Model Based Meta Analysis to Characterize the Dose-Efficacy Profile of Recombinant FSH for Controlled Ovarian Stimulation

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Objective: In order to support dose selection of recombinant follicle-stimulating hormone (recFSH) in future studies, a model-based meta-analysis of available clinical outcome data was conducted to characterize the dose-efficacy relationship of recFSH in subjects undergoing controlled ovarian stimulation (COS).

Methods: A comprehensive database of summary level clinical outcomes for recFSH was constructed from publicly available sources and Merck-conducted clinical study results. A systemic search of electronic sources such as journal articles, conference reports and abstracts through PubMed, EMBASE, and regulatory agency websites was conducted. Additionally, internal reports from Merck clinical studies from 1984 until 2014 for randomized controlled trials investigating different doses of recFSH in COS were included. From these sources, oocyte retrievals, corresponding recFSH doses with demographic information, e.g. age and body weight were extracted. Data were analyzed by graphical evaluation followed by model based meta analysis. Multiple structural models were explored to describe the dose-efficacy relationship and covariate effects were tested. R-3.1.2 was used for data programming and modeling.

Results: A database of 19 randomized controlled trials, 31 arms in adult women aged from 18 to 42 years old representing a total of 4471 subjects treated with recFSH dosing from 100 to 300 IU was assembled. Oocyte retrieval was modeled as a function of recFSH doses. The relationship between recFSH dose and oocyte retrieval was assumed to be a sigmoid $E_{\text{max}}$ model with Hill coefficient. This was based on model selection criteria as well as previous modeling experience with individual level data:

$$N_{\text{ooc}} = \frac{(E_{\text{max}} \cdot \text{dose}^n)}{(\text{dose}^n + ED_{50}^n)}$$

As shown in Table 1, a shallow dose response for recFSH at doses > 150 IU was identified. Age or body weight was not found to be significant covariate as only summary level information rather than individual level data were available.

Table 1 Simulated RecFSH dose-response at clinical relevant doses based on the model based meta analysis

<table>
<thead>
<tr>
<th>recFSH Dose</th>
<th>100 IU</th>
<th>150 IU</th>
<th>200 IU</th>
<th>250 IU</th>
<th>300 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted Mean Oocytes Count</td>
<td>7.16 (4.7 – 8.3)</td>
<td>9.99 (8.8 – 10.7)</td>
<td>10.6 (9.7 – 11.3)</td>
<td>10.83 (9.9 – 11.5)</td>
<td>10.94 (9.9 – 11.7)</td>
</tr>
</tbody>
</table>

Note: 10,000 simulations conducted incorporating parameter uncertainty

Conclusions: A shallow dose-response relationship of recFSH for COS was established by leveraging internal and external data. Modeling results suggest that a plateau in response was achieved around a dose of 150 IU. RecFSH doses of >150 IU are expected to result in similar outcome for oocyte retrieval. This work demonstrates the value of model-based meta-analysis in integrating available literature evidence to support dose selection of recFSH.