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

Kyle Baron\textsuperscript{1}, Oliver Pohl\textsuperscript{2}, Matthew Riggs\textsuperscript{1}, Jonathan French\textsuperscript{1}, Jean-Pierre Gotteland\textsuperscript{2}, Ramon Garcia\textsuperscript{1}

\textsuperscript{1}Metrum Research Group, \textsuperscript{2}ObsEva SA
HPG Axis, Endometriosis, and Bone Health

![Diagram showing the HPG axis with linzagolix affecting GnRH, which leads to FSH and LH stimulating the gonad (ovary) to produce progesterone and estradiol, affecting bone health and endometriosis symptoms.]
**Decision Informatics Model-Based Workflow**

**Linzagolix Dose**

**Population PK**

**PK-E2 Exposure Response**

<table>
<thead>
<tr>
<th>Metric</th>
<th>MIN</th>
<th>OPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmenorrhea</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>NM Pelvic Pain</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Overall Pelvic Pain</td>
<td>-1.7</td>
<td>-2.6</td>
</tr>
<tr>
<td>Uterine Bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar Spine BMD</td>
<td>-2.2%</td>
<td>LOWER BOUND</td>
</tr>
</tbody>
</table>

**Dosing regimen**
- once daily
- 25 to 200 mg

**Daily exposure**
- metric
- 24-hr AUC

**Decrease estradiol**
- confirm target
- 20-50 pg/mL

**Decrease pain bleeding**

**Possible BMD losses**
- maximize
- minimize
# PK and PK/PD Data Set

<table>
<thead>
<tr>
<th></th>
<th>PK</th>
<th>E2</th>
<th>NMPP VRS</th>
<th>DYS VRS</th>
<th>OPP NRS</th>
<th>UTERINE BLEEDING</th>
<th>LS BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy Volunteers</strong></td>
<td>![check]</td>
<td>![check]</td>
<td></td>
<td>![check]</td>
<td>![check]</td>
<td>![check]</td>
<td>PK/PD Trials Only</td>
</tr>
<tr>
<td>MAD/SAD (C09070)</td>
<td>![check]</td>
<td>![check]</td>
<td></td>
<td>![check]</td>
<td>![check]</td>
<td>![check]</td>
<td></td>
</tr>
<tr>
<td>PK/PD Trial 1 and 2 [1,2]</td>
<td>![check]</td>
<td>![check]</td>
<td></td>
<td>![check]</td>
<td>![check]</td>
<td>![check]</td>
<td></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>![check]</td>
<td>![check]</td>
<td></td>
<td>![check]</td>
<td>![check]</td>
<td>![check]</td>
<td>![check]</td>
</tr>
<tr>
<td>EDELWEISS</td>
<td>![check]</td>
<td>![check]</td>
<td></td>
<td>![check]</td>
<td>![check]</td>
<td>![check]</td>
<td></td>
</tr>
<tr>
<td>Phase 2 Trial</td>
<td>![check]</td>
<td>![check]</td>
<td></td>
<td>![check]</td>
<td>![check]</td>
<td>![check]</td>
<td></td>
</tr>
</tbody>
</table>

- **Patients**: 25 - 200 mg QD x 24 w
- **Healthy Volunteers**: 100 - 200 mg QD x 42 - 70 d
- **SAD**: 12.5 - 400 mg
- **MAD**: 100 - 400 QD x 7d
- **E2**: modeling used sparse measurements
- **NMPP/DYS - VRS**: responder rate
- **OPP - NRS**: raw score, 0-10
- **Bleeding**: fraction of days / month
- **BMD**: lumbar spine

PK/PD Modeling PK and PK-E2

Linzagolix PK
- 2-compartment, zero + first-order absorption
- fixed allometric scaling
- CL: 0.422 L/hr (58 kg)

PK-E2
- direct sigmoid Imax model
- exposure: daily AUC
- AUC$_{50}$: 168 $\mu$g*hr/mL
Efficacy OPP, NMPP, DYS, Uterine Bleeding

- **Efficacy modeling**
  - **Outcome** average daily pain & bleeding per month at 6 months
  - **Model** logistic & zero-inflated beta regression models for repeated measures
  - Controlled for baseline pain / bleeding, race, weight, & health status

- Lower E2 associated with
  - Increased non-menstrual & dysmenorrhea pain reduction
  - Decreased overall pelvic pain & % of bleeding days
Linzagolix Doses to Control BMD Loss at 6 months

Linzagolix dose → decrease estradiol → possible BMD losses → controlled BMD loss

Dose Selection **Balance Efficacy & Safety** at 6 months

linzagolix dose → decrease pain bleeding → controlled BMD losses

**Graph:**
- Probability vs. Linzagolix dose (mg)
- LS BMD: Blue line
- DYS VRS: Green line
- NMPP VRS: Yellow line
- OPP NRS: Red line

**Legend:**
- Optimal efficacy, minimal BMD
Model-Based Dose Selection for Phase 3 Trials

2-compartment PK, fixed allometric scaling
CL: 0.422 L/hr at 58 kg

PK-E2 model - direct sigmoidal Imax model
AUC$_{50}$: 168 µg*hr/mL

Optimal efficacy targets likely with doses ≥ 75 - 100 mg QD
Model: logistic and zero-inflated beta regression

Doses ≤ 125 mg QD with 90% CI lower bound not exceeding -2.2% △ LS BMD at 24 weeks
Model: OpenBoneMin QSP

- E2 in 20 - 50 pg/mL window a reasonable target
- Doses for pivotal Phase 3 trials
  - Endometriosis - 75 mg daily
  - Uterine Fibroids - 100 mg daily

controlled BMD loss at week 24

- dosing regimen
- daily exposure
- decrease estradiol
- decrease pain bleeding

once daily 25 to 200 mg
metric 24-hr AUC
target window 20-50 pg/mL
maximize

ACoP10 October, 2019
Thank You

- E2 in **20 - 50 pg/mL window** a reasonable target for balancing efficacy and safety

- Doses for pivotal Phase 3 trials
  - Endometriosis: 75 mg QD, EDELWEISS 2 & 3
  - Uterine Fibroids: 100 mg QD, PRIMROSE 1 & 2