Model-based Dose Selection for a GnRH Receptor Antagonist in Endometriosis and Uterine Fibroids (UF) to Reduce Symptoms While Preventing Lumbar Spine Bone Mineral Density (BMD) Loss

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Objectives

Linzagolix is a GnRH receptor antagonist in development for the treatment of endometriosis or UF symptoms. Analysis objectives were: (1) Develop longitudinal exposure-response models for dysmenorrhea (DYS, menstrual pain), non-menstrual and overall pelvic pain (NMPP, OPP), bleeding days, and BMD in endometriosis patients to support linzagolix dose selection in pivotal Phase 3 trials and (2) assess the viability of an estradiol (E2) target range as an efficacy and safety indicator.

Methods

Models for linzagolix pharmacokinetics (PK), E2, DYS, NMPP, OPP and BMD measurements were developed from 2 trials in patients with endometriosis and 3 healthy volunteer trials. Simulated daily linzagolix AUC derived from 2-compartment population PK model drove changes in E2 (direct sigmoidal Imax model) over 24 weeks on treatment (dose range: 25 to 200 mg daily). Model-predicted E2 were used to drive changes in DYS, NMPP, OPP, and bleeding (efficacy), and BMD (safety). DYS, NMPP, OPP, and bleeding were modeled using logistic and zero-inflated beta regression models for repeated measures, controlled for baseline pain/bleeding, race, weight, health status. BMD changes were described using a bone health quantitative systems pharmacology (QSP) model [1]. Candidate linzagolix doses were evaluated for likelihood of achieving pre-defined, literature-derived pain and BMD targets by integrated simulation from models for PK, PK-E2, E2-DYS, E2-NMPP, and E2-BMD. Candidate linzagolix doses for consideration in pivotal Phase 3 trials were those that lowered E2 sufficiently to meet pain (efficacy) targets while retaining enough E2 to maintain BMD (safety) targets.

Data

- **EDELWEISS (NCT02778399)** - patients
  - PK, E2, uterine bleeding
  - DYS & NMPP (VRS), OPP (NRS), LS BMD
  - Linzagolix dose: 50-200 mg QD x 24w
- **Phase 2 Trial** - patients
  - PK, E2, uterine bleeding
  - DYS & NMPP (VRS), OPP (NRS), LS BMD
  - Linzagolix dose: 25-100 mg QD x 24w
- **PK/PD Trial 1 & 2** - healthy volunteers
  - PK, E2, uterine bleeding
  - Linzagolix dose: 100-200 mg QD x 42-70d
- **SAD/MAD (C09070)** - healthy volunteers
  - PK: 12.5-400 mg SD; 100-400 mg QD x 7d

Conclusions & References

- Linzagolix can target E2 ranges appropriately
  - Target range: 20 to 50 pg/mL
- Doses for pivotal Phase 3 trials
  - Endometriosis - 75 mg daily
  - Uterine Fibroids - 100 daily
- **References**

1. Pohl O et al. Reproductive Sciences (in press)
2. Pohl O et al. (2018) J Clin Endocrinol Metab.: doi: 10.1210/jc.2017-01875; **PMID: 29216361**
3. Riggs MM, et al. (2012) CPT:PSP 1.: doi.org/10.1038/psp.2012.10; **PMID: 23887363**

Results

Figure 1: MODEL-BASED DECISION INFORMATICS
Simulated E2 from PK-E2 model drove efficacy (dysmenorrhea, pelvic pain & bleeding) & safety (BMD) outcomes. MIN/OPT: minimal / optimal criteria for dose selection. BMD criteria were based on lower bound of 90% CI at week 24.

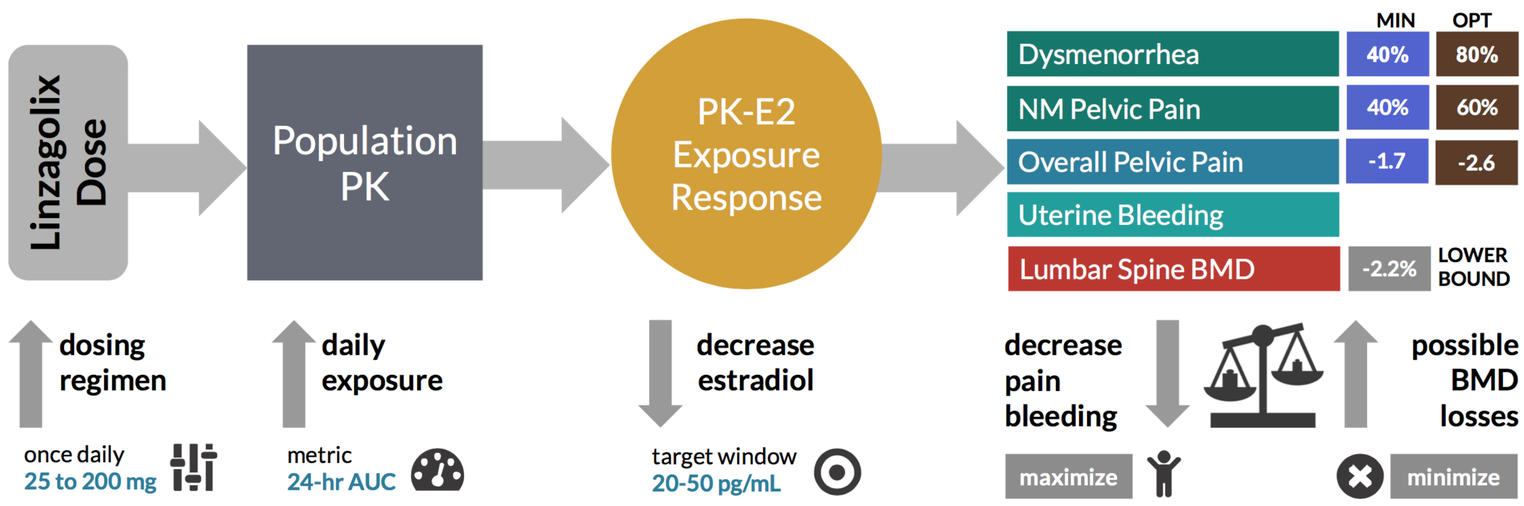

Figure 2: PK & PK-E2 model. Left: AUCss calculated from CL_i and dose. Right: VPC for PK-E2 model. Shaded: simulated 5th/50th/95th percentiles; Dashed lines: quantiles calculated on observed data. Points: observations. Linzagolix CL: 0.422 L/hr (PK model); AUC_{50}: 168 μg*hr/mL (PK-E2 model).

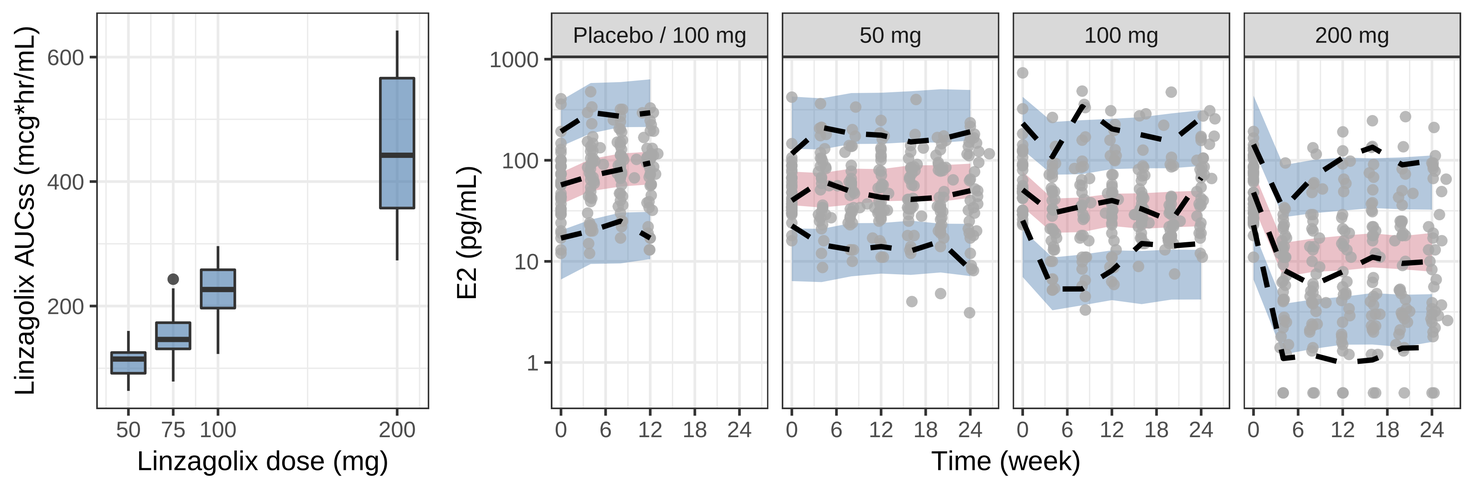

Figure 3: E2-efficacy relationships for pain and bleeding outcomes at 6 months. NMPP: non-menstrual pelvic pain reduction; DYS: dysmenorrhea pain reduction, OPP: overall pelvic pain, Uterine Bleeding: % bleeding days.

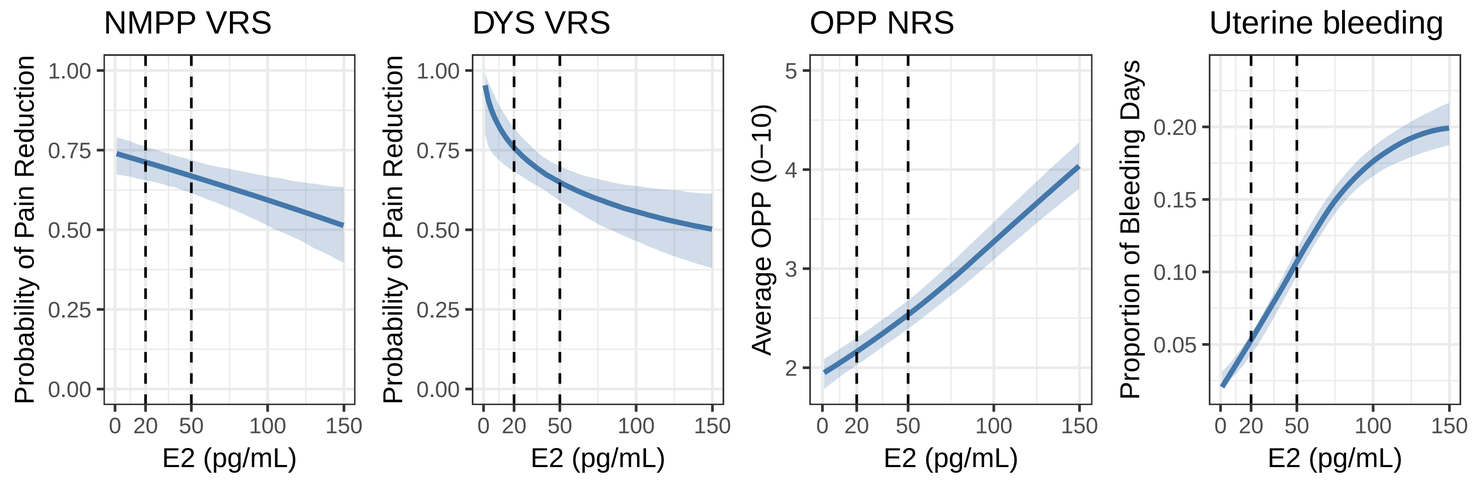

Figure 4: Simulated week 24 LS BMD versus E2 (top) and linzagolix dose (bottom). Simulated E2 drove BMD changes in QSP model [1].

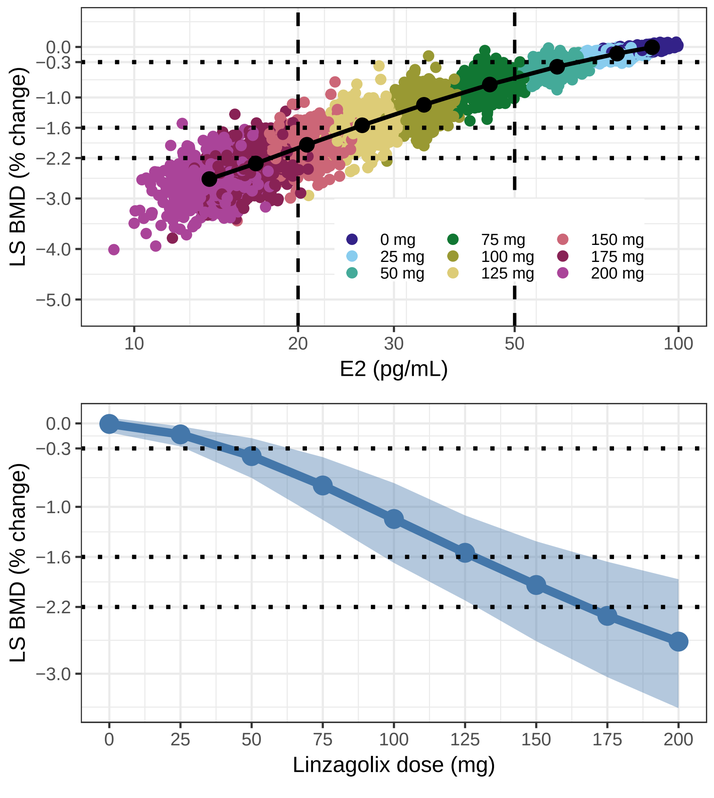

Figure 5: Linzagolix dose selection; minimal criteria (top) and hybrid criteria (optimal efficacy, minimal BMD; bottom). Criteria defined in figure 1.