A model-based analysis to guide gonadotropin-releasing hormone receptor antagonist use for management of endometriosis

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Aims: To identify linzagolix doses, an oral GnRH receptor antagonist, that effectively lower oestradiol (E2) to relieve endometriosis-related pelvic pain without compromising bone health.

Methods: Integrated statistical, pharmacokinetic–pharmacodynamic and systems pharmacology models were developed from Phase 1 and 2 clinical trial data in healthy volunteers and patients, receiving linzagolix 25–200 mg daily or placebo, and analysed simultaneously. The main outcome measures were pelvic pain scores for dysmenorrhoea, nonmenstrual pelvic pain (NMPP), uterine bleeding and lumbar spine bone mineral density (BMD).

Results: Linzagolix pharmacokinetics were described by a 2-compartment model with sequential zero/first-order absorption process (CL/F: 0.422 L/h). E2 changes over time were well described as a function of linzagolix 24-hour AUC (AUC50: 1.68 × 10^5 ng h/mL). For a Caucasian reference patient, a change in E2 from 50–20 pg/mL at 24 weeks increased the odds of relief of dysmenorrhoea 1.33-fold and NMPP 1.07-fold (95% CI: 1.22–1.47 and 1.02–1.12, respectively) and decreased bleeding days by 1.55 (95% CI: 1.39–1.72). A previously validated quantitative systems pharmacology BMD model was adjusted to the clinical data. The mean week 24 lumbar spine BMD change from baseline ranged from −0.092% in the 50 mg dose, −1.30% in the 100 mg dose group and −2.67% in the 200 mg dose group.

Discussion: The previously-reported E2 target range (20–50 pg/mL) to balance efficacy and safety endpoints was confirmed. Linzagolix once daily doses between 75–125 mg daily were expected to meet endometriosis-associated pain, efficacy, and BMD loss targets in Caucasian patients.

KEYWORDS
endometriosis, GnRH antagonist, linzagolix

There is no principal investigator for this paper.

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INTRODUCTION

Endometriosis is an oestrogen-dependent, painful, chronic disorder affecting 6–10% of reproductive age women caused by implantation of endometrial tissue and its subsequent ectopic extraterine growth. Oestrogen stimulates local and systemic inflammation, and promotes implantation and maintenance of endometrial tissue in the peritoneum, playing an important role in endometriosis pathophysiology. The main symptoms of endometriosis include dysmenorrhoea (DYS), nonmenstrual pelvic pain (NMPP), dyspareunia, pain with urination or bowel movements, and infertility.

Several therapeutic options are available for treating the symptoms and the underlying pathophysiology of endometriosis. Nonsteroidal anti-inflammatory drugs can help control inflammation and pain symptoms. Combination oral contraceptives or progestins can provide relief by inhibiting ovulation to impede the proliferation of endometrial tissue and bleeding during the menstrual cycle.

Gonadotropin-releasing hormone (GnRH) agonists offer another hormonal therapeutic approach for treatment of endometriosis, often used in patients with severe disease who are no longer responding to oral contraceptives. GnRH agonists, however, can cause an initial flare in the disease and symptoms. With continued administration, GnRH agonists eventually desensitize GnRH receptors in the pituitary gland, resulting in complete suppression of circulating oestradiol (E2) and subsequent inhibition of growth of endometrial implants. Decrease in oestrogen under continued GnRH agonist therapy can be so severe that hypoestrogenic effects, including menopausal symptoms in the short term and osteopenia in the long-term, can become problematic. The extent of bone demineralization due to hypoestrogenaemia is proportional to time and limits the duration of GnRH agonist monotherapy to 6 months. Hormonal add-back therapy (ABT) with an oestrogen and progestogen or progestogen alone, commonly co-administered with GnRH agonists, partially replenishes the circulating oestrogen to prevent bone mineral density (BMD) loss and vasomotor symptoms.

Therefore, antioestrogenic interventions must reduce oestrogen levels enough to affect the pathogenesis of endometriosis, while maintaining a minimum level of circulating oestrogen to prevent hypoestrogenic adverse effects. This balance according to the oestrogen threshold hypothesis and previous quantitative systems pharmacology (QSP) work by Riggs et al. found partial suppression of E2 (serum levels between 20 and 50 pg/ml) as a starting point for target E2 ranges. In contrast to GnRH agonists, GnRH antagonists can produce immediate reductions in follicle-stimulating hormone, LH, and circulating oestrogen, avoiding the initial disease flare. Additionally, since the GnRH antagonists act directly on GnRH receptors in the pituitary gland, the antagonist can be optimally dosed to reduce oestrogen, mitigate adverse bone health sequelae from hypoestrogenaemia, and potentially prevent the need for ABT. In 2018, the Food and Drug Administration approved the first oral GnRH receptor antagonist indicated for management of pain associated with endometriosis in over a decade. The antagonist exhibits rapid, sustained, dose-dependent reduction in E2 and correspondingly in BMD and NMPP at month 3.

What is already known about this subject

- Linzagolix is an oral GnRH receptor antagonist in development for the treatment of endometriosis and uterine fibroid symptoms that works by dose dependently reducing oestradiol and thus allows balancing efficacy with minimizing adverse effects to bone health for successful dosing.

What this study adds

- This integrated modelling and simulation study indicated that linzagolix can target oestradiol ranges appropriately to maximize efficacy without the need of hormonal add-back therapy to protect bone health and determined linzagolix 75 mg daily as an optimal dose regimen for consideration in pivotal Phase 3 endometriosis trials.
| Study number and title | Endpoints | Population | Linzagolix doses studied | Duration |
|------------------------|-----------|------------|--------------------------|----------|
| KLH1101                | PK: d 1 and 9 | 49 (SAD) and 42 (MAD) healthy pre- and postmenopausal women | SAD: 12.5, 25, 50, 100, 200, 400 mg × 1 MAD: 100, 200, 400 mg daily × 7 | 1–8 d |
| EDELWEISS NCT02778399 | PK: d 1 and 9, predose at wk 4 and 16, and postdose at wk 8, 12, 20 and 24 Pelvic pain: VRS for pelvic pain: no, mild, moderate, severe E2: d 1 and wk 4, 8, 12, 16, 20, 24, 28, 36 Bleeding: none, spotting, bleeding, heavy bleeding DXA: baseline, wk 12, 24, 48 | 330 women aged 18–45 years with endometriosis | Placebo, 50, 75, 100 and 200 mg daily fixed dose groups Titrated dose group: 75 mg daily for 12 wk followed by either 50, 75, or 100 mg daily | 24 wk |
| 16-OBE2109-011         | PK: predose on d 8, 15, 22, 29, 36; full profile on d 43 E2: predose on d 1, 8, 15, 29, 36 and on d 43 and 55; predose 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 and 24 hours postdose on d 22 Bleeding: none, spotting, bleeding, heavy bleeding | 75 healthy women of child-bearing potential | Placebo, 100, and 200 mg daily | 42 d |
| 17-OBE2109-008         | PK: predose on d 1, 15, 29, 43, 57, 71 E2: predose on d 1, 15, 29, 43, 57, 71 and 84 (the follow-up visit) Bleeding: none, spotting, bleeding, heavy bleeding | 32 healthy women aged 18–48 years | Placebo, 100 and 200 mg daily; 1 mg/0.5 mg add-back | 70 d |
| KLH1204 NCT02778919    | PK: 2 hours postdose at wk 0 and 4, and predose at wk 4, 12, 16, 20 and 24 and postdose at wk 8 VRS for pelvic pain: absent, slight, mild, moderate, severe E2: d 1 and wk 4, 8, 12, 16, 20, 24 Bleeding: spotting, mild, comparable to menses, severe DXA: baseline, wk 12, 24 | 440 Japanese women with endometriosis | Placebo, 25, 50, 75, 100 mg daily | 24 wk |

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, oestradiol; MAD, multiple ascending doses; PD, pharmacodynamic; PK, pharmacokinetic; SAD, single ascending doses; VRS, verbal rating scale.
METHODS

2.1 Data

Data were pooled across 5 clinical trials conducted in healthy volunteers (HVs) or patients with endometriosis, or endometriosis and uterine fibroids. Robust PK data from Phase 1 studies in Caucasian and non-Caucasian HVs (KLH1101, 16-OBE2109-011, 17-OBE2109-008, and KLH1204) and sparse PK data from Phase 2b EDELWEISS study in patients and HVs (Table 1) was incorporated. Patients in the EDELWEISS study received doses ranging from 25 to 200 mg once daily for 24 weeks and HVs received 100–200 mg once daily for 42–70 days. At least 1 linzagolix PK measurement and 1 E2 measurement (measured at each study visit) were required for data inclusion in the analysis.

The population PK analysis data set included 4250 linzagolix concentration observations from 756 subjects, approximately 24% of subjects and 55% of observations were from HVs. The analysis data set for PK-E2 modelling included 4674 E2 observations from 724 subjects, with approximately 15% of subjects and observations as HVs. A summary of the study participants characteristics contributing data to either the population PK analysis set (which did not include subjects receiving placebo doses) or the PK-E2 analysis set (which included subjects receiving placebo doses but did not include HVs in study KLH1101) is shown in Table 3. A full description of the data disposition for each model is provided in the Supporting Information along with an explanation for the methods of covariate selection for the PK model.

The current analysis was intended to guide dose selection in a Caucasian/non-Asian population. While PK, E2 and efficacy endpoints were comparable across different race groups, differences in bone remodelling dynamics across race groups had been previously reported and thus precluded joint analysis of BMD data in Asian and Caucasian populations. The analysis of PK, E2 and efficacy endpoints included both non-Caucasian and Caucasian subjects to reduce parameter uncertainty.

Efficacy endpoints included number of bleeding days, NMPP on nonbleeding days and dysmenorrhoea pain on bleeding days (DYS). For efficacy modelling, daily individual predicted E2 values were averaged across 28-day time intervals (representative of a nominal month) and used as the primary predictor for each efficacy endpoint. More details on efficacy endpoints are given in the Data section of the Supporting Information.

Lumbar spine BMD was measured in patients using dual-energy X-ray absorptiometry (DXA) utilizing GE Lunar or Hologic equipment at baseline, week 12 and week 24 and analysed as the percent change from baseline at weeks 12 and 24. The E2-BMD analysis data set included 401 LS BMD observations in 230 Caucasian patients enrolled in the EDELWEISS study. Mechanistic modelling of the effect of E2 changes on BMD in patients utilized a previously published mechanistic QSP model, following the approach taken by Riggs et al.9

The NMPP and DYS analysis data set had a total of 619 patients, with 243 subjects in EDELWEISS and 376 subjects in KLH1204. The analysis endpoints for modelling of NMPP and DYS were monthly binary values, categorized by response/nonresponse. Subjects were classified as a responder if the monthly change of NMPP or DYS score achieved a threshold and the use of analgesics did not increase by more than 15% from baseline. Further details are provided in the Supporting Information.

The analysis data set for uterine bleeding included a total of 724 subjects, with 619 endometriosis patients from EDELWEISS and KLH1204 and 105 HVs from studies 16-OBE2109-011 and 17-OBE2109-008. The average number of bleeding days in the 28-day interval at baseline for Caucasian and non-Caucasian subjects was similar, but HVs had 3.56 bleeding days while endometriosis patients had 5.53 bleeding days.

2.2 Integrated modelling strategy

A decision informatics model-based workflow was implemented to evaluate linzagolix dose candidates for study in Phase 3 clinical trials (Figure 1). All subject data (i.e., HVs and patients) were incorporated into a population PK model to explore dose-exposure relationships and identify sources of variability in PK parameters and concentrations. A second model (PK-E2) evaluated linzagolix exposure (e.g., AUC) and E2 levels, and allowed for

![Figure 1](https://example.com/figure1.png)

**Figure 1** Modelling and simulation workflow to evaluate linzagolix doses for testing in pivotal Phase 3 trials. Dysmenorrhoea, nonmenstrual (NM) pelvic pain were efficacy endpoints in the dose decision workflow. Lumbar spine bone mineral density (BMD) was the safety endpoint in the dose decision workflow using a target corresponding to an expected change from baseline of –1.6%. DC: decision criterion; E2: oestradiol; PK: pharmacokinetic
quantification of differences in HVs and patients. In the third stage, target criteria were established for both efficacy (DYS, NMPP) and safety (BMD) endpoints (Table 2), the basis for different outcome models. The combined set of outcome models were used to simulate clinical endpoints for different candidate linzagolix doses, and the doses that were likely to achieve several (or all) endpoint targets with high probability were identified as candidates for study in pivotal Phase 3 studies. See the Supporting Information for additional software details and model equations.

**Table 2**  Targets used for evaluation of linzagolix dose candidates for testing in pivotal Phase 3 clinical trials. All clinical targets were evaluated at week 24

| Target | Value |
|--------|-------|
| DYS–VRS (% of responders) | 80 |
| NMPP–VRS (% of responders) | 60 |
| LS BMD mean CFBL (%) | −1.6 |

Abbreviations: BMD, bone mineral density; CFBL, change from baseline; DYS, dysmenorrhoea; LS, lumbar spine; NMPP, nonmenstrual pelvic pain; VRS, verbal rating scale.

**Table 3**  KLH1101, 16-OBE2109-011 and 17-OBE2109-008 were conducted in healthy subjects. Subject weight, age and baseline oestradiol (E2) are given as median (standard deviation) calculated from baseline values

| Study         | Subjects | Percent Caucasian | Weight (kg) | Age (y) | Baseline E2 (pg/mL) |
|---------------|----------|-------------------|-------------|---------|---------------------|
| KLH1101       | 77       | 70                | 64.4 (11.2) | 40 (15.2) | --                  |
| 16-OBE2109-011| 73       | 99                | 62.8 (9.02) | 33 (6.95) | 25.0 (13.5)         |
| 17-OBE2109-008| 32       | 100               | 64.8 (7.90) | 35 (6.64) | 20.5 (13.5)         |
| EDELWEISS     | 244      | 94                | 65.5 (17.8) | 32 (6.07) | 53.0 (7.98)         |
| KLH1204       | 376      | 0                 | 53.9 (9.16) | 37 (6.47) | 44.0 (40.9)         |
| KLH1201       | 24       | 0                 | 53.4 (8.03) | 35.1 (6.90) | --                 |
| KLH1202       | 109      | 0                 | 54.1 (6.74) | 35.5 (6.62) | --                 |
| KLH1203       | 21       | 0                 | 53.1 (7.62) | 34.7 (6.57) | --                 |

**Table 4**  Parameter estimates for the final population pharmacokinetic model

| Parameter | Value | 95% CI         | Shrinkage (%) |
|-----------|-------|----------------|---------------|
| **Structural parameters** |       |                |               |
| CL/F (L/h) | 0.422 | 0.393–0.455    |               |
| V2/F (L)   | 5.13  | 4.19–6.18      |               |
| Q/F (L/h)  | 0.168 | 0.130–0.225    |               |
| V3/F (L)   | 3.12  | 2.83–3.41      |               |
| KA (L/h)   | 2.49  | 2.04–3.08      |               |
| D1 (h)     | 0.644 | 0.314–1.24     |               |
| **Covariate effects** |       |                |               |
| CL/F ~ non-Caucasian | 1.08  | 1.05–1.12      |               |
| CL/F ~ (weight 58 kg) | 0.75  | FIXED          |               |
| V2/F ~ (weight 58 kg) | 1.00  | FIXED          |               |
| **Interindividual variability (log-normal)** |       |                |               |
| IIV-CL/F   | 0.0354| 0.0271–0.0498  | 16.5          |
| IIV-V2/F   | 0.0444| 0.0203–0.115   | 62.0          |
| IIV-D1     | 0.510 | 0.230–1.41     | 46.2          |
| IIV-σ^2    | 0.764 | 0.505–1.11     | 24.8          |
| **Residual variability (proportional error)** |       |                |               |
| EDELWEISS data | 0.118 | 0.0698–0.206   |               |
| All other studies | 0.0389 | 0.0309–0.0502 |               |

Abbreviations: CI, confidence interval. IIV-σ^2: subject-level variability on the residual error variance; CL/F, clearance; D1, zero-order input duration; KA, absorption rate constant; Q/F, intercompartmental clearance; V2/F, central volume; V3/F, peripheral volume.
2.3 | Simulation to support dose selection for phase 3 trials

Integrated simulations from the PK, PK-E2, pain and bleeding models were used to evaluate candidate doses for study in Phase 3 trials enrolling Caucasian patients with endometriosis. First, target criteria were established for both efficacy (DYS, NMPP) and safety (BMD) endpoints (Table 2). Efficacy criteria were selected considering the confirmatory Phase 3 clinical trial results of another GnRH receptor antagonist at the highest dose (200 mg elagolix, twice daily).14 The LS BMD target was based on the clinical results of high dose elagolix (300 mg, twice daily), fully suppressing E2 levels, together with a low-dose ABT, a combination that was considered suitable for long-term GnRH antagonist treatment and which resulted in a mean BMD loss of 1.6% (90% CI: −1 to −2).15 PK for each candidate linzagolix dose were simulated and used to drive simulated longitudinal E2 vs. time profiles. These simulated E2 data were then used to generate predictions under the DYS, NMPP and LS BMD models 24 weeks after the start of treatment. The probability of meeting the targets of each endpoint was calculated across all replicate simulations for each dose. Doses were evaluated from 0 to 200 mg daily in 25-mg increments. (Table 3)

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.16

| Table 5 | Parameter estimates for the final pharmacokinetic–oestradiol (E2) model |
|---------------------------------|------------------|------------------|------------------|
| Parameter                        | Value            | 95% CI           | Shrinkage (%)    |
| Structural parameters            |                  |                  |                  |
| Baseline E2, patients (pg/mL)    | 59.1             | 52.5–65.6        |                  |
| Baseline E2, healthy (pg/mL)     | 26.6             | 23.3–29.8        |                  |
| Linzagolix AUC50 (ng h/mL)       | 1.68 × 10^5      | 1.44 × 10^5–1.91 × 10^5 |
| Sigmoidicity parameter           | 1.78             | 1.49–2.08        |                  |
| Placebo increase factor          | 0.65             | 0.465–0.834      |                  |
| Placebo effect rate constant (1/wk) | 0.231           | FIXED            |                  |
| E2 increase rate on add-back therapy (pg/mL/wk) | 1.58           | 0.990–2.16      |                  |
| Covariate effects                |                  |                  |                  |
| Baseline E2 ~ (weight 58 kg)    | −0.699           | −0.958 to −0.441 |                  |
| Baseline E2 ~ (age 35 y)        | 0.0829           | −0.157 to 0.323  |                  |
| Baseline E2 ~ non-Caucasian     | 0.804            | 0.702–0.907      |                  |
| Baseline E2 ~ linzagolix drug effect | −0.120          | −0.212 to −0.0279 |                  |
| Interindividual variability (additive on log-scale) |                  |                  |                  |
| IIV-baseline E2                  | 0.310            | 0.262–0.358      | 11.9             |
| Residual variability (additive on log-scale) |                  |                  |                  |
| Patients                         | 0.610            | 0.571–0.649      |                  |
| Healthy                          | 0.241            | 0.179–0.303      |                  |

Abbreviation: CI, confidence interval.
3 | RESULTS

3.1 | Data

Linzagolix population PK were best described with a 2-compartment, linear PK model (Table 4) using a sequential zero-order/first-order process (CL/F: 0.422 L/h). E2 changes over time were well described as a function of linzagolix 24-hour AUC (AUC50: $1.68 \times 10^7$ ng h/mL). Model-predicted areas under the concentration–time curve at steady state (AUCss) for individuals in the EDELWEISS study are shown in Figure 2. The PK-E2 model estimates revealed approximately 2-fold higher baseline E2 in Caucasian patients relative to Caucasian HVs (Table 5). There was a modest inverse relationship between weight and baseline E2, but no statistically significant relationship was detected between baseline E2 and patient age at baseline (Table 5). Visual predictive check for the E2 vs. time data in the EDELWEISS study showed that data simulated from the model were like these E2 observations (Figure 3). Model-based E2 predictions under this model (Figure 4) were used to drive changes in clinical outcome models described below.

The effect of E2 on DYS differed by time interval but generally, lower E2 was associated with a higher probability of DYS and NMPP pain relief (Table 6 and Figure 5). For a Caucasian reference patient, a change in E2 from 50–20 pg/mL at 24 weeks increased the odds of relief of DYS 1.33-fold and NMPP 1.07-fold (95% CI: 1.22–1.47 and 1.02–1.12, respectively) and decreased bleeding days by 1.55 (95% CI: 1.39–1.72). For uterine bleeding, because a direct effect of E2 on bleeding could not be formulated using a single parameter, the effect of change in E2 from 50 to 20 pg/mL at week 24 was computed using simulations in the same manner as for the pain endpoints (Table 7 and Figure 6).

Finally for the safety endpoint, a previously validated QSP BMD model was adjusted to the clinical data. The mean week...
24 LS BMD change from baseline ranged from −0.092% in the 50 mg dose, −1.30% in the 100 mg dose group, and −2.67% in the 200 mg dose group. All structural model parameters were fixed to values reported in Riggs et al.\textsuperscript{9} and only parameters in the E2 scaling function were estimated (see Equation 6 from Riggs et al.\textsuperscript{9} and Table 8). The model was able to describe these dose-dependent changes in LS BMD at the 12- and 24-week visits (Figure 7).

### 3.2 | Dose selection

#### 3.2.1 | Efficacy simulations (DYS, NMPP)

For a given dose, the final estimated Pop-PK E2 model was used to simulate E2 values at 24 weeks. The simulated E2 values were used to obtain predicted values of pain and bleeding using the final estimated pain and bleeding models accounting for parameter uncertainty.

| Covariate                      | DYS VRS pain Estimate* | 95% CI   | NMPP VRS pain Estimate* | 95% CI   |
|-------------------------------|------------------------|----------|--------------------------|----------|
| Intercept (odds)               | 6.27                   | 1.46–26.9| 0.326                    | 0.0937–0.559|
| Baseline pain                 | 1.23                   | 0.367–4.13| 0.987                    | 0.966–1.01|
| Non-Caucasian                 | 253                    | 29.9–2140| 2.4                      | 1.47–3.33|
| Weight                        | 0.966                  | 0.909–1.03| 5.94                     | 3.57–8.31|
| Days 29–56                    | 47.2                   | 7.58–294 | 9.17                     | 5.41–12.9|
| Days 57–84                    | 75.9                   | 11.1–518 | 17                       | 9.77–24.3|
| Days 85–112                   | 6.29                   | 1.10–36.1| 16.1                     | 9.21–23.0|
| Days 113–140                  | 23.9                   | 3.57–160 | 0.987                    | 0.978–0.995|
| Days 141–168                  | 8.21                   | 1.39–48.4| 0.326                    | 0.0937–0.559|
| E2                            | 0.703                  | 0.474–1.04| 0.987                    | 0.966–1.01|
| Baseline pain × E2            | 1.10                   | 0.805–1.50|                          |           |
| Non-Caucasian × E2            | 0.294                  | 0.169–0.512|                        |           |
| Weight × E2                   | 1.00                   | 0.988–1.02|                          |           |
| Days 29–56 × E2               | 0.362                  | 0.225–0.583|                        |           |
| Days 57–84 × E2               | 0.355                  | 0.217–0.580|                        |           |
| Days 85–112 × E2              | 0.733                  | 0.465–1.16|                        |           |
| Days 113–140 × E2             | 0.503                  | 0.308–0.823|                        |           |
| Days 141–168 × E2             | 0.665                  | 0.419–1.05|                        |           |

Abbreviations: CI, confidence interval; E2, oestradiol; VRS, verbal rating scale.
These predicted values were used to compute the probability of achieving a target response or better. For Caucasian patients, the probability of surpassing the NMPP target was over 95% for doses ≥50 mg (Figure 9). For DYS, the probability of surpassing the DYS target was over 95% at doses of 75 mg or greater.

### 3.3 Safety simulations (BMD)

Simulations from the E2-BMD model under different candidate doses in a Caucasian population are shown in Figure 10. Doses between 75 and 150 mg daily were associated with week 24 E2 concentrations in the proposed target window of 20–50 pg/mL. Furthermore, doses <100 mg daily were expected to result in LS BMD declines that do not exceed −1.6% at week 24.

### 3.4 Integrated simulations

Linzagolix doses of 75 to 100 mg daily are expected to meet the decision target with high (>95%) probability for efficacy (DYS, NMPP) and safety (BMD) endpoints (Figure 9).

### 4 DISCUSSION

Pharmacotherapy has a pivotal role in symptom-relief for endometriosis, an oestrogen-dependent gynaecological condition. The GnRH

### TABLE 7 Parameter estimates for the final uterine bleeding model. Estimates correspond to odds ratios except for intercept parameters, which correspond to odds

| Parameter                      | Bleeding | 95% CI          |
|-------------------------------|----------|-----------------|
| Mean                          |          |                 |
| Intercept (odds)              | 0.120    | 0.109–0.134     |
| Baseline bleeding/pain        | 6.01     | 4.25–8.58       |
| Non-Caucasian                 | 1.08     | 1.02–1.16       |
| Healthy                       | 0.714    | 0.631–0.800     |
| Weight                        | 0.968    | 0.951–0.988     |
| Days 29–56                    | 1.179    | 1.09–1.29       |
| Days 57–84                    | 1.13     | 1.03–1.24       |
| Days 85–112                   | 1.17     | 1.07–1.28       |
| Days 113–140                  | 1.21     | 1.09–1.35       |
| Days 141–168                  | 1.23     | 1.13–1.35       |
| E2                            | 1.04     | 1.02–1.06       |
| Probability of 0              |          |                 |
| Intercept (odds)              | 0.683    | 0.528–0.878     |
| Baseline bleeding/pain        | 0.0916   | 0.0307–0.226    |
| Non-Caucasian                 | 0.421    | 0.390–0.457     |
| Days 29–56                    | 1.33     | 1.05–1.69       |
| Days 57–84                    | 1.39     | 1.10–1.71       |
| Days 85–112                   | 1.33     | 1.07–1.69       |
| Days 113–140                  | 1.50     | 1.18–1.93       |
| Days 141–168                  | 1.52     | 1.19–1.96       |
| E2                            | 0.683    | 0.528–0.878     |

Abbreviation: CI, confidence interval.

### TABLE 8 Parameter estimates for the final bone mineral density (BMD) model. All parameter estimates were derived from patients enrolled in the EDELWEISS trial. The 95% confidence intervals (CI) were calculated from 500 bootstrap replicates

| Parameter                      | Value    | 95% CI          |
|-------------------------------|----------|-----------------|
| Structural parameters         |          |                 |
| BMD E2-transform E250 (pg/mL) | 0.202    | 0.135–0.401     |
| BMD E2-transform sigmoidicity | 1.17     | 0.791–1.93      |
| Residual variability          |          |                 |
| Additive error (percent change from baseline) | 5.75 | 5.12–6.42 |

Abbreviation: CI, confidence interval.
Antagonist linzagolix is a promising new potential treatment option. Linzagolix allows dose-dependent control of E2 levels reducing endometriosis-associated pain, but it is associated with hypoestrogenic adverse effects, including hot flushes and BMD loss, when E2 production is fully suppressed. Models relating pharmacokinetics, pharmacodynamics, and clinical outcomes are routinely used to support dose selection in clinical drug development. Specifically, mechanistic, systems-based modelling has been previously used to balance benefits and risks for GnRH receptor modulators in the treatment of endometriosis. QSP integrates the characteristics of a drug (dose, 

**Figure 7** Lumbar spine bone mineral density (LS BMD) observed and model-predicted values by linzagolix dose for Caucasian patients enrolled in EDELWEISS. The red lines and points mark the median model predicted values. The boxplots summarize observed LS BMD values at the nominal visit week. Baseline (week 0) LS BMD values are zero by definition and were not included in the model estimation data set; they are included here only for context.

**Figure 8** Predictions of dysmenorrhoea (DYS) and nonmenstrual pelvic pain (NMPP) pain endpoints at 24 weeks of Caucasian reference patients. Line is median prediction and shaded area is 95% confidence interval. Horizontal red line is target criteria. Vertical dashed lines are values at 20 and 50 pg/mL. Box plot is distribution of oestradiol (E2) for subjects at a given dose. E2: oestradiol; VRS: verbal rating scale.
dosing regimen, or a full pharmacokinetic submodel) with target biology and functional endpoints\textsuperscript{18}. The analyses herein used simulated E2 from the derived PK-E2 model to drive efficacy and safety outcomes and support the selection of linzagolix doses for use in Phase 3 studies enrolling Caucasian patients with endometriosis. QSP was particularly useful in this context to explore linzagolix doses that lower E2 to an optimal level for pain relief with minimal BMD losses.

Population PK modelling described linzagolix dose–exposure relationships and included weight effects on CL/F and V2/F using fixed allometric scaling values. Overall, estimated PK were similar between Caucasian and non-Caucasian subjects, except for a statistically significant covariate on CL/F that may not be considered clinically significant. After characterizing linzagolix exposure, a model was developed to characterize the relationship between linzagolix exposure and E2 lowering in endometriosis patients and HVs. Linzagolix was found to decrease E2 in an exposure-dependent manner with AUC\textsubscript{50} of $1.68 \times 10^5$ ng h/mL (90% CI: $1.44 \times 10^5$ to $1.91 \times 10^5$).

Clinical outcome models for pain were developed as a function of modelled E2. As for the BMD submodel, an existing QSP model of bone health was adapted to the needs of this study\textsuperscript{19,20}. This model was shown to be valid for bone metabolism and pathologies such as osteoporosis, chronic kidney disease, menopause transition, and hypoparathyroidism\textsuperscript{10}. The model was integrated with additional PK models to describe pharmacological effects of parathyroid analogue (teriparatide\textsuperscript{21}), calcium sensing receptor modulators,\textsuperscript{22} exogenous vitamin D\textsuperscript{23}, sclerostin inhibition\textsuperscript{24} and receptor activator of nuclear factor-κB ligand inhibition\textsuperscript{19,25}.

Decision criteria based on available clinical data for this class of drugs\textsuperscript{14,26} were established for efficacy (pain) and safety (LS BMD) endpoints that maximized discrimination between different doses and evaluated 24 weeks after the first dose. In the Caucasian patient population, doses from 75 mg reached efficacy targets with high probability for DYS and NMPP endpoints. As for the BMD target, doses below 150 mg fulfilled the bone safety criterion (Figure 9).

**FIGURE 9** Dose selection for Caucasian patients. The probabilities of satisfying the decision targets are shown vs. linzagolix daily dose (mg). LS BMD: lumbar spine bone mineral density; DYS: dysmenorrhoea; NMPP: nonmenstrual pelvic pain

**FIGURE 10** Model-based assessment of expected lumbar spine bone mineral density (LS BMD) changes at week 24 in Caucasian patients. Pharmacokinetic, oestradiol (E2) and LS BMD were simulated from the final models at different linzagolix doses, incorporating uncertainty in the fixed effect parameter estimates only. $n = 500$ parameter sets were used for the simulation. Horizontal reference lines indicate week 24 BMD target (−1.6% change from baseline). (A) LS BMD vs. E2. The vertical dashed reference lines mark E2 values of 20 and 50 pg/mL. (B) Simulated LS BMD vs. linzagolix dose. The line and points mark the median simulated percent change from baseline and the shaded area indicates the 95% prediction interval.
Linzagolix was also effective in reducing bleeding at all doses, with higher doses showing greater reduction in proportion of bleeding days (Figure 6). Since there were no prespecified targets for uterine bleeding, an approach when comparing doses is to consider the highest linzagolix dose which does not negatively impact BMD. For the described patient population, 100 mg (a dose expected to satisfy the pain and safety decision target) is estimated to reduce the number of bleeding days by 60% relative to baseline. In addition to the endometriosis indication, linzagolix may control heavy menstrual bleeding in patients with other hormone-dependent conditions such as uterine fibroids, common benign oestrogen-sensitive tumours in the uterus.27 A recent study of another GnRH receptor antagonist has shown dose-dependent efficacy in patients with uterine fibroids.28 However in this analysis, there was not sufficient available data to properly differentiate the bleeding efficacy of linzagolix in endometriosis patients with co-existing uterine fibroids compared to endometriosis-only patients. Understanding exposure-response relationships for linzagolix with the current work may help support future dose selection for the uterine fibroid indication as well as potential to extrapolate to other patient populations.

Another objective for the analysis was to evaluate the viability of E2 as a surrogate for the efficacy and safety endpoints in the Caucasian populations. The term surrogate is used here in a non-technical sense, only to indicate that effective and safe therapy with linzagolix could potentially be inferred if E2 values are lowered into a validated target range. The proposed E2 target range of 20–50 pg/mL appeared to align fairly well with meeting targets for DYS pain and, to a lesser degree, NMPP (Figure 8). Targeting the E2 concentration of 20–50 pg/mL was also associated with LS BMD reductions that generally did not exceed the target of −1.6% at 24 weeks for Caucasian patients (Figure 10).

Overall, the previously reported E2 target range (20–50 pg/mL) to balance efficacy and safety endpoints was confirmed. Linzagolix doses between 75 and 125 mg daily were expected to meet pain and BMD targets in Caucasian endometriosis patients. The dose level selected for confirmatory linzagolix Phase 3 studies in endometriosis (NCT03992846, NCT03986944)29,30 was 75 mg once daily, and is thus a safety-oriented choice within the identified optimal dose range.

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CONTRIBUTORS
J.-P.G. and O.P. from ObsEva designed the trials, acquired the data, interpreted results, contributed to the writing, and reviewed the manuscript. K.B., M.R., J.F. and R.G. from Metrum Research Group planned and conducted all data analyses, interpreted results, contributed to the writing, and reviewed the manuscript.

DATA AVAILABILITY STATEMENT
Research data are not shared.

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