**Suppl 6.** Risk of Bias in Included Studies

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study Name/ID** | **Selection Bias** | **Performance Bias** | **Detection Bias** | **Reporting Bias** | **Attrition Bias** | **Comments** |
| Taylor 2017 - Elagolix Phase 3 RCTs (Elaris EM-I & EM-II, NCT01620528/NCT01931670) [43] | Low | Low | Low | Low | Some concerns | Computer-generated randomization via IVRS with central allocation; multicenter double-blind, placebo-controlled design; pain outcomes captured in electronic diaries by blinded participants; trials prospectively registered and all prespecified endpoints reported; 6-month completion rates 74.9% (EM-I) & 77.4% (EM-II) with ≈ 23% drop-out but balanced across groups, sensitivity analyses performed to address missing data. |
| Surrey 2018 - Elagolix Long-term Extension EM-III/IV (NCT01760954/NCT02143713)  [44] | Unclear | Low | Some concerns | Low | Some concerns | Only included prior phase III completers who had received Elagolix, no re-randomization, possible selection of previously good responders; dose-level double-blind, double-dummy; primary endpoint was patient-reported electronic pain diary, patients aware of continued active treatment; registered and fully reported; 6-month drop-out 17-22%, similar across groups. |
| Osuga 2021 - Relugolix Phase 2 Open-label Extension (NCT01452685) [45] | High | High | High | Low | Some concerns | Extension phase only enrolled “completers” continuing original dose, no re-randomization; open-label design, both participants and investigators knew oral vs injection assignment; main outcome included patient-reported VAS pain, self-assessed and not blinded; registered and all prespecified endpoints reported; 24-week attrition ≈18%, similar between groups, FAS analysis used, but may still impact long-term results. |
| Osuga 2021 - Relugolix Phase II RCT (NCT01458301) [46] | Low | Low | Low | Low | Low | Computer randomization + central concealment; double-blind, double-dummy design; main outcome was patient pain diary VAS, blinding maintained; registered and all prespecified endpoints reported; attrition < 10%, balanced across groups. Overall low risk of bias. |
| Donnez 2020 - Linzagolix Phase 2b RCT (EDELWEISS, NCT02778399) [47] | Low | Low | Low | Low | Low | Computer-generated block randomization and central allocation; triple-blind for participants, investigators, and operators; primary endpoint was daily electronic pain diary, outcome assessors blinded; pre-registered and all endpoints fully reported; 12-week completion ≈ 88%, 24-week ≈ 77%, attrition balanced across groups, < 10% and FAS analysis used. Overall low risk of bias. |
| TERRA Study - ASP1707 Phase II RCT (NCT01767090) [48] | Low | Low | Low | Low | Low | Computer-generated block randomization + central concealment; ASP1707 vs placebo double-blind, identical tablet appearance; primary endpoint was daily electronic diary and central lab results; pre-registered and all endpoints fully reported; 24-week completion ≈ 77%, similar drop-out rates between groups, FAS/ITT analyses performed. Overall low risk of bias. |
| Harada 2022 - Relugolix Phase 3 RCT (NCT03931915) [49] | Low | Low | Low | Low | Low | Computer-generated block randomization + central allocation; double-blind, double-dummy design; primary endpoints were patient-reported electronic VAS and central lab assessments; pre-registered and all endpoints fully reported; 24-week attrition ≤ 5%, well-balanced, FAS/ITT analysis used. |
| Tezuka 2023 - Linzagolix in Rat Endometriosis Model [50] | Unclear | Unclear | High | Unclear | Low | 8 groups, 14 rats each; only stated “grouped according to cyst volume,” no description of random sequence or allocation concealment; no mention of blinding in intervention; cyst volume assessed visually by researchers, no blinding of assessors reported; no trial registration, selective reporting risk unclear; no attrition reported, all 112 rats analyzed. |
| Diamond 2014 - Elagolix Phase 2 RCT (NCT00797273) [52] | Low | Low | Low | Low | High | Computer IVRS randomization (1:1:1) + double-dummy blinding; primary endpoints were electronic NRS diary and central lab parameters; registration number public, all prespecified endpoints reported; 155 randomized, only 102 completed 24 weeks (34% attrition), placebo → Elagolix crossover led to uneven attrition, FAS analysis used but still high attrition bias. |
| Surrey 2019 - Elagolix Phase III RCT (EM-I, NCT01620528) [53] | Low | Low | Low | Low | High | Computer randomization (2:2:3), double-blind, double-dummy; primary outcome was patient PROMIS fatigue scale, outcome assessor blinded; registered and all endpoints reported; 6-month completion ≈ 67% (371→248, 246→172, 243→165), three arms with ≈ 30% attrition, mITT analysis used but high attrition may impact estimates. |
| Carr 2018 - Elagolix ± Add-back Phase 2b RCT (NCT01817530) [54] | Low | Low | Low | Low | Some concerns | Interactive response system 1:1:1:1 computer randomization, central allocation; double-blind, double-dummy; main endpoint was objective alkaline hematin method + electronic diary, assessors blinded; registered on ClinicalTrials.gov, all prespecified endpoints reported; 571 screened, 567 randomized, completion rate cohort 1 = 80%, cohort 2 = 75%, four-arm attrition 20-25%, ITT analysis but attrition slightly high, so “some concerns”. |
| SPIRIT 1 & 2 - Relugolix + E2/NETA Phase III Replication RCT (NCT03204318/NCT03204331) [55] | Low | Low | Low | Low | Low | Two multicenter studies, computer block randomization (IVRS/IWRS), double-blind, double-dummy; main endpoints were electronic NRS diary and central lab/imaging center assessment; pre-registered and all endpoints fully reported; 24-week attrition 15-18%, balanced between groups, mITT/FAS analysis. Overall low risk of bias. |
| Pohl 2020 - Linzagolix 200 mg ± Add-back Phase I Randomized Open-Label Study (EudraCT 2017-003822-34) [57] | Unclear | High | High | Low | Low | Single-center, open-label, 32 cases 1:1 randomized; random sequence generation and allocation concealment not disclosed; participants/investigators unblinded; main outcome was self-reported bleeding diary; registered and fully reported; 3/32 (9%) attrition, balanced between groups. |