Supplementary Material

Systematic review with meta-analysis: Efficacy and safety of lusutrombopag for severe thrombocytopenia in patients with chronic liver disease undergoing invasive procedures

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Supplementary Material

Figure S1. Flowchart depicting the articles screened, excluded, and included for the systematic review

1612 Records identified from:
Electronic databases\(^a\) (n=1606)
Unpublished sources/clinical study reports (n=5)
Added for cross-referencing only (n=1)

Records excluded after title/abstract review:
Duplicates (n=428)
Wrong study design (n=156)
Wrong publication type\(^b\) (n=63)
Wrong population/indication (n=914)

Full-text records screened (n=51)

Records excluded:
Sub-study (no additional data) (n=15)
Wrong design/study incomplete (n=2)
Used for cross-referencing only (n=9)

Reports assessed for eligibility (n=25)

Reports excluded:
Not primary publication (n=16)
Citation reporting 2 studies (n=1)
Not drug of interest (n=5)

Studies included in review and meta-analysis (n=3)

\(^a\)EMBASE/MEDLINE (Feb 2019), PubMed (e-publications/ahead of print/in process) (Feb 2019), Cochrane Central Register of Controlled Trials (Feb 2019), Cochrane Database of Review Effects Cochrane Database of Systematic Reviews (Feb 2019), Cochrane Heath Technology Assessment Database (October 2016)/National Institute for Health Health Technology Assessment (June 2018).

\(^b\)Letters, study protocols, commentaries, monographs, editorials, press articles, protocols, horizon scanning documents.
Table S1. Criteria for downgrading evidence

| Domain            | Example                                                                                                                                 |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Risk of bias      | Lack of allocation concealment or blinding, incomplete accounting of patients as per their allocated treatment (per protocol analysis or subgroups analysis determined by outcome which occur after randomisation), incomplete reporting of outcomes, other bias/concerns as determined by two reviewers |
| Inconsistency     | Substantial heterogeneity                                                                                                                                                                      |
| Indirectness      | PICO criteria not relevant to study outcomes, not consistent with target population                                                                                                             |
| Imprecision       | Small studies or small effect size; inferences are likely to change (95% CI likely to cross/not cross line of no effect) if number of studies increases/decreases                                           |
| Publication bias  | There are likely to be unpublished studies                                                                                                                                                      |

PICO, population or problem, intervention or exposure, comparison, outcome.
Table S2. Scheme for downgrading evidence

| Downgrade | Reason |
|-----------|--------|
| 0         | No serious concern exists, do not downgrade risk of bias from the baseline risk of bias (eg, high for RCTs) |
| -1        | Serious concern exists, downgrade the evidence one level, eg, from high to moderate |
| -2        | Very serious concern exists, downgrade the evidence two levels |
Table S3. Overall grade for risk of bias of evidence

| Assessment | GRADE | Interpretation |
|------------|-------|----------------|
| 4          | High  | ⬤⬤⬤⬤ | High confidence that the true effect lies close to the estimate of the effect |
| 3          | Moderate | ⬤⬤⬤ | Moderate confidence in the effect estimate. True effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| 2          | Low   | ⬤⬤⬤ | Limited confidence in the effect estimate. True effect may be substantially different from the effect estimate. |
| 1          | Very low | ⬤⬤⬤ | Low confidence in the effect estimate. True effect is likely to be substantially different from the effect estimate. |
Table S4. Clinical Efficacy and Safety Systematic Review Search Strategy\textsuperscript{a} for EMBASE and Medline Databases\textsuperscript{b}

| Order | Query |
|-------|-------|
| #1    | 'invasive procedure'/exp OR 'elective surgery'/exp OR (((invasive OR elective OR scheduled) NEAR/2 (procedure OR procedures OR surgery OR surgeries OR surgical)):ti,ab,kw,lnk) |
| #2    | operative blood loss'/exp OR (((operative OR perioperative OR periprocedural OR major OR fatal) NEAR/2 ('blood loss' OR bleeding OR bleed OR hemorrhage OR haemorrhage)):ti,ab,kw,lnk) |
| #3    | 'radiofrequency ablation'/exp OR 'microwave coagulation therapy'/exp OR 'chemoembolisation'/exp OR 'gastrointestinal endoscopy'/exp OR 'endoscopic injection sclerotherapy'/exp OR 'endoscopic variceal ligation'/exp OR 'liver biopsy'/exp OR 'hepatic artery ligation'/exp |
| #4    | ((liver OR hepatic OR transhepatic OR variceal OR varices) NEAR/2 (embolisation OR embolisation OR chemoembolisation OR ablation OR ligation OR biopsy)):ti,ab,kw,lnk |
| #5    | 'thrombocyte transfusion'/exp OR 'thrombocytopenia'/exp OR 'platelet count'/exp OR thrombocytopenia:ti,ab,kw,lnk OR 'thrombocyte count'/exp OR (((thrombocyte OR platelet) NEAR/2 (transfusion OR count OR counts)):ti,ab,kw,lnk) |
| #6    | 'surgery'/exp OR surgery:ti,ab,kw,lnk OR surgeries:ti,ab,kw,lnk OR surgical:ti,ab,kw,lnk OR operative:ti,ab,kw,lnk OR perioperative:ti,ab,kw,lnk OR operation:ti,ab,kw,lnk |
| #7    | #1 OR #2 OR #3 OR #4 OR #5 OR #6 |
| #8    | 'thrombopoietin receptor agonist'/exp OR (((thrombopoietin NEAR/1 receptor):ti,ab,kw,lnk) OR (((thrombopoietin NEAR/1 receptor):ti,ab,kw,lnk) |
| #9    | lusutrombopag'/exp OR lusutrombopag:ti,ab,tn,lnk,kw OR mulpleta:ti,ab,tn OR 's-888711':ti,ab,tn |
| #10   | avatrombopag'/exp OR 'avatrombopag':ti,ab,tn,lnk,kw OR doptelet:ti,ab,tn OR 'akr 501':ti,ab,tn OR akr501:ti,ab,tn OR 'ym 477':ti,ab,tn OR ym477:ti,ab,tn |
| #11   | 'romiplostim'/exp OR romiplostim:ti,ab,tn,lnk,kw OR nplate:ti,ab,tn OR remiplistim:ti,ab,tn |
| #12   | 'eltrombopag'/exp OR eltrombopag:ti,ab,tn,lnk,kw OR promacta:ti,ab,tn OR revolade:ti,ab,tn |
| #13   | #8 OR #9 OR #10 OR #11 OR #12 |
| #14   | 'randomized controlled trial':de OR 'single blind procedure':de OR 'double blind procedure':de OR 'phase 3 clinical trial (topic)'/exp OR 'phase 2 clinical trial (topic)'/exp OR 'crossover-procedure'/exp |
| #15   | 'trial':ti,ab OR 'placebo*':ab,ti,kw,lnk OR 'random*':ab,ti,kw,lnk OR 'crossover*':ab,ti,kw,lnk OR 'cross over*':ab,ti,kw,lnk OR 'allocat*':ab,ti,kw,lnk OR (((doubl* OR singl*) NEAR/1 (blind* OR mask*)):ab,ti,kw,lnk) |
The structured search strategy was a combination of search strings adapted for each database. For electronic searches: (indication) AND/OR (treatments of interest) AND (study design).
For registry searches/hand searching: (treatments of interest) +/- (indication).

Search Strategies for PubMed (e-publications-ahead-of-print/in process), Cochrane Database of CDSR, NIHR-HTA, and conference proceedings (American Society of Haematology, European Haematology Association, European Association for the Study of the Liver, International Liver Congress, American Association for the Study of Liver Diseases; 2016-2018) can be provided upon request.
Table S5. Criteria for Inclusion in the Systematic Literature Review of Randomised Controlled Trials of Lusutrombopag Efficacy and Safety

| Study Characteristic | Inclusion Criteria |
|----------------------|--------------------|
| **Population**       | Adults (18+) with CLD  
                      | Patient scheduled for planned invasive procedure or surgery  
                      | Patient presenting with severe thrombocytopenia (platelet count < 50 × 10⁹/L) |
| **Intervention**     | Lusutrombopag used as per license for the treatment of thrombocytopenia in CLD patients undergoing invasive procedures |
| **Control**          | TPO-RAs used as per license (or license pending) or as routine practice for the pre-surgical treatment of thrombocytopenia in CLD patients  
                      | Placebo/best supportive care |
| **Outcomes**         | Key outcomes:  
                      | Treatment response  
                      | Platelet transfusion requirements  
                      | Completion of scheduled surgery  
                      | Bleeding events  
                      | Rescue therapy  
                      | Other adverse events  
                      | Deaths during study |
| **Study design**     | Prospective study  
                      | Randomised controlled trial  
                      | Parallel design  
                      | Placebo or active-control  
                      | Minimum of 7 days follow-up |
| **Publications**     | Full-text publications  
                      | Abstracts/posters published from 2015  
                      | Clinical trial registry records |
| **Duplicate citation** | Multiple citations of a study with additional outcomes data not reported in primary publication |

aFull-text or translation of full-text available in English.
Supplementary Material 1. GRADE assessment and downgrades
For the GRADE assessment, the following downgrades were applied: risk of bias assessment for data as per randomised groups=4 (data are from RCTs with low risk of bias); risk of bias assessment for trial arm subgroups data=3 (allocation to subgroup not part of the randomisation sequence); indirectness=0 (all studies are within scope); publication bias=0 (all possible studies included). A downgrade of one level was applied for some outcomes for the remaining domains of inconsistency (moderate statistical heterogeneity or higher) and/or imprecision (zero events in one or more study arm and large confidence intervals). For the subgroup analysis, a downgrade of one level was applied as the patient subgroups were not randomly allocated at study baseline.

Supplementary Material 2. Alternative random-effects analyses
Three methods for estimation of τ² were considered, namely DerSimonian and Laird (D-L), restricted maximum likelihood (REML), and empirical Bayes. The DerSimonian and Laird [1] method derives the between-study variance estimate τ² from the Cochran’s Q statistic for statistical heterogeneity [2-4]. This method is included in several meta-analysis software packages (such as STATA, SAS, SPSS, RevMan, R, Comprehensive Meta-Analysis), though it can also be reproduced without specialised software. As such, it has become a commonly used method for random-effects meta-analysis. The disadvantage of D-L is that it may produce false statistically significant results as it may underestimate τ², especially when the heterogeneity is large and the number of studies is small [5,6]. In the REML method [7], the derivative of the restricted log-likelihood function is set to zero and solved for τ² by a process of iteration (initial value of τ²≥0). For dichotomous outcome data, the
REML estimator has been shown to be less biased than the D-L estimator but may also underestimate $\tau^2$ if data are sparse [8-10]. Therefore, a third method, empirical Bayes, was considered. The empirical Bayes method also requires an iterative process to solve a special form of the generalised Q-statistic, and may be less negatively biased than DL and REML, but may also be less efficient due to sampling errors and result in larger 95% CIs [11-14].

For these analyses, the pooled summary effect being estimated is the treatment effect, ie, the relative effect of treatment with lusutrombopag versus control (placebo) and is expressed as an odds ratio (OR) with the 95% confidence interval (CI) as a measure of uncertainty around the treatment effect estimate.
|                                | D-L                | REML               | Empirical Bayes | I² (D-L) |
|--------------------------------|--------------------|--------------------|-----------------|---------|
| **Efficacy: Platelet count response** |                    |                    |                 |         |
| Platelet count ≥50 × 10⁹/L & increase of ≥20 × 10⁹/L from baseline | 21.89 (8.04, 59.62); 0.36 | 22.18 (7.86, 62.65); 0.41 | 20.84 (8.56, 50.71); 0.23 | 45%     |
| Platelet count ≥50 × 10⁹/L on day of procedure | 12.37 (4.08, 37.48); 0.63 | 12.22 (4.25, 35.16); 0.55 | 11.89 (4.55, 31.08); 0.41 | 68%     |
| **Efficacy: Platelet transfusion requirements** |                    |                    |                 |         |
| No platelet transfusion and no rescue procedure for bleeding (Up to 7 days after procedure) | 10.51 (3.20, 34.52); 0.77 | 10.34 (3.38, 31.57); 0.65 | 10.09 (3.61, 28.21); 0.52 | 73%     |
| No platelet transfusion during the 35-day study period | 11.24 (2.83, 44.61) 1.13 | 11.01 (3.13, 38.82) 0.9 | 10.81 (3.34, 35.00) 0.74 | 79%     |
| No platelet transfusion prior to procedure | 12.37 (4.08, 37.48) 0.63 | 12.22 (4.25, 35.16) 0.55 | 11.89 (4.55, 31.08) 0.41 | 68%     |
| Safety                        | D-L                                   | REML                                   | Empirical Bayes                  | I² (D-L) |
|------------------------------|---------------------------------------|----------------------------------------|----------------------------------|----------|
| Total Treatment-emergent AEs | 0.91 (0.54, 1.53); 0.00*              | 0.91 (0.54, 1.53); 0.00                | 0.91 (0.54, 1.53); 0.00          | 0%       |
| Severe Treatment-emergent AEs| 0.83 (0.45, 1.55); 0.00               | 0.83 (0.45, 1.55); 0.00                | 0.83 (0.45, 1.55); 0.00          | 0%       |
| Serious AEs                  | 0.77 (0.31, 1.95); 0.00               | 0.77 (0.31, 1.95); 0.00                | 0.77 (0.31, 1.95); 0.00          | 0%       |
| Treatment-related AEs        | 1.74 (0.24, 12.60); 1.98              | 1.70 (0.25, 11.60); 1.81               | 1.62 (0.27, 9.80); 1.49          | 66%      |
| Treatment-emergent Thrombosis| 0.79 (0.18, 3.35); 0.00               | 0.79 (0.18, 3.35); 0.00                | 0.79 (0.18, 3.35); 0.00          | 0%       |
| Any bleeding (any severity)  | 0.45 (0.22, 0.93); 0.00               | 0.45 (0.22, 0.93); 0.00                | 0.45 (0.22, 0.93); 0.00          | 0%       |

aConsidered by investigator to be related to study drug

AEs, adverse events; D-L, DerSimonian and Laird; ITT, intent-to-treat; REML, restricted maximum likelihood.
**Figure S2. Forest plot of primary composite outcome (no platelet transfusion and no rescue procedure for bleeding up to 7 days after procedure) for individual studies: A) ITT; B) PP**

**A)**

| Study | Treatment | Control | Odds Ratio with 95% CI | Weight (%) |
|-------|-----------|---------|------------------------|------------|
|       | Yes | No | Yes | No |                                   |            |
| **Global** |       |       |       |       |                                   |            |
| L-PLUS 2 | 70 36 | 31 76 | 4.52 [2.54, 8.02] | 45.76 |                         |
| Heterogeneity: $\hat{\tau}^2 = 0.00, \hat{\rho}^2 = .%$, $H^2 = .$ |       |       | 4.52 [2.54, 8.02] |        |            |
| Test of $\theta = 0; Q(0) = 0.00, p = .$. |       |       |                        |        |            |

| Japan |       |       |       |       |                                   |            |
|       |       |       |       |       |                                   |            |
| L-PLUS 1 | 37 12 | 6 42 | 21.58 [7.37, 63.24] | 33.72 |                         |
| Tateishi, 2019 | 13 3 | 3 12 | 17.33 [2.92, 103.02] | 20.61 |            |
| Heterogeneity: $\hat{\tau}^2 = 0.00, \hat{\rho}^2 = 0.00%$, $H^2 = 1.00$ |       |       | 20.36 [8.11, 51.11] |        |            |
| Test of $\theta = 0; Q(1) = 0.04, p = 0.64$ |       |       |                         |        |            |

| Overall |       |       |       |       | 10.09 [3.61, 28.21] | 28.21 |
| Heterogeneity: $\hat{\tau}^2 = 0.52, \hat{\rho}^2 = 64.42%$, $H^2 = 2.81$ |       |       |                        |        |            |
| Test of group differences: $Q_a(1) = 7.40, p = 0.01$ |       |       |                         |        |            |

**Results of a random-effects empirical Bayes model.**

Dotted line represents ‘no-effect,’ where odds ratio=1.

CI, confidence interval; ITT, intent-to-treat; PP, per protocol.

**B)**

| Study | Treatment | Control | Odds Ratio with 95% CI | Weight (%) |
|-------|-----------|---------|------------------------|------------|
|       | Yes | No | Yes | No |                                   |            |
| **Global** |       |       |       |       |                                   |            |
| L-PLUS 2 | 66 25 | 18 71 | 10.41 [5.21, 20.81] | 67.52 |                         |
| Heterogeneity: $\hat{\tau}^2 = 0.00, \hat{\rho}^2 = .%$, $H^2 = .$ |       |       | 10.41 [5.21, 20.81] |        |            |
| Test of $\theta = 0; Q(0) = -0.00, p = .$. |       |       |                        |        |            |

| Japan |       |       |       |       |                                   |            |
|       |       |       |       |       |                                   |            |
| L-PLUS 1 | 35 11 | 5 39 | 24.82 [7.85, 76.49] | 24.41 |                         |
| Tateishi, 2019 | 10 2 | 3 9 | 15.00 [2.02, 111.17] | 8.07 |            |
| Heterogeneity: $\hat{\tau}^2 = 0.00, \hat{\rho}^2 = 0.00%$, $H^2 = 1.00$ |       |       | 21.90 [8.07, 59.43] |        |            |
| Test of $\theta = 0; Q(1) = 0.18, p = 0.67$ |       |       |                         |        |            |

| Overall |       |       |       |       | 13.26 [7.51, 23.42] | 23.42 |
| Heterogeneity: $\hat{\tau}^2 = 0.00, \hat{\rho}^2 = 0.00%$, $H^2 = 1.00$ |       |       |                        |        |            |
| Test of group differences: $Q_a(1) = 1.44, p = 0.23$ |       |       |                         |        |            |

**Results of a random-effects empirical Bayes model.**

Dotted line represents ‘no-effect,’ where odds ratio=1.
Supplementary Material 3. Post hoc Subgroup analysis: Pre-procedure lusutrombopag without platelet transfusion vs placebo with platelet transfusion

To replicate real world clinical practice, a post hoc subgroup analysis was conducted to assess the mean difference in platelet count for the subgroup of patients receiving lusutrombopag 3 mg without platelet transfusion compared to the subgroup of patients receiving placebo with platelet transfusion. The mean difference in platelet count was estimated between these two subgroups at time points before, during, and after the procedure window. In the subgroup of patients who were treated with lusutrombopag 3 mg and did not receive a platelet transfusion, platelet counts before the procedure (Day 8) and after the procedure window (Day 17) were significantly higher than in the placebo-treated subgroup who received a platelet transfusion. The mean difference in platelet count after receiving lusutrombopag only versus placebo with platelet transfusion at Day 8 was $25.52 \times 10^9/L$ (95% CI: 22.21, 28.82; p<0.0001, moderate risk of bias, groups not randomly allocated at study baseline) (Figure S3A). At Day 10, mean difference in platelet count was $34.97 \times 10^9/L$ (95% CI: 30.66, 39.27), at Day 12, mean difference was $34.18 \times 10^9/L$ (95% CI: 30.40, 37.95), and at Day 14, the mean difference in platelet count was $31.25 \times 10^9/L$ (95% CI: 26.93, 35.56; p<0.0001 for all, moderate risk of bias) (Figure S3B-D). After the procedure window on Day 17, the mean difference in platelet count between patients receiving lusutrombopag only, versus those receiving placebo and a platelet transfusion was $27.07 \times 10^9/L$ (95% CI: 23.02, 31.11; p<0.0001; moderate risk of bias) (Figure S3E). This significant difference in platelet count was sustained during
the post-procedure period through Day 21 and Day 28 (Day 21, p<0.0001, Figure S3F; Day 28, p=0.0001, Figure S3G).
Figure S3. Forest plot showing the mean difference in platelet counts for patients receiving lusutrombopag only pre-procedure versus those receiving placebo and a platelet transfusion before the procedure.

Results of a random-effects empirical Bayes model.
Dotted line represents ‘no-effect,’ where mean difference=0. Mean difference>0 favours lusutrombopag only (no platelet transfusion) compared to platelet transfusion (and placebo).

CI, confidence interval; SD, standard deviation.
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