Impact of body weight of IVF/ICSI patients on the pharmacokinetics and pharmacodynamic responses to FE 999049, a recombinant FSH derived from a human cell-line

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Introduction
Body weight / BMI has been hypothesised to be a predictor of ovarian response to gonadotropin therapy. FE 999049 is a recombinant FSH derived from a cell-line of human fetal retinal origin (PER.C6®) being developed for controlled ovarian stimulation to induce multiple follicles for IVF/ICSI. Differences in glycosylation profile as well as pharmacokinetic and pharmacodynamic profiles between FE 999049 and existing recombinant FSH products derived from a Chinese Hamster Ovary (CHO) cell line have been reported.1

The present study investigates the following questions:
• How does female body weight influence the pharmacokinetic profile during controlled ovarian stimulation?
• What are the implications for the pharmacodynamic response to FE 999049?

Materials & Methods
This is an explorative analysis of a randomised, assessor-blind, multicentre trial investigating FE 999049 for controlled ovarian stimulation for IVF/ICSI. A total of 222 patients aged 18-37 years with a BMI of 18.5-32.0 kg/m² were randomised to FE 999049 throughout stimulation.

The body weight ranged from 46 to 95 kg, with an average of 63 ± 9 kg and a median of 61 kg. The main baseline characteristics are displayed in Table 1. There were no relevant differences across the studied population.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Below median body weight (N=114)</th>
<th>Above median body weight (N=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>61.8 (9.5)</td>
<td>62.9 (9.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.6 (3.2)</td>
<td>32.8 (3.2)</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>6.9 (2.0)</td>
<td>7.5 (2.7)</td>
</tr>
<tr>
<td>Estradiol (pmol/L)</td>
<td>144 (50.1)</td>
<td>152 (53.8)</td>
</tr>
<tr>
<td>Inhibin B (ng/L)</td>
<td>78.4 (30.1)</td>
<td>86.9 (32.4)</td>
</tr>
<tr>
<td>Inhibin A (ng/L)</td>
<td>17.9 (9.3)</td>
<td>15.6 (5.2)</td>
</tr>
<tr>
<td>AMH (pmol/L)</td>
<td>17.9 (9.5)</td>
<td>18.4 (10.0)</td>
</tr>
<tr>
<td>Antral follicle count</td>
<td>14.0 (4.3)</td>
<td>13.8 (4.7)</td>
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Data are mean (SD)

Randomisation was stratified by serum AMH and centre. Patients underwent stimulation in a GnRH antagonist cycle (ganirelix 0.25 mg/day from day 6). Stimulation was done as soon as 3 follicles ≥ 17 mm were observed, and oocyte retrieval took place 36±2h after triggering.

Serum samples for endocrine profile were analysed centrally and follicular development was assessed locally by ultrasound on stimulation day 4 (i.e., after 3 days of treatment), stimulation day 6 (i.e., after 5 days of treatment and before start of GnRH antagonist) and at the end of stimulation. Total follicular volume was defined as the sum of the volume of all follicles.

Data were analysed on the log-scale using a linear model with body weight and log-transformed body weight as predictors of the quantitative impact. Patients were grouped above and below the median body weight. As the duration of stimulation was significantly (p=0.002) different between body weight groups, analysis was performed separately at the end of stimulation (i.e., after 3 days of treatment).

Results
With increasing body weight, serum concentrations of FSH, estradiol, inhibin B and inhibin A on stimulation day 4 and 6 decreased significantly (p<0.001 for all parameters at both time points).

On stimulation day 6, the effect of body weight was also observed for follicular development as shown by significantly lower average follicle size and follicular volume (p<0.001 for both parameters) with increasing body weight.

On stimulation day 5, the estradiol, inhibin B and inhibin A levels and follicular volume were 41%, 12% and 20%, respectively, greater in women with lower body weight compared to those with higher body weight.

Figure 2. Total follicular volume

Conclusions
• During stimulation with FE 999049, circulating levels of FSH were significantly negatively influenced by body weight, with patients at a lower body weight having higher serum FSH than those with higher body weight.

• Body weight also had a significant inverse relationship with estimable inhibin B, inhibin A and follicular development during stimulation with FE 999049, with lower weight patients having greater responses than higher weight patients.

• As body weight has a significant impact on serum FSH concentrations and consequently on follicular development and endocrine profile after treatment with FE 999049, considerations should be given to gonadotropin dosing regimen taking the pharmaco kinetic-pharmacodynamic data into account in order to optimise ovarian response.

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