**Effects of progesterone and estradiol on QT subintervals over the course of a menstrual cycle**

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### Introduction

QTc intervals have been observed to be longer in women than in men and this sex difference is apparent only after puberty, which suggests that sex hormones play a role [1]. The effect of sex steroid hormones on cardiac repolarization, mainly estradiol, progesterone and testosterone, has long been suspected but the mechanisms involved in the modulation of cardiac repolarization have not yet been completely clarified [2]. This study aimed to assess whether there is a reliable evidence for the influence of a menstrual cycle on the duration of cardiac sub-intervals. The goal is to provide further mechanistic insights into hormonal control of human ventricular repolarization and influence of gonadal hormones on different ion channel currents.

### Methods

This was a randomised, Phase 1 study, primarily designed to assess the safety, tolerability, pharmacokinetic and pharmacodynamic effects of a novel IMP in healthy female participants of childbearing potential that required a run-in period for the synchronisation of all female participants' menstrual cycles (Figure 1). The study was approved by the local ethics committee South Central - Berkshire B Research Ethics Committee (EudraCT Number: 2018-003702-36). This study showed that the tested IMP had no effects on QTc, and those data are not reported here. The study was conducted in 45 women, aged 20-37, with a BMI between 16.5 and 29.9 kg/m². Intensive cardiac assessments were conducted and levels of estradiol and progesterone were measured in blood drawn on Days -21, -5, 1, 2 and 14 to examine the relationship between sex hormones and QTc/QTcF. ECG recordings were taken after a meal on Days -21, -5 and 14 in order to reduce bias for diurnal QTc variation.

All ECG recordings were obtained in triplicate performed at one-minute intervals over three minutes for each time point to confirm accuracy and 14 in order to reduce bias for diurnal QTc variation.

### Results

**Figure 1:** Study design.

**Figure 2:** The effect of sex hormones on AP and ECG. Estrogen lengthens the QTc, while testosterone and progesterone shortens ventricular repolarization.

**Figure 3:** Changes from baseline for estradiol and progesterone.

**Figure 4:** Changes from baseline for cardiac subintervals.

Table 1: Significant estimates of fixed effects of sex hormones on cardiac parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model</th>
<th>Effect</th>
<th>Effect estimate</th>
<th>SE</th>
<th>t.d.f.</th>
<th>T value</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Progesterone, without baseline</td>
<td>1065.6</td>
<td>-0.158</td>
<td>0.0218</td>
<td>Inf</td>
<td>-7.23</td>
<td>-0.194 -0.122</td>
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<td>QTcF</td>
<td>Oestradiol without baseline</td>
<td>1225.5</td>
<td>0.013</td>
<td>0.0080</td>
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<td>1.58</td>
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<tr>
<td>QRSE</td>
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<td>0.5</td>
<td>0.21</td>
<td>Inf</td>
<td>2.28</td>
<td>0.1 0.8</td>
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<tr>
<td>JTpc</td>
<td>Oestradiol without baseline</td>
<td>1144.8</td>
<td>0.020</td>
<td>0.0060</td>
<td>Inf</td>
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<td>0.011 0.030</td>
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<td>TpTe</td>
<td>Baseline only</td>
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<td>-0.16</td>
<td>0.056</td>
<td>Inf</td>
<td>-3.19</td>
<td>-0.27 0.00</td>
</tr>
</tbody>
</table>

### Summary of Conclusions

- This study showed a significant positive effect of estradiol on QTcF (0.013 ms per ng/L), which was driven by a positive effect of estradiol on JTpc (0.020 ms per ng/L). We hypothesise that this is due to the down regulation of Ick and Ik reducing repolarisation reserve.
- There was significant negative effect of progesterone on heart rate (-0.158 ms per nmol/L).
- The limitations of this study are that the assessment of the IMP required hormonal preparation, using progestin and ultragen. These drugs may have may have limited the ability to observe estrogen-induced changes on QTc over the course of the natural menstrual cycle: progestin’s active ingredient is estradiol valerate, which is biologically equivalent to endogenous estrogen. Ultragen is known to increase progesterone levels [3].
- This was a hypothesis-generating work that demonstrated two things: Firstly, females are needed in TQT studies to identify any sex differences for a given drug. Further work should be conducted to determine if the relationships between cardiac subinterval duration and hormone levels are direct or indirect.

### References