Author's response to reviews

Title: Efficacy of tibolone and raloxifene for the maintenance of skeletal muscle strength, bone mineral density, balance, body composition, cognitive function, mood / depression, anxiety and quality of life / well-being in late postmenopausal women [greater than or equal to] 70 years: Study design of a randomized, double blind, double dummy, placebo-controlled, single-center trial

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Version: 4 Date: 11 March 2008

Author's response to reviews: see over
Coverletter:

Efficacy of tibolone and raloxifene for the maintenance of skeletal muscle strength, bone mineral density, balance, body composition cognitive function, mood/depression, anxiety and quality of life / well-being in late postmenopausal women ≥ 70 years: Study design of a randomized, double-blind, double-dummy, placebo-controlled, single-center trial

MS: 1718357312166511
Didy E Jacobsen(1) §, Monique M Samson(1), Yvonne T van der Schouw(2), Diederick E Grobbee(2), Harald J Verhaar(1),

Dear Editorial Team and reviewer,

We like to respond to the questions raised by our manuscript.

1. We do not have a trials registration number, because when the trial started this was not obligatory. After your comment we submitted the trial for registration in the NTR , Nederlands Trial Register (the Netherlands Trial Register). A registration number will follow.

2. It is also our concern that the tibolone-placebo comparison might be underpowered. But previous randomized controlled trials were conducted with a comparable number of participants and similar measurements, and reported significant effects for tibolone for one year, especially on body composition, see summary in these tables:

Effect of tibolone on body composition:

<table>
<thead>
<tr>
<th>Article</th>
<th>Study design</th>
<th>Number</th>
<th>Age (yrs)</th>
<th>Study time</th>
<th>Effect</th>
<th>Dropout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meeuwsen, Endocrinology</td>
<td>RCT</td>
<td>N=85</td>
<td>54.2 (4.7)</td>
<td>1 year</td>
<td>positive*</td>
<td>7.1%</td>
</tr>
<tr>
<td>Endocrinology Placebo 2001</td>
<td>Double-blind</td>
<td>43 placebo &gt; 42</td>
<td>54.0 (4.1)</td>
<td></td>
<td>4.7%</td>
<td></td>
</tr>
<tr>
<td>Endocrinology Placebo 2001</td>
<td>Double-blind</td>
<td>42 tibolone &gt; 39</td>
<td>54.4 (5.2)</td>
<td></td>
<td>7.1%</td>
<td></td>
</tr>
<tr>
<td>Tommaselli, Menopause 2006</td>
<td>RCT</td>
<td>N=75&gt;68</td>
<td>48.7 (4.2)</td>
<td>1 year</td>
<td>positive*</td>
<td>16%</td>
</tr>
<tr>
<td>Tommaselli, Menopause 2006</td>
<td>no treatment 25&gt;21</td>
<td>49.4 (3.9)</td>
<td></td>
<td></td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Tommaselli, Menopause 2006</td>
<td>tibolone 25&gt;23</td>
<td>51.4 (3.5)</td>
<td>1 year</td>
<td></td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Hanggi, Clinical Endocrinology 1998</td>
<td>randomized trial</td>
<td>N= 117 &gt; 100</td>
<td>52.4 (3.0)</td>
<td>2 years</td>
<td>positive*</td>
<td>15%</td>
</tr>
<tr>
<td>Hanggi, Clinical Endocrinology 1998</td>
<td>controls 26</td>
<td>52.0 (2.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanggi, Clinical Endocrinology 1998</td>
<td>oral HRT 26</td>
<td>51.7 (3.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanggi, Clinical Endocrinology 1998</td>
<td>transdermal HRT 20</td>
<td>51.9 (2.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanggi, Clinical Endocrinology 1998</td>
<td>tibolone 28</td>
<td>53.7 (3.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Meeuwsen et al reported a significant effect of tibolone on handgrip strength compared to placebo in post-menopausal women and a trend towards a positive effect on isometric knee extension strength, adjusted for body mass index.

We expect we can not fulfill the secondary aim to see whether there is a difference between tibolone and raloxifene. But we do not want to leave this out, because it is part of the protocol. Tibolone can improve muscle strength and body composition in a positive way. This is already studied and there are several explanations for this effect.

In the paper in the data-analysis section (page 10-11) the analysis of the probably underpowered tibolone – placebo comparison is discussed as follows: “If both show a significant beneficial effect, the difference between tibolone and raloxifene will be analysed. However, this is not expected. After termination of the Tibolone-arm during our study, our concern is that the tibolone-placebo comparison will be underpowered. Analyses will be done with 3 months, 6 months en 12 months (n=44) data to determine whether there is a treatment effect of tibolone. In previous studies with a comparable number of participants or fewer, a significant beneficial effect was reported on body composition after 1 year of treatment (43, 44), so we might find an effect as well.”.

3. A randomization list without stratification using sub-blocks of 12 was computer-generated by the hospital pharmacy of the University Medical Center of Utrecht with computer programm Design, a program based on DOS (1988). In the paper on page 4: The Design and method section this is described as follows: “Participants were randomly assigned by the hospital pharmacy of the University Medical Center of Utrecht using computer program “Design” to one of the three treatment groups in a 1:1:1 ratio after baseline measurements had been taken. The sub-blocks contained 12 numbers.”.

4. The study medication was presented as a double dummy design due to the different form of the tibolone and raloxifene tablets. A placebo tablet matching the alternative treatment accompanied each active treatment. In this way the trial medication was blinded. We added the following to page 4: The Design and Method section to clarify: “We do not expect that unblinding by symptoms will occur. In a diary we actively inquired about leg cramps and flushing. These have been reported to be side effects of raloxifene, but only in 0-10% for leg cramps and more than 10% for flushing (16). Leg cramps also occur often in women of this age.”.

We hope you will consider our manuscript for publication, after the adjustments we made in the manuscript.
Yours sincerely,

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