## Indirect treatment comparison for Esmya® and GnRH

Since direct head-to-head randomized control trial (RCT) data is not available, an indirect treatment comparison (ITC) is required to compare the efficacy of Ryeqo® and Esmya® (UPA 5mg) and GnRH (leuprorelin 3.75mg). Several approaches are available to conduct ITCs but the well-know, pragmatic Bucher method [83] ensures transparency at a level that is acceptable to a wide variety of health technology assessment (HTA) bodies. The outcomes of the ITC are used in conjunction with a quality of life (QoL) algorithm that translates disease specific outcomes (menstrual blood loss, MBL) into health utilities, which are ultimately used to calculate quality-adjusted life-years (QALYs) in the economic model.

To estimate QoL on the population level, the following outcomes were estimated through an ITC and used in the model:

- Mean MBL volume for Ryeqo®, ulipristal acetate (UPA) 5mg (Esmya®), and leuprorelin 3.75mg, at week 4, 8, 12, and 24, respectively.

### Study selection

The Bucher method implies that pairs of studies are compared, and evidence from a full or extended treatment network is not included.

To be considered for inclusion in the ITC, the study had to fulfill the following criteria:

- Randomized control trial
- Trial arms include placebo, UPA 5mg, Ryeqo® or leuprorelin 3.75mg
- Patient population consist of women of reproductive age with symptomatic uterine fibroids
- MBL is included as outcome

Twelve trials were identified for possible inclusion in the ITC from the systematic literature review on efficacy and safety performed by Myovant and updated by Gedeon Richter (date of search: 19 Nov 2020). From the identified eligible trials, the best available trials were selected for comparison based on similarity of endpoints and population, trial quality and size.

Similarity of endpoints was the main reason for exclusion. To be fit for purpose, the outcomes of the ITC were aligned with the inputs of the QoL algorithm. The QoL algorithm in the model has been developed for MBL as a continuous variable, i.e. mean MBL volume. Therefore, mean MBL volume was the target outcome of the ITC. Moreover, different methods such as alkaline hematin (AH) method or PBAC, can be used to estimate MBL volume. The calibration coefficients to the alkaline hematin method differ between studies and have to be publicly available to translate PBAC into AH measurement and facilitate comparison. In addition, endpoints should be measured at similar time points during the trial.

The LIBERTY 1 & 2 trials, and PEARL I & II trials were included in the ITC. Data on mean MBL volume at different time points where available from the Clinical Study Reports (CSRs).

The trials as well as the rationale for inclusion and exclusion are listed in *Table 1*.

*Table 1. Identified trials based on inclusion criteria*

| Trial | N | Interventions | MBL outcome(s) | Rationale for inclusion/exclusion | Comment |
|---|---|---|---|---|---|
| **LIBERTY 1 & 2 (pooled)** | 277 | Ryeqo®; Placebo | • Mean MBL at baseline & follow-up visits<br>• MBL change from baseline<br>• Rate of patients with MBL response defined as MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume | Included:<br>• Main study of Ryeqo®<br>• Mean MBL and change in MBL from baseline available for all follow-up visits | Access to CSR |
| **PEARL I** | 242 | UPA 5mg; UPA 10mg; Placebo | • Consecutive 28-day PBAC scores<br>• % of patients with a reduction in uterine bleeding defined as PBAC score <75 (summed over the preceding 28-day period) | Included:<br>• Mean PBAC and change in PBAC from baseline available for all follow-up visits from CSR<br>• Translation of PBAC to AH MBL publicly available | Access to CRS |
| **PEARL II** | 307 | UPA 5mg; UPA 10mg; Leuprorelin 3.75 mg | • Consecutive 28-day PBAC scores<br>• % of patients with a reduction in uterine bleeding defined as PBAC score <75 (summed over the preceding 28-day period) | Included:<br>• Same as PEARL I<br>• Enables an extended network to compare Ryeqo® with leuprorelin | Access to CRS |
| **VENUS I** | 157 | UPA 10mg; UPA 5mg; Placebo | • Rate of patients with 0 days of heavy bleeding and ≤ 8 days of bleeding (spotting permitted) | Excluded:<br>• MBL endpoint not sufficiently similar to Ryeqo® studies | |
| **VENUS II** | 432 | UPA 10mg; UPA 5mg; Placebo | • Rate of patients with 0 days of heavy bleeding and ≤ 8 days of bleeding (spotting permitted) | Excluded:<br>• MBL endpoint not sufficiently similar to Ryeqo® studies | |
| **Irahara 2020** | 121 | Leuprorelin 1.88/3.75mg; UPA 2.5mg; UPA 5mg; UPA 10mg; Placebo | • % of patients bleeding 8 days or less and no heavy bleeding from day 29 to day 84 | Excluded:<br>• Leuprorelin unblinded<br>• MBL endpoint not sufficiently similar to Ryeqo® studies (difficult to translate to AH method) | |

| Trial | N | Interventions | MBL outcome(s) | Rationale for inclusion/exclusion | Comment |
|---|---|---|---|---|---|
| **ASTEROID 2** | 172 | Vilaprisan 2mg; UPA 5mg; Placebo | • Rate of patients with <80 ml as assessed by the menstrual pictogram and >50% reduction from baseline during the last 28 days of treatment | Excluded:<br>• Average MBL volume not available in publication | |
| **Armstrong 2010** | 57 | UPA 10mg; UPA 20mg; Placebo | • Rate of patients with suppression of bleeding (threshold not given) | Excluded:<br>• Relatively small sample size<br>• Available in conference abstract only, not sufficiently detailed | |
| **Friedman 1991** | 214 | Leuprorelin 3.75mg Placebo | • Haematocrit pre/post treatment | Excluded:<br>• Old study<br>• MBL endpoint not comparable with Ryeqo® studies | |
| **Schlaff 1989** | 11 | Leuprorelin 3.75mg Placebo | • Resolution of 'bleeding ' (details not reported) | Excluded:<br>• Old study<br>• Insufficiently detailed reporting of outcome<br>• Small sample size | |
| **Stovall 1995** | 265 | Leuprorelin 3.75mg; Leuprorelin 7.5mg Placebo | • Median number of bleeding days, per 30 days | Excluded:<br>• Old study<br>• MBL endpoint not sufficiently similar to Ryeqo® studies (difficult to translate to AH method) | |
| **Barra 2019 (tak-385-cct-002)** | 281 | Leuprorelin 1.88/3.75mg; Relugolix monotherapy; Placebo | • Rate of patients with PBAC score < 10 | Excluded:<br>• Mean MBL volume not available (apart from baseline)<br>• Calibration to AH not available | Access to CRS |

CSR: Clinical Study Report. PBAC: Pictorial Blood Loss Assessment Chart. MBL: Menstrual Blood Loss. AH: Alkaline Hematin

## Method

The following sets of comparisons were conducted:

- Ryeqo® vs. UPA 5mg (indirect comparison via placebo)
- UPA 5mg vs. leuprorelin 3.75mg (direct comparison)

Given that no study could be included with a common comparator arm between Ryeqo® and leuprorelin (GnRH) the relative effect had to be estimated from an extended network. This method implicitly assumes that the UPA arms in PEARL I and PEARL II can be set equal. This assumption is reasonable given the similarity between the studies in terms of study design, inclusion criteria and patient characteristics. Figure 1 provides an overview of the comparisons.

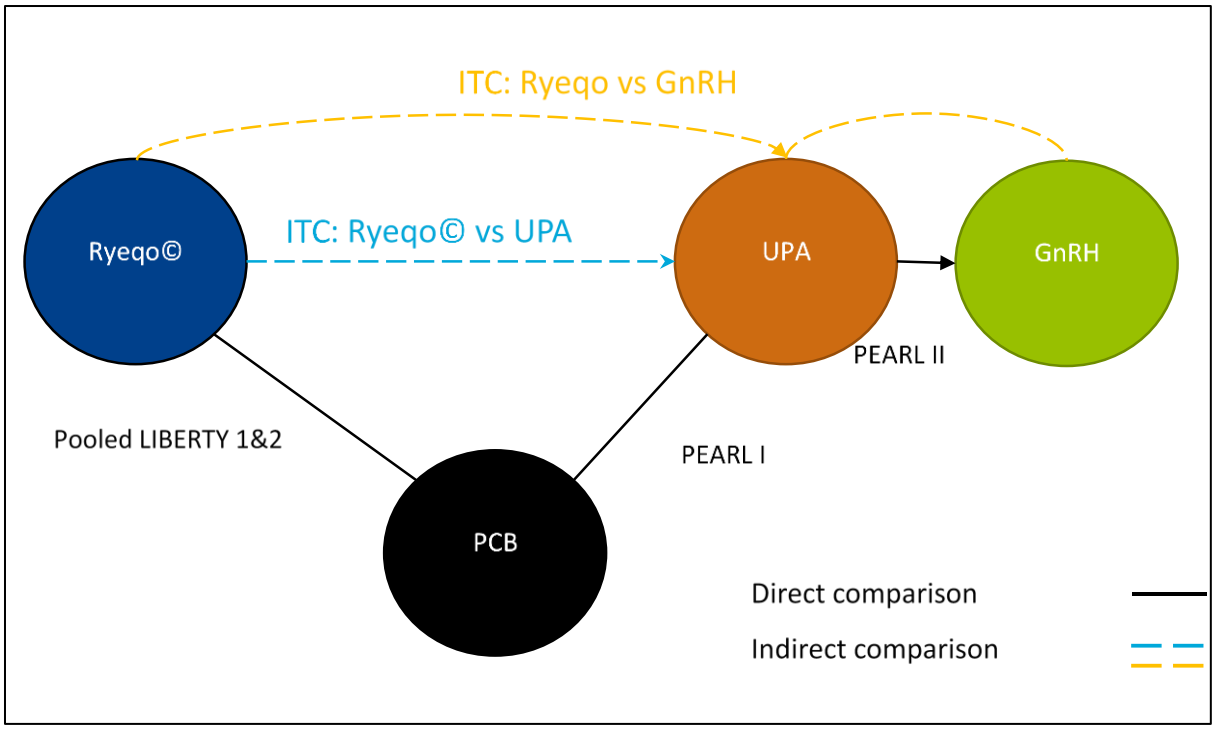



*Figure 1. Indirect comparison overview*

Mean percentage change from baseline (CFB) in MBL at 4, 8, 12, and 24 weeks from LIBERTY 1 and 2 were pooled based on sample size (mITT population). Mean PBAC at 5, 9, 13 (non-missing values) and 26 weeks extracted from PEARL I & II. ITT population was included for 5-, 9-, and 13-week mean PBAC. Twenty-six-week mean PBAC was extracted for the per-protocol population, separately for patients without hysterectomy or endometrium ablation after treatment and patients without surgery after treatment.

While mean percentage CFB was extracted directly from LIBERTY 1 and 2, CFB in percent in PEARL I and II were calculated based on mean CFB at follow-up and baseline values. PBAC scores from PEARL I & II were transformed to MBL (alkaline hematin method) using 0.8*PBAC=MBL [41]. The coefficient of 0.8 was based on the validation described in the PEARL I study. Mean difference in MBL percentage CFB for Ryeqo® vs. placebo and UPA vs. placebo, respectively, were calculated based on pooled LIBERTY 1 and 2, and PEARL I data.

To get mean difference in MBL percentage CFB for Ryeqo® vs UPA, mean difference in percentage CFB of Ryeqo® vs. placebo and UPA vs. placebo were used in a Bucher ITC. The formula below describes the calculation of ITC mean difference, where MD=mean difference.

$$ITC\ MD\ (Ryeqo\ vs. UPA) = MD_{Ryeqo\ vs.placebo} - MD_{UPA\ vs.placebo}$$

Mean difference in percentage CFB in MBL of UPA vs. GnRH from PEARL II was calculated in the same way as for UPA vs. placebo from PEARL I. Mean MBL values for Placebo were retrieved directly from the LIBERTY studies.

Extracted trial data used in the treatment comparison are described in *Table 2*.

*Table 2. Trial data extracted*

| Study | Treatments | Source | Week | N | Mean MBL %-CFB | Effect size (diff. in means) |
|---|---|---|---|---|---|---|
| LIBERTY 1, 2 | • Ryeqo©<br>• Placebo | mITT population | 4 | • 143<br>• 211 | • -46%<br>• -13% | -33% |
| LIBERTY 1, 2 | • Ryeqo©<br>• Placebo | mITT population | 8 | • 193<br>• 218 | • -79%<br>• -9% | -70% |
| LIBERTY 1, 2 | • Ryeqo©<br>• Placebo | mITT population | 12 | • 195<br>• 203 | • -84%<br>• -10% | -74% |
| LIBERTY 1, 2 | • Ryeqo©<br>• Placebo | mITT population | 24 | • 179<br>• 186 | • -85%<br>• -18% | -67% |
| PEARL 1 | • UPA 5mg<br>• Placebo | ITT population | 5 | • 95<br>• 48 | • -3%<br>• +11% | -13% |
| PEARL 1 | • UPA 5mg<br>• Placebo | ITT population | 9 | • 95<br>• 48 | • -82%<br>• -8% | -75% |
| PEARL 1 | • UPA 5mg<br>• Placebo | ITT population non-missing | 13 | • 82<br>• 36 | • -89%<br>• -26% | -63% |
| PEARL 1 | • UPA 5mg<br>• Placebo | PP population no hysterectomy/ endometrium ablation | 26 | • 72<br>• 30 | • -22%<br>• -33% | +11% |
| PEARL 1 | • UPA 5mg<br>• Placebo | ITT population no surgery | 26 | • 50<br>• 22 | • -19%<br>• -16% | -4% |
| PEARL 2 | • Leuproreline 3.75mg<br>• UPA 5mg | ITT population | 5 | • 98<br>• 99 | • +20%<br>• -11% | +31% |
| PEARL 2 | • Leuproreline 3.75mg<br>• UPA 5mg | ITT population | 9 | • 98<br>• 99 | • -93%<br>• -89% | -4% |
| PEARL 2 | • Leuproreline 3.75mg<br>• UPA 5mg | ITT population non-missing | 13 | • 93<br>• 93 | • -91%<br>• -90% | -1% |
| PEARL 2 | • Leuproreline 3.75mg<br>• UPA 5mg | PP population no hysterectomy/ endometrium ablation | 26 | • 65<br>• 68 | • -12%<br>• -35% | +23% |
| PEARL 2 | • Leuproreline 3.75mg<br>• UPA 5mg | PP population no surgery | 26 | • 38<br>• 40 | • -2%<br>• -16% | +14% |

To transform ITC results to model input MBL bleeding scores for GnRH and UPA were calculated by using the MBL scores for Ryeqo® at different time points combined with the mean difference from the ITC, using the following equation:

$$\overline{MBL\ \%CFB}_{B,t} = \overline{MBL\ \%CFB}_{A,t} - MD_{AB,\,t}$$

where

- $MD_{AB,\,t}$= *Mean difference in %-CFB in MBL volume between treatment A and B at time t*
- $\overline{MBL\ \%CFB}_{A,t}$= *Mean %-CFB in MBL volume at time t for treatment A*
- $\overline{MBL\ \%CFB}_{B,t}$= *Mean %-CFB in MBL volume at time t for treatment B*

MBL CFB by time point and treatment were then applied to mean MBL in the based on the LIBERTY studies.

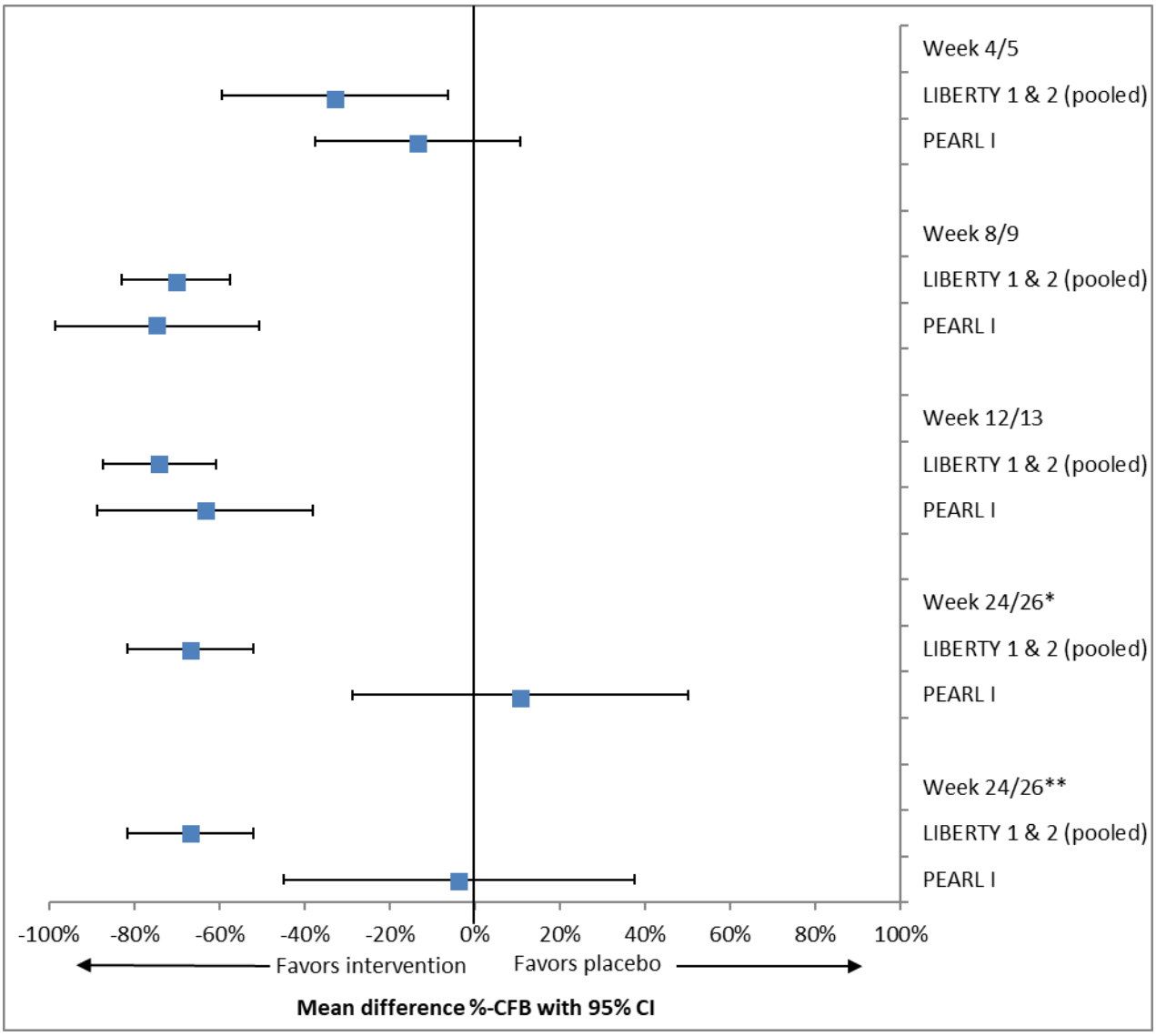
## Results

*Figure 2* shows results from the individual studies (pooled LIBERTY 1 and 2, and PEARL I) of intervention (Ryeqo®/UPA) vs. placebo. *Table 3*–*Table 4* shows the results on mean difference in percentage CFB from the ITC for Ryeqo® vs UPA, and the direct comparisons of GnRH vs UPA, respectively. To be used in the cost-effectiveness model, mean MBL by treatment and time point, was calculated using the formulas shown below. The transformed model input is described in *Table 5*.

$$EQ5D = \alpha + \beta_1 \text{MBL volume} + \beta_2 \text{Age at baseline} + \varepsilon, \qquad \text{(Equation 1)}$$

Mean percentage decrease in MBL was larger (19.43% at week 4) for Ryeqo® compared with UPA (*Table 3*). At week 8, however, UPA had a slightly larger percentage decrease compared with Ryeqo® (4.53%). At week 12, Ryeqo® had a larger decrease compared with UPA (10.73%). At week 24, Ryeqo® had a substantially larger decrease in MBL compared with UPA (for both populations from PEARL I and II, i.e. without hysterectomy/endometrium ablation and without surgery, respectively). This finding was expected since UPA was discontinued in the PEARL trials after week 13. MBL results at week 24 were therefore not included in the model. The $Chi^2$ heterogeneity test indicates whether the observed differences in results are due to chance alone. The low p-value for week 24 results ($p<0.05$) indicate that there is hetereogeneity of intervention effects. For week 4–13 results, no indications of heterogeneity was found. However, care must be taken when interpreting the $Chi^2$ test which has a low power when the number of studies included is low (n=2).

At week 4, leuprorelin had a smaller decrease in MBL compared with UPA, but a larger decrease at week 8 and 12. This entails that Ryeqo® had a larger decrease in MBL, and consequently absolute MBL value (*Table 5*), at week 4 compared with UPA and leuprorelin. At week 8, Ryeqo® had a smaller decrease in MBL compared with UPA and leuprorelin and therefore a higher absolute MBL value. At week 12, absolute MBL was lower in Ryeqo® compared with UPA and leuprorelin.




*Per-protocol population in PEARL I without hysterectomy or endometrium ablation **Per-protocol population in PEARL I without surgery
Note: Treatment in the PEARL I and II trials was discontinued after week 13.

*Figure 2. Forest plot of mean difference in percentage CFB in MBL for Ryeqo® vs. placebo (LIBERTY 1 & 2 pooled) and UPA vs. placebo (PEARL I)*

*Table 3. ITC results*

| | Mean difference %-CFB Week 4 | Mean difference %-CFB Week 8 | Mean difference %-CFB Week 12 | Mean difference %-CFB Week 24-no hysterectomy* (UPA patients not on treatment) | Mean difference %-CFB Week 24-no surgery** (UPA patients not on treatment) |
|---|---|---|---|---|---|
| Ryeqo© vs. UPA | -19.43% | +4.53% | -10.73% | -77.63% | -63.06% |

| | Mean difference %-CFB Week 4 | Mean difference %-CFB Week 8 | Mean difference %-CFB Week 12 | Mean difference %-CFB Week 24-no hysterectomy* (UPA patients not on treatment) | Mean difference %-CFB Week 24-no surgery** (UPA patients not on treatment) |
|---|---|---|---|---|---|
| Heterogeneity statistic $Chi^2$ | 1.125 (p=0.289) | 0.107 (p=0.744) | 0.538 (p=0.463) | 13.021 (p<0.001) | 7.936 (p=0.005) |

CFB: Change from baseline
*No hysterectomy or endometrium ablation post treatment in the PEARL trials.
**No surgery post treatment in the PEARL trials.
Note: Treatment in the PEARL I and II trials was discontinued after week 13.

*Table 4. Results from the direct comparison of leuprorelin v UPA*

| | Mean difference %-CFB Week 4 | Mean difference %-CFB Week 8 | Mean difference %-CFB Week 12 | Mean difference %-CFB Week 24-no hysterectomy* | Mean difference %-CFB Week 24-no surgery** |
|---|---|---|---|---|---|
| Leuprorelin vs. UPA | +31.14% | -3.79% | -1.50% | +23.45% | +14.12% |

Note: Treatment in the PEARL I and II trials was discontinued after week 13.

*Table 5. Model input*

| | Baseline | Week 4 | Week 8 | Week 12 |
|---|---|---|---|---|
| Ryeqo© | 229.1 | 115.8 | 51.3 | 37.8 |
| UPA | 229.1 | 160.3 | 40.9 | 62.3 |
| Leuprorelin | 229.1 | 231.6 | 32.2 | 58.9 |

Note: Treatment in the PEARL I and II trials was discontinued after week 13. MBL results at week 24 were therefore not included in the model.

## Limitations

The indirect treatment comparison has some limitations.

MBL outcomes were not measured at same time points in the LIBERTY and PEARL trials. In LIBERTY, MBL was measured at week 4, 8, 12, and 24 and at week 5, 9, 13, and 26 in PEARL. Although MBL was measured only one week apart for those follow-ups relevant for the cost-effectiveness model (4/5, 8/9, 12/13), the effect of Ryeqo® might be slightly underestimated if it can be assumed that both treatments have a similar time-to-effect.

Another limitation is that the trial populations (LIBERTY 1 and 2, PEARL I and II) are assumed to be similar in all factors that may affect outcome. This assumption has to be made when conducting a Bucher indirect comparison. Patients in the PEARL trials had higher average bleeding scores at baseline compared with patients in the LIBERTY trial which may indicate that patients with more severe bleeding were included in the PEARL trials. For example, median MBL at baseline in the placebo group was 186 in LIBERTY 1, and median PBAC in PEARL I was 376 (corresponding to approximately 301 AH MBL).