**Suppl 5.** Summary of Findings: Impact of Add-Back Therapy (ABT) on Drug Use

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| **Outcome** | **Elagolix + ABT (vs. placebo)** | **Relugolix + CT (vs. placebo)** | **Linzagolix + ABT (vs. placebo)** |
| Bone mineral density | Substantial BMD loss on elagolix was *attenuated* by ABT (but still loss occurred).**Certainty:** Moderate (fibroid studies only). | BMD loss minimal on relugolix + ABT: LS spine ~-0.7% at 24 wks (near placebo levels), versus ~-2.0% without ABT.**Certainty:** High (consistent RCT data). | BMD essentially preserved: < 1% change at 6 mo.**Certainty:** Moderate (single trial, 6-mo). |
| Vasomotor (hot flushes) | Hot flushes were reported on elagolix + ABT, more than placebo. ABT did *not* eliminate flushes (no direct ABT vs no-ABT data).**Certainty:** Low (indirect evidence) | Hot flushes occurred in relugolix + ABT group (common AE). Presumed reduced vs. no-ABT (since combination therapy). **Certainty:** Moderate (some AE data, no direct ABT comparison). | Low flush rates with linzagolix + ABT: EDELWEISS3 found only mild hypoestrogenic AEs; a small study showed no flushes when ABT started immediately.**Certainty:** Moderate (consistent RCT and small-study data). |
| Pain relief | Elagolix + ABT greatly reduced bleeding but pain was not measured in fibroid trials (no data on dysmenorrhea/NMPP). **Certainty:** Very low (no evidence). | Relugolix + ABT significantly improved endometriosis pain: ~75% vs. ~28% dysmenorrhea responders; NMPP also improved.**Certainty:** High (two large RCTs). | Linzagolix + ABT (200 mg) significantly reduced dysmenorrhea and NMPP vs placebo at 3 months. 75 mg alone helped dysmenorrhea only.**Certainty:** High (RCT evidence). |
| Bleeding control | Elagolix + ABT sharply reduced heavy bleeding in fibroids (85% response vs 27% placebo). (Not an endometriosis outcome.)**Certainty:** Moderate (direct trial, but fibroids). | Not applicable (endometriosis trials did not measure menstrual bleeding).**Certainty:** - | In a small healthy-women study, immediate ABT gave rapid amenorrhea and less spotting than delayed ABT. (No patient data on bleeding.)**Certainty:** Low (indirect, non-patient data). |
| Overall safety | Elagolix + ABT caused hypoestrogenic AEs (hot flushes, metrorrhagia) and some BMD loss. ABT mitigated bone loss.**Certainty:** Moderate (trial data). | Relugolix + ABT was well tolerated; common AEs were headache, nasopharyngitis, hot flush. No deaths or serious concerns reported.**Certainty:** High (two RCTs). | Linzagolix + ABT was well tolerated: most common AE headache; hot flushes were rare (absent with immediate ABT).**Certainty:** Moderate (single RCT + small study). |