Application of a Multiscale Physiologically-Based Bone and Calcium Systems Model to Guide the Development of GnRH receptor modulators for the Management of Endometriosis

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Abstract

Objective

Provide model-based decision support for gonadotropin releasing hormone (GnRH) modulator programs intended for the management of EM.

1. Establish quantitative relationship between estradiol (E2) and endometriosis efficacy endpoints.
2. Predict the consequences of these E2 levels required for efficacy on Bone Mineral Density (BMD).
3. Explore alternative (shorter) study designs using Bone Markers (BM) to predict for long-term BMD effects.

Methods

Data - Bone Markers and Bone Mineral Density (summary level literature data)
• Estimation Dataset
  • Full GnRH suppression: leuprolide8,9,10 and triptorelin11
  • Partial GnRH suppression: elagolix12
  • Assumed E2 baseline concentration of 100 pg/mL
  • E2 → 10 pg/mL (90% depletion) → full GnRH suppression
  • E2 → 20 pg/mL (80% depletion) → elagolix 250 mg OD
  • E2 → 40 pg/mL (60% depletion) → elagolix 150 mg OD
  • Evaluation Dataset (13 studies, publication years 1990–2006)
  • GnRH agonist treatments (leuprolide, nafarelin, triptorelin, and goserelin)
  • Provided external evaluation of the 6-month BMD predictions

Results - Bone Markers and Bone Mineral Density

- Equation (1): Link bone markers with BMD
  \[
  \frac{BMD_{	ext{EL}}}{BMD_{	ext{HS}}^{\text{baseline}}} = \frac{f_{\text{HS}}(\text{E2})}{f_{\text{EL}}(\text{E2})}
  \]

- BM and BMD model predictions (Table 1, Figure 2)

Table 1: Model Predicted BM and BMD Changes from Baseline

<table>
<thead>
<tr>
<th>E2 (pg/mL)</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>20</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>40</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.4%</td>
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<td>60</td>
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<td>0.4%</td>
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<tr>
<td>80</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Figure 2: Observed and Predicted BMD and Bone Markers versus Time

- Range of acceptable 6-month BMD changes (e.g., ~0.8% up toward ~1.6%)
- Minimal early differentiation of BM and BMD across doses
- BMD changes are delayed compared to the E2 decrease
- Literature evaluation dataset for E2 and BMD (Figure 3)
- Model prediction across a continuous range of 10–80 pg/mL
- Predicted the broader literature database
- Supported E2 as reliable predictor of 6-month BMD

Figure 3: Observed (set) and Simulated BMD versus E2

- Efficacy: ESSS

- P(ESSS=0 | E2 > 80 pg/mL) ~ 15%
- P(ESSS=0) increased to 26% and 29% at E2 = 40 and 20 pg/mL, respectively
- P(ESSS=0) decreased from 27% to 19% as E2 decreased (60 → 20 pg/mL)

Figure 4: Predicted ESSS versus E2

- Efficacy versus Side Effect

- E2 measured as early as 1-2 months after treatment initiation, was shown to be a reliable predictor of 6-month BMD change.
- Bone markers, as affected through GnRH inhibition, were projected to change too slowly to provide reliable dose differentiation earlier than at least 3-month study duration
- GnRH receptor modulation targeting E2 in the range of 10–80 pg/mL, are expected to provide efficacious EM pain response while minimizing BMD effects (Figure 5)
- Model-based approach has provided a quantitative framework for preclinical and clinical research efforts focused on mechanisms that modulate E2 levels.

Conclusions

- E2, measured as early as 1–2 months after treatment initiation, was shown to be a reliable predictor of 6-month BMD change.
- Bone markers, as affected through GnRH inhibition, were projected to change too slowly to provide reliable dose differentiation earlier than at least 3-month study duration
- GnRH receptor modulation targeting E2 in the range of 10–80 pg/mL, are expected to provide efficacious EM pain response while minimizing BMD effects (Figure 5)
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References

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