| L-PLUS 1[c] (1304M0631) | Yes | Yes | No | Yes [8] | Yes [9] | Yes [10] |
| M0626 [c] (1208M0626) | Yes | Yes | No | Yes [11] | Yes [12] | Yes [13] |

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

The study pool used in the benefit assessment of lusutrombopag versus the ACT consists of the L-PLUS 2, L-PLUS 1, and M0626 RCTs, coinciding with the company's study pool.

### 2.3.2 Study characteristics

Table 6 and Table 7 present the studies used in the benefit assessment.

Table 6: Characteristics of the included studies – RCT, direct comparison: lusutrombopag 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] |
|---|---|---|---|---|---|---|
| L-PLUS 2 | RCT, double-blind, parallel-group | Adults (≥ 18 years) with CLD[b]<br>▪ with a baseline platelet count < 50 x $10^9$/L prior to randomization<br>▪ who were scheduled to undergo an invasive procedure[c] likely to require platelet transfusion<br>▪ Child-Pugh stage A or B<br>▪ ECOG-PS 0 or 1<br>▪ WHO bleeding score < 2 | Lusutrombopag (N = 108)<br>Placebo (N = 107) | Screening: 1–28 days<br>Treatment: 7 days<br>Follow-up observation: 28 days after completion of treatment | A total of 138 study centres in Argentina, Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Poland, Romania, Russia, South Korea, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States<br>07/2015–04/2017 | Primary: percentage of study participants who required no platelet transfusion prior to the invasive procedure and no rescue therapy for acute bleeding from randomization through 7 days after the invasive procedure<br>Secondary: outcomes of the categories of mortality, morbidity, AEs |
| L-PLUS 1 | RCT, double-blind, parallel-group | Adults (≥ 20 years) with CLD[b]<br>▪ Baseline platelet count < 50 x $10^9$/L at the time of screening<br>▪ who were scheduled to undergo an invasive procedure[c]<br>▪ Child-Pugh stage A or B<br>▪ ECOG-PS 0 or 1<br>▪ WHO bleeding score < 2 | Lusutrombopag (N = 49)<br>Placebo (N = 48) | Screening: 1–28 days<br>Treatment: 7 days<br>Follow-up observation: 28 days after completion of treatment | 81 centres in Japan<br>10/2013–05/2014 | Primary: percentage of study participants without platelet transfusion prior to the invasive procedure<br>Secondary: outcomes of the categories of mortality, morbidity, AEs |

Table 6: Characteristics of the included studies – RCT, direct comparison: lusutrombopag 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] |
|---|---|---|---|---|---|---|
| M0626 | RCT, double-blind, parallel-group | Adults (≥ 20 years) with CLD[b]<br>▪ Baseline platelet count < 50 x $10^9$/L at the time of screening<br>▪ who were scheduled to undergo percutaneous ablation of the liver due to HCC<br>▪ Child-Pugh stage A or B<br>▪ ECOG-PS 0 or 1<br>▪ WHO bleeding score < 2 | Lusutrombopag 3 mg (N = 16)<br>Lusutrombopag 2 mg (N = 15)[d]<br>Lusutrombopag 4 mg (N = 15)[d]<br>Placebo (N = 15) | Screening: 1–28 days<br>Treatment: 7 days<br>Follow-up observation: 28 days after completion of treatment | 63 centres in Japan<br>08/2012–04/2013 | Primary: percentage of study participants who required no platelet transfusion prior to percutaneous liver ablation<br>Secondary: outcomes of the categories of mortality, morbidity, AEs |

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Excluded were patients with haematopoietic tumour or malignant accompanying tumour where the invasive procedure was not intended to treat said tumour, patients with congenital, immune-induced, or drug-induced thrombocytopenia or thrombocytopenia due to another cause as well as patients with signs or a history of thrombotic or thomboembolic disorders, liver transplantation, or splenectomy.
c. Excluded procedures were laparotomy, thoracotomy, craniotomy, open heart surgery, organ extirpation and partial organ resections (except endoscopic biopsies).
d. This arm is irrelevant for the assessment and is not presented in the following tables.

AE: adverse event; CLD: chronic liver disease; ECOG: Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma; N: number of randomized patients; RCT: randomized controlled trial; WHO: World Health Organization

Table 7: Characteristics of the intervention – RCT, direct comparison: lusutrombopag vs. placebo (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| L-PLUS 2 | Lusutrombopag 3 mg/day for 7 days[a] | Placebo daily for 7 days[a] |
| | **Pretreatment**<br>Disallowed:<br>▪ blood transfusion within 14 days prior to randomization (except transfusion of red cell concentrates or albumin products)<br>▪ certain invasive procedures[b] within 90 days prior to randomization or no invasive procedures within 14 days prior to randomization (except treatment of gastro-oesophageal varices)<br>▪ prior administration of lusutrombopag<br>**Concomitant treatment**<br>Disallowed:<br>▪ blood products and blood components (see rescue therapy below for exceptions)<br>▪ within 90 days prior to study start and during the study:<br>▫ oncology drugs (except TACE or lipiodol injection prior to the study or as a planned intervention in liver ablation or coagulation during the study)<br>▫ interferon preparations<br>▫ other TPO receptor agonists<br>▫ radiotherapy, bloodletting<br>▪ macrophage colony stimulating products, granulocyte colony stimulating products, erythropoietin, desmopressin products, monoethanolamine oleate<br>▪ invasive procedures other than those planned in the study<br>Allowed<br>▪ prophylactic administration of platelet concentrates[c]<br>▪ rescue therapy for bleeding[d]<br>▪ antithrombotic drugs[e] for rescue therapy in case of suspected or confirmed thrombotic events with a platelet count ≥ 200 × $10^9$/L<br>▪ vitamin K – if taken at a constant dose ≥ 28 days prior to randomization | |
| L-PLUS 1 | Lusutrombopag 3 mg/day for 7 days[a] | Placebo daily for 7 days[a] |
| | **Pretreatment**<br>Disallowed:<br>▪ antithrombotic drugs within 14 days prior to study start<br>▪ blood transfusion within 14 days prior to randomization (except transfusion of red cell concentrates or albumin products)<br>▪ TPO receptor agonists<br>▪ certain invasive procedures[b] within 90 days prior to randomization or no invasive procedures within 14 days prior to randomization (except treatment of gastro-oesophageal varices)<br>**Concomitant treatment**<br>▪ as for L- PLUS 2 | |

Table 7: Characteristics of the intervention – RCT, direct comparison: lusutrombopag vs. placebo (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| M0626 | Lusutrombopag 3 mg/day for 7 days[a] | Placebo daily for 7 days[a] |
| | **Prior treatment**<br>Disallowed:<br>▪ antithrombotic drugs within 7 days prior to study start<br>▪ blood transfusion within 14 days prior to study start (except red cell concentrates or albumin products)<br>▪ TPO receptor agonists<br>▪ certain invasive procedures[b] within 90 days or treatment of liver tumours within 14 days prior to study start<br><br>**Concomitant treatment**<br>Disallowed:<br>▪ certain invasive procedures[b] and treatments[f] of liver disease<br>▪ haemostatics (except for rescue therapy in bleeding)<br>▪ further restrictions as for L-PLUS 2<br>Allowed:<br>▪ as for L- PLUS 2 | |

a. Platelet count was done on Days 5 through 7. Treatment was discontinued at a count ≥ 50 × $10^9$/L and an increase by ≥ 20 × $10^9$/L from baseline.
b. Excluded procedures differed between studies and were, among others, laparotomy, thoracotomy, craniotomy, open heart surgery, organ extirpation or partial organ resection (except endoscopic biopsies), partial splenic embolization, and hepatectomy.
c. Prophylactic platelet transfusion was carried out if the following criterion was met: platelet count < 50 × $10^9$/L on Day 8 or later ≤ 2 days prior to the procedure.
d. Platelet transfusions, red cell concentrates, albumin preparations.
e. Heparin, acetylsalicylic acid, dipyridamole, ticlopidine, urokinase.
f. Percutaneous liver ablation or ethanol injection therapy, TACE, lipiodol injection with anticancer drugs, transarterial embolization (except lipiodol injection for marking) as well as endoscopic injection sclerotherapy and liver transplantation as concomitant therapy.

RCT: randomized controlled trial; TACE: transcatheter arterial chemoembolization; TPO: thrombopoietin.

## Study design

The L-PLUS 2, L-PLUS 1, and M0626 studies are double-blind RCTs comparing lusutrombopag with placebo. L-PLUS 2 is a multinational study, whereas L-PLUS 1 and M0626 were conducted only in Japan.

All 3 studies included adult patients with CLD of different aetiologies and severe thrombocytopenia (platelet count < 50 x $10^9$/L) who were to undergo an invasive procedure. The L-PLUS 2 and L-PLUS 1 studies allowed many invasive procedures but disallowed laparotomies, thoracotomies, craniotomies, open heart surgery, organ extirpations, or partial organ resections. The M0626 study included only patients who were to undergo percutaneous ablation of the liver due to hepatocellular carcinoma (HCC). The studies randomly allocated patients to the arms lusutrombopag (L-PLUS 2: N = 108; L-PLUS 1: N = 49; M0626: N = 16) and placebo (L-PLUS 2: N = 107; L-PLUS 1: N = 48; M0626: N = 15). Randomization was

stratified by baseline platelet count ($< 35 \times 10^9$/L versus $\geq 35 \times 10^9$/L [L-PLUS 2] or $< 35 \times 10^9$/L versus $\geq 35 \times 10^9$/L to $< 45 \times 10^9$/L versus $\geq 45 \times 10^9$/L [L-PLUS 1, M0626]), planned invasive procedure (liver ablation/coagulation versus other [L-PLUS 2, L-PLUS 1]) or Child-Pugh stage (A versus B [M0626]).

In all 3 studies, the severity of liver disease had to be categorized as Child-Pugh stage A or B. Patients were excluded from participation if they had signs or a history of thromboses or thromboembolic disease.

In all 3 studies, patient treatment with lusutrombopag was largely in line with the specifications of the SPC [14]. On Treatment Days 5, 6, and 7, the platelet count was taken, and treatment was stopped in patients who simultaneously exhibited a count $\geq 50 \times 10^9$/L as well as an increase by $\geq 20 \times 10^9$/L from baseline. Other concomitant treatments were allowed under restrictions.

Prophylactic platelet transfusions were allowed in all 3 studies, with specifications differing between studies. The need for platelet transfusion before the invasive procedure was determined using the platelet count measured preoperatively (≤ 2 days prior to the procedure). The L-PLUS 2 study required platelet transfusions at preoperative platelet counts $< 50 \times 10^9$/L. The L-PLUS 1 and M0626 studies allowed prophylactic platelet transfusions at counts $< 50 \times 10^9$/L. In the M0626 study, prophylactic platelet transfusions were to be foregone at preoperative platelet counts $> 50 \times 10^9$/L. The number and timing of platelet transfusions as well as their justification were to be documented (see below on the implementation of the ACT).

Platelet transfusions due to bleeding were also allowed as part of rescue measures.

The primary outcome of the L-PLUS 2 study was the percentage of patients who required no platelet transfusion prior to the invasive procedure and no rescue therapy for bleeding from randomization through 7 days after a planned procedure. The primary outcome of the L-PLUS 1 and M0626 studies was the percentage of study participants without platelet transfusion prior to the invasive procedure. Patient-relevant outcomes on all-cause mortality, morbidity, and AEs were additionally recorded. Invasive procedures were performed after completion of treatment with the study drug, on Study Days 9 through 14. The subsequent follow-up phase ended a maximum of 35 days after randomization.

**Implementation of the ACT**

The G-BA specified the ACT of watchful waiting. It was assumed that, where indicated, platelet transfusions were administered in both study arms. The reasons must be documented.

In the studies conducted by the company, patients in the comparator arm received a placebo. All of the company's studies allowed prophylactic platelet transfusions only under certain conditions. As described above, the transfusions were linked directly to the platelet count prior to the procedure. At a platelet count $< 50 \times 10^9$/L, platelet transfusions were required in the

L-PLUS 2 study and recommended in the other 2 studies. The dossier's Module 4 A did not document whether, and if so which. individual patient criteria other than platelet count played a role in the decision for or against prophylactic platelet transfusion.

The company's approach was not appropriate. According to guidelines, the indication for platelet transfusion is established based on an overall consideration of various factors, including platelet count and function, bleeding risk associated with the planned procedure, bleeding symptoms, other reasons for abnormal coagulation, history of bleeds, portal hypertension as well as the underlying illness, comorbidities, and comedications [15,16]. A patient-specific assessment of the risk of bleeding associated with the procedure and other patient-specific factors is recommended for establishing the therapeutic indication for platelet transfusion [16]. Citing the above aspects in an earlier benefit assessment, the G-BA stated that according to current medical knowledge, no standardized criteria for assessing patient need for transfusion can be derived [17].

The information provided in Module 4 A shows that in the L-PLUS 2, L-PLUS 1, and M0626 studies, platelet transfusions were administered almost exclusively prophylactically. The dossier's Module 4 A does not provide any information on the justifications of platelet transfusions, despite the G-BA explicitly requiring this information. Patient characteristics (mean baseline platelet count of about $37 \times 10^9$/L through $42 \times 10^9$/L) or the types of procedures performed in the 3 studies do not, by themselves, substantiate the indication for prophylactic platelet transfusion for patients in whom a platelet count $< 50 \times 10^9$/L was measured directly prior to the invasive procedure. Therefore, it is impossible to assess whether prophylactic platelet transfusions were required by each of the patients who received them in the 3 studies. Therefore, the presented studies on lusutrombopag implemented the ACT only with limitations. In particular, this means that the outcome of patients without transfusion cannot be interpreted in the present scenario (see Section 2.4.1).

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations – RCT, direct comparison: lusutrombopag vs. placebo (multipage table)

| Study | L-PLUS 2 | | L-PLUS 1 | | M0626 | |
|---|---|---|---|---|---|---|
| Characteristic<br>Category | Lusutrombopag | Placebo | Lusutrombopag | Placebo | Lusutrombopag | Placebo |
| | N = 108 | N = 107 | N[a] = 48 | N = 48 | N = 16 | N = 15 |
| Age [years], mean [min; max] | 55 [19; 81] | 56 [19; 83] | 69 [51; 81] | 67 [40; 88] | 67 [53; 80] | 71 [51; 85] |
| Sex [f/m], % | 40/60 | 36/64 | 56/44 | 38/63 | 44/56 | 47/53 |
| Ancestry, n (%) | | | | | | |
| White | 85 (79) | 86 (80) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Asian | 15 (14) | 17 (16) | 48 (100) | 48 (100) | 16 (100) | 15 (100) |
| Other | 6 (6)[b] | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Unknown | 2 (2) | 4 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Baseline platelet count [$\times 10^9$/L], mean [min; max] | 37.7 [13; 54] | 37.4 [12; 55] | 40.9 [23; 49] | 39.9 [23; 55] | 41.8 [17; 67] | 41.8 [34; 49] |
| Platelet count at screening [$\times 10^9$/L], n (%) | | | | | | |
| < 35 | 36 (33) | 38 (36) | 7 (15) | 10 (21) | 3 (19) | 4 (27) |
| ≥ 35 | 71 (66) | 68 (64) | 41 (85) | 38 (79) | 13 (81) | 11 (73)[c] |
| Unknown | 1 (1) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Child-Pugh stage, n (%) | | | | | | |
| A | 72 (67) | 63 (59) | 26 (54) | 22 (46) | 9 (56) | 9 (60) |
| B | 33 (31) | 43 (40) | 22 (46) | 26 (54) | 7 (44) | 6 (40) |
| C | 3 (3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Unknown | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Cause of disease, n (%) | | | | | | |
| Hepatitis B | 24 (22) | 21 (20) | 4 (8) | 8 (17) | 3 (19) | 1 (7) |
| Hepatitis C | 51 (47) | 51 (48) | 39 (81) | 32 (67) | 11 (69) | 12 (80) |
| Alcohol-related liver disease | 24 (22) | 26 (24) | 2 (4) | 6 (13) | 2 (13) | 1 (7) |
| Non-alcohol-related liver disease | 12 (11) | 15 (14) | 3 (6) | 4 (8) | 0 (0) | 1 (7) |
| Autoimmune hepatitis | 5 (5) | 5 (5) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

Table 8: Characteristics of the study populations – RCT, direct comparison: lusutrombopag vs. placebo (multipage table)

| Study | L-PLUS 2 | | L-PLUS 1 | | M0626 | |
|---|---|---|---|---|---|---|
| Characteristic Category | Lusutrombopag | Placebo | Lusutrombopag | Placebo | Lusutrombopag | Placebo |
| | N = 108 | N = 107 | N[a] = 48 | N = 48 | N = 16 | N = 15 |
| Invasive procedures performed, n (%) | | | | | | |
| Liver | 20 (19) | 20 (19) | 34 (71)[c] | 33 (69[c] | 16 (100) | 15 (100) |
| Percutaneous RFA | 4 (4) | 1 (1) | 21 (44[c]) | 20 (42[c]) | 16 (100) | 15 (100) |
| TACE | 11 (10) | 9 (8) | 13 (27) | 11 (23) | 0 (0) | 0 (0) |
| Liver biopsy | 3 (3) | 6 (6) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Other | 2 (2) | 4 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Gastrointestinal | 61 (56) | 60 (56) | 8 (17)[c] | 10 (21)[c] | 0 (0) | 0 (0) |
| EVL | 32 (30) | 29 (27) | 6 (13) | 8 (17) | 0 (0) | 0 (0) |
| EIS | 1 (1) | 1 (1) | 2 (4) | 2 (4) | 0 (0) | 0 (0) |
| Endoscopy (excluding EVL, EIS) | 28 (26) | 30 (28) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Other | 21 (19) | 18 (17) | 6 (13) | 6 (13) | 0 (0) | 0 (0) |
| Tooth extraction | 13 (12) | 11 (10) | ND | ND | 0 (0) | 0 (0) |
| Other | 8 (7) | 7 (7) | ND | ND | 0 (0) | 0 (0) |
| Not performed | 6 (6) | 9 (8) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| Treatment discontinuation, n (%)[d] | 1 (1[c]) | 1 (1[c]) | 1 (2[c]) | 0 (0) | 0 (0) | 0 (0) |
| Study discontinuation, n (%)[e] | 10 (9)[c] | 5 (5)[c] | 1 (2[c]) | 1 (2[c]) | 0 (0) | 0 (0) |

a. A total of 49 patients were randomized to this arm. One patient did not receive any treatment and was disregarded in this table, except under treatment and study discontinuations.
b. IQWiG calculation, combining Native Americans and Alaska Natives, African Americans, and Other.
c. IQWiG calculation.
d. In each of the intervention arms of the L-Plus 2 and L-PLUS 1 studies, 1 patient did not receive any treatment; the discontinuation in the L-PLUS 2 study's control arm was upon the patient's wishes.
e. In the L-PLUS 2 study, common reasons for study discontinuation in the intervention versus control arm were adverse events (3 versus 1 patient) and discontinuation by patient (4 versus 3 patients).

EIS: endoscopic injection sclerotherapy; EVL: endoscopic variceal ligation; f: female; IQWiG: Institute for Quality and Efficiency in Health Care; m: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; RFA: radiofrequency ablation; SD: standard deviation; TACE: transarterial chemoembolization

Demographic characteristics are largely balanced between the 2 studies performed in Japan, L-PLUS 1 and M0626, as well as between their study arms. Patients were of Asian ancestry, and their average age was about 70 years. In the multinational L-PLUS 2 study, the study population was largely white, and at a mean of about 55 years, they were slightly younger than the patients in the L-PLUS 1 and M0626 studies.

In all 3 studies, chronic liver disease was largely due to chronic viral hepatitis; further causes were alcohol-related liver disease or non-alcoholic steatohepatitis. The percentage of patients with alcohol-related liver disease was much lower in the L-PLUS 1 and M0626 studies carried out in Japan. More than half of the included patients were in Child-Pugh stage A. As per the studies' inclusion criteria, all patients had severe thrombocytopenia with a mean platelet count of about $37 \times 10^9$/L though $42 \times 10^9$/L. The invasive procedures comprised, in particular, all procedures performed on the liver as well as gastrointestinal endoscopic procedures, with predominantly liver-related procedures having been carried out in L-PLUS 1, and more than half of patients receiving a gastrointestinal endoscopic procedure in L-PLUS 2. In contrast, the M0626 study included only patients who were to undergo percutaneous ablation of the liver due to HCC.

**Risk of bias across outcomes (study level)**

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: lusutrombopag vs. placebo

| Study | Adequate random sequence generation | Allocation concealment | Blinding | | Nonselective reporting | Absence of other aspects | Risk of bias at study level |
|---|---|---|---|---|---|---|---|
| | | | Patients | Treating staff | | | |
| L-PLUS 2 | Yes | Yes | Yes | Yes | Yes | Yes[a] | Low |
| L-PLUS 1 | Yes | Yes | Yes | Yes | Yes | Yes | Low |
| M0626 | Yes | Yes | Yes | Yes | Yes | Yes | Low |

a. Date of database cut-off is missing. However, the major changes listed in SAP version 2.0 from 5 June 2017 do not affect the assessment of the risk of bias across outcomes. This aspect was taken into account in the assessment of the risk of bias on the outcome level.
RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the 3 studies L-PLUS 2, L-PLUS 1, and M0626.

**Transferability of the study results to the German health care context**

The company deems the results of the L-PLUS 2, L-PLUS 1, and M0626 studies and their metaanalysis to be extrapolatable to the German healthcare context by arguing as follows:

In the largest, multinational study L-PLUS 2, the vast majority (79.5%) of patients is of white ancestry, and both their age and their disease characteristics reflect the characteristics of the target population in the German healthcare context. The majority of patients was treated at study sites in Europe and North America, i.e. in countries where the standards of medical care are high and comparable to those in Germany. Furthermore, the presented L-PLUS 2 subgroup analyses demonstrate the absence of effect modifications regarding the subgroup of ancestry for all of the patient-relevant outcomes.

The results of the Japanese studies L-PLUS 1 and M0626 can be extrapolated to the German healthcare context as well. According to the European Medicines Agency's comparability concept, study results can be extrapolated from one region to another (in this case, from Japan to Germany) if the therapeutic indication as well as the mechanism of action, effectiveness, and safety of the drug are comparable in both regions. The company argues that lusutrombopag meets all 3 criteria of this concept.

Furthermore, the company argues that the subgroup analyses of the metaanalyses did not reveal any effect modifications regarding the subgroup of ancestry for any of the investigated patient-relevant outcomes.

## 2.4 Results on added benefit

### 2.4.1 Outcomes included

The following patient-relevant outcomes were to be taken into account in the assessment:

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

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

Table 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: lusutrombopag vs. placebo

| Study | Outcomes | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All-cause mortality | Patients without transfusion | Bleeding WHO grade ≥ 2 | Health-related quality of life | SAEs | Discontinuation due to AEs | Thromboembolic events (SMQ[a], AEs) | Further specific AEs |
| L-PLUS 2 | Yes | No[b] | Yes | No[c] | Yes | Yes | Yes | No[d] |
| L-PLUS 1 | Yes | No[b] | No[e] | No[c] | Yes | Yes | Yes | No[d] |
| M0626 | Yes | No[b] | No[e] | No[c] | Yes | Yes | Yes | No[d] |

a. MedDRA SMQs "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous" and "embolic and thrombotic events, venous".
b. No usable data.
c. Outcome not recorded.
d. No further specific AEs were identified.
e. No data are available on this operationalization of bleeding.

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

**Outcome of patients without transfusion**

In the company's studies, the decision to administer prophylactic platelet transfusion was largely based on the criterion of platelet counts $< 50 \times 10^9$/L prior to the invasive procedure (see Section 2.3.2). Disregarding the G-BA's note, the company's Module 4 A did not provide the justification for the platelet transfusions performed in the study. Overall, it is not possible to determine whether the patients actually needed the platelet transfusions, which were almost exclusively administered prophylactically. The outcome of patients without transfusion can therefore not be interpreted and will be disregarded in the benefit assessment (supplementary presentation in Appendix B of the full dossier assessment).

**Response**

To derive added benefit, the company's dossier uses the outcome of response – referred to by the company's Module 4 A as successful treatment of severe thrombocytopenia. The company argues that severe thrombocytopenia ($< 50 \times 10^9$/L) represents an AE of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 and has direct and immediate patient-

relevant consequences in clinical care. Therefore, it deems successful treatment of severe thrombocytopenia to be patient relevant. To support its argument, the company refers to the inclusion of the AE outcome of severe neutropenia (CTCAE ≥ 3) in the early benefit assessment A14-25 (eribulin) [18].

Neither the company's reasoning regarding the outcome's patient relevance nor the reference to the approach taken in A14-25 are appropriate.

Any AE which (1) occurs for the first time during drug treatment of an oncological disease, (2) is based on laboratory readings, and (3) is severe (CTCAE grade ≥ 3) is to be deemed patient relevant (see AE neutropenia in A14-25 [18]). In contrast, severe thrombocytopenia in the therapeutic indication of CLD is a consequence of the existing underlying illness of the patients included in the study rather than representing an AE. These patients have often adapted to lower platelet counts; due to a rebalanced haemostatic system, directly and immediately patient-relevant consequences might therefore not occur in everyday clinical care [19-23]. In invasive procedures, the risk of bleeding of a patient with severe thrombocytopenia is determined not solely by the platelet count, but also by a series of other factors (see Section 2.3.2). A temporary increase in platelet count above a certain threshold therefore neither eliminates thrombocytopenia – but at best alleviates it temporarily – nor eliminates the bleeding risk.

The outcome of response was therefore disregarded in the present benefit assessment.

**Outcomes on side effects**

For the side effect outcomes (AEs, SAEs), the company has submitted analyses excluding thromboembolic events as well as bleeding events (SMQs "embolic and thrombotic events, arterial", "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous", and "embolic and thrombotic events, venous"; the SMQs "haemorrhage terms" and the Preferred Term [PT] "platelet count decreased"). While thromboembolic events can be morbidity-related, they typically represent potential side effects of therapy; excluding thromboembolic events is not appropriate. Therefore, disease-relevant events were not included in the analyses for the present benefit assessment. Overall, a comparison of prevalence rates between the 2 operationalizations reveals only minor differences, rendering an interpretation of total rates possible. In the present assessment, thomboembolic events (SMQ) are used as specific AEs.

**Analyses presented by the company**

In Module 4 A, the company presents results of the L-PLUS 2, L-PLUS 1, and M0626 studies separately and additionally provides a metaanalysis, excepting sensitivity analyses. The metaanalyses were carried out using a fixed effect model (FEM) with the inverse variance method. Due to differences in study characteristics, this model is not appropriate for the 3 available studies. The company calculated metaanalyses using System Organ Class (SOC)/PT only for some of the AEs. The rationale used by the company to select these AEs according to SOC/PT is unclear.

Where necessary, the dossier assessment was based on metaanalytical calculations by IQWiG using a random effect model (REM) according to Knapp-Hartung.

### 2.4.2 Risk of bias

Table 11 presents the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and risk of bias at outcome level – RCT, direct comparison: lusutrombopag vs. placebo

| Study | Study level | Outcomes | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | All-cause mortality | Patients without transfusion | Bleeding WHO grade ≥ 2 | Health-related quality of life | SAEs | Discontinuation due to AEs | Thromboembolic events (SMQ[a], UEs) | Further specific AEs |
| L-PLUS 2 | L | L | –[b] | L | –[c] | L | L | L | –[d] |
| L-PLUS 1 | L | L | –[b] | –[e] | –[c] | L | L | L | –[d] |
| M0626 | L | L | –[b] | –[e] | –[c] | L | L | L | –[d] |

a. MedDRA SMQs "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous" and "embolic and thrombotic events, venous".
b. No usable data.
c. Outcome not recorded.
d. No further specific AEs were identified.
e. No data are available on this operationalization of bleeding.

AE: adverse event; H: high; IQWiG: Institute for Quality and Efficiency in Health Care; 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 all 3 studies, the risk of bias is rated as low for the available data from the employed outcome operationalizations.

### 2.4.3 Results

Table 12 summarizes the results comparing lusutrombopag with placebo for the treatment of severe thrombocytopenia in patients with CLD who are scheduled to undergo an invasive procedure.

Where necessary, IQWiG calculations are provided in addition to the data from the company's dossier. The forest plots of the IQWiG-calculated metaanalyses are found in Appendix C of the full dossier assessment. Tables on common AEs SAEs, and discontinuation due to AEs are found in Appendix D of the full dossier assessment.

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: lusutrombopag vs. placebo (multipage table)

| Outcome category<br>Outcome<br>Study | Lusutrombopag | | Placebo | | Lusutrombopag vs. placebo |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | RR [95% CI]; p-value |
| **Mortality** | | | | | |
| All-cause mortality | | | | | |
| L-PLUS 2 | 107 | 3 (2.8) | 107 | 0 (0) | 7.00 [0.37; 133.90]; 0.095[a] |
| L-PLUS 1 | 48 | 0 (0) | 48 | 0 (0) | – |
| M0626 | 16 | 0 (0) | 15 | 0 (0) | – |
| Total | | | | | _[b] |
| **Morbidity** | | | | | |
| Patients without transfusion | No usable data | | | | |
| Bleeding WHO grade ≥ 2[c] | | | | | |
| L-PLUS 2 | 107 | 1 (0.9) | 107 | 1 (0.9) | 1.00 [0.06; 15.78]; > 0.999[a] |
| L-PLUS 1 | | ND | | ND | – |
| M0626 | | ND | | ND | – |
| Total | | | | | _[d] |
| **Side effects** | | | | | |
| AEs (supplementary information) | | | | | |
| L-PLUS 2 | 107 | 51 (47.7) | 107 | 52 (48.6) | – |
| L-PLUS 1 | 48 | 45 (93.8) | 48 | 48 (100) | – |
| M0626 | 16 | 16 (100) | 15 | 15 (100) | – |
| SAEs | | | | | |
| L-PLUS 2 | 107 | 7 (6.5) | 107 | 7 (6.5) | 1.02 [0.37; 2.80]; 0.971[e] |
| L-PLUS 1 | 48 | 1 (2.1) | 48 | 4 (8.3) | 0.48 [0.11; 2.05]; 0.195[e] |
| M0626 | 16 | 1 (6.3) | 15 | 1 (6.7) | 0.76 [0.11; 5.42]; 0.819[e] |
| Total | | | | | 0.79 [0.30; 2.13]; 0.419[f] |
| Discontinuation due to AEs | | | | | |
| L-PLUS 2 | 107 | 0 (0) | 107 | 1 (0.9) | 0.33 [0.01; 8.09]; 0.529[a] |
| L-PLUS 1 | 48 | 0 (0) | 48 | 0 (0) | – |
| M0626 | 16 | 0 (0) | 15 | 0 (0) | – |
| Total | | | | | _[b] |

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: lusutrombopag vs. placebo (multipage table)

| Outcome category<br>Outcome<br>Study | Lusutrombopag | | Placebo | | Lusutrombopag vs. placebo |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | RR [95% CI]; p-value |
| Thromboembolic events (SMQ [g], AEs) | | | | | |
| L-PLUS 2 | 107 | 2 (1.9) | 107 | 2 (1.9) | 1.02 [0.15; 6.99]; 0.988[e] |
| L-PLUS 1 | 48 | 1 (2.1) | 48 | 1 (2.1) | 0.91 [0.10; 8.05]; 0.950[e] |
| M0626 | 16 | 0 (0) | 15 | 1 (6.7) | 0.25 [0.01; 4.23]; 0.221[e] |
| Total | | | | | 0.75 [0.15; 3.79]; 0.530[f] |

a. IQWiG calculation, unconditional exact test (CSZ method according to [24]).
b. No metaanalysis was carried out because no event occurred in 2 of 3 studies.
c. Module 4 A presents results for severe bleeding (SAE) for all 3 studies. In total, such events occurred in 1 patient each of the L-PLUS-1 and M0626 studies. Furthermore, over the entire study durations, 1 patient in the L-PLUS 2 study and 2 patients in the L-PLUS 1 study received rescue therapy for acute bleeding.
d. No metaanalysis was carried out because in 2 of 3 studies, no WHO severity rating was available for the events.
e. According to the company, effect and CI were measured using the CMH method, stratified in M0626 by platelet count and Child-Pugh classification, in L-PLUS 1 and L-PLUS 2 by platelet count and invasive procedure; a zero-cell correction of 0.5 was used, where applicable; p-value was calculated by means of the CMH test for the L-PLUS 1 and M0626 studies and with the aid of the Wald test for the L-PLUS 2 study; not stated whether p-values for RR or other effect measures.
f. Metaanalysis using random effect model according to the Knapp and Hartung method; IQWiG calculation from the effect estimators reported by company and calculated with stratification.
g. Summarized from the following SMQs :"embolic and thrombotic events, vessel type unspecified and mixed arterial and venous" and "embolic and thrombotic events, venous".

AE: adverse event; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; CSZ: convexity, symmetry, z score; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with (at least 1) event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; WHO: World Health Organization

On the basis of the available information, at most proof, e.g. of an added benefit, can be determined for all outcomes.

## Mortality

### *All-cause mortality*

For the outcome of all-cause mortality, the L-PLUS 2 study fails to show a statistically significant difference between treatment groups. No patients died in the L-PLUS 1 and M0626 studies. Consequently, there is no hint of added benefit of lusutrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

**Morbidity**

***Patients without transfusion***

For the outcome of patients without transfusion, no usable data are available. Consequently, there is no hint of added benefit of lusutrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

***WHO grade ≥ 2 bleeding events***

For the outcome of WHO grade ≥ 2 bleeding events, the L-PLUS 2 study shows no statistically significant difference between treatment groups. No data are available for the L-PLUS 1 and M0626 studies. Consequently, there is no hint of added benefit of lusutrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

**Health-related quality of life**

No data are available for the outcome of health-related quality of life because the L-PLUS 2, L-PLUS 1, and M0626 studies did not survey this outcome. Consequently, there is no hint of added benefit of lusutrombopag in comparison with watchful waiting; an added benefit is therefore not proven.

**Side effects**

***SAEs***

For the outcome of SAEs, the metaanalysis of the studies does not show any statistically significant differences between treatment groups. Consequently, there is no hint of greater or lesser harm from lusutrombopag in comparison with watchful waiting; greater or lesser harm is therefore not proven.

***Discontinuation due to AEs***

For the outcome of discontinuation due to AEs, the L-PLUS 2 study shows no statistically significant difference between treatment groups. Only 1 patient in the comparator arm discontinued treatment due to adverse events. In the L-PLUS 1 and M0626 studies, there were no patients with event. Consequently, there is no hint of greater or lesser harm from lusutrombopag in comparison with watchful waiting; greater or lesser harm is therefore not proven.

***Thromboembolic events (SMQ, AEs)***

The metaanalysis of the studies showed no statistically significant difference between treatment groups for the outcome of thromboembolic events. Consequently, there is no hint of greater or lesser harm from lusutrombopag in comparison with watchful waiting; greater or lesser harm is therefore not proven.

### 2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account in the present assessment:

- age (< 65 / ≥ 65 years)
- sex (male/female)

In the L-PLUS 2 study, these characteristics were predefined for the outcome of patients without transfusion.

No suitable operationalization was available for an analysis of the potential effect modifier of disease severity.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Presented are only the results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

No relevant effect modification with a statistically significant and relevant effect were found for any of the available subgroup analyses of the analysed effect modifiers regarding patient-relevant outcomes.

## 2.5 Probability and extent of added benefit

The probability and extent of 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 IQWiG General Methods [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 extent of the respective added benefit at outcome level was estimated based on the results presented in Section 2.4 (see Table 13).

Table 13: Extent of added benefit at outcome level: lusutrombopag vs. placebo

| **Outcome category**<br>**Outcome** | **Lusutrombopag vs. placebo**<br>**Proportion of events (%)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent** |
|---|---|---|
| **Mortality** | | |
| All-cause mortality | 0–2.8% vs. 0%[b]<br>RR: NC | Lesser/added benefit not proven |
| **Morbidity** | | |
| Patients without transfusion | No usable data | Lesser/added benefit not proven |
| Bleeding WHO grade ≥ 2 | 0.9% vs. 0.9%[b]<br>RR: NC | Lesser/added benefit not proven |
| **Health-related quality of life** | | |
| Not recorded | | |
| **Side effects** | | |
| SAEs | 2.1–6.5% vs. 6.5–8.3%[b]<br>RR: 0.79 [0.30; 2.13]<br>p = 0.419 | Greater/lesser harm not proven |
| Discontinuation due to AEs | 0% vs. 0.9%[b]<br>RR: NC | Greater/lesser harm not proven |
| Thromboembolic events | 0–2.1% vs. 1.9–6.7%[b]<br>RR: 0.75 [0.15; 3.79]<br>p = 0.530 | Greater/lesser harm not proven |

a. Probability provided if statistically significant differences are present.
b. Minimum and maximum event rates per treatment arm in the included studies; for WHO grade ≥ 2 bleeding, data available only from 1 study.

AE: adverse event; CI: 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 14 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 14: Favourable and unfavourable effects from the assessment of lusutrombopag in comparison with watchful waiting

| **Favourable effects** | **Unfavourable effects** |
|---|---|
| – | – |

Overall, there is no favourable or unfavourable effect of lusutrombopag in comparison with watchful waiting for patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure.

In summary, for the treatment of patients with severe thrombocytopenia and CLD who are scheduled to undergo an invasive procedure, there is no hint of added benefit of lusutrombopag in comparison with the ACT of watchful waiting; added benefit is therefore not proven.

Table 15 summarizes the results of the assessment of added benefit of lusutrombopag in comparison with the ACT.

Table 15: Lusutrombopag – 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] | Added benefit not proven |
| a. Presented is the respective ACT specified by the G-BA.<br>b. It was assumed that, where indicated, platelet transfusions were administered in both study arms. The reasons must be documented.<br>c. The L-PLUS 2, L-PLUS 1, and M0626 studies were to include only patients in Child-Pugh stage A or B. It remains unclear whether the observed effects can be extrapolated to patients in Child-Pugh stage C.<br>ACT: appropriate comparator therapy; CLD: chronic liver disease; G-BA: Federal Joint Committee | | |

The assessment described above deviates from the company's assessment. For patients with CLD and severe thrombocytopenia who must undergo an invasive procedure, the company derived proof of considerable 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.

**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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