OBSTETRICS & GYNECOLOGY

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Date: May 24, 2019
To: "Sheryl A Kingsberg" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-803

RE: Manuscript Number ONG-19-803

Bremelanotide for the Treatment of Hypoactive Sexual Desire Disorder: Two Randomized Phase 3 Trials

Dear Dr. Kingsberg:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jun 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Kingsberg and colleagues report results from two RCT's examining bremelanotide for the treatment of hypoactive sexual desire disorder (HSDD). Comments for the authors:

Overall

1. Why are two studies combined into a single analysis? Even if they were of a similar design it may not be statistically valid to simply combine them. The justification for this should be clearly described in the Methods.

Abstract

2. Sample size justification does not need to stated in the Results section.

3. Magnitude of difference in sexual desire and sexual distress should be quantified.

4. Are the outcomes of each individual study statistically significant?

Introduction

5. What RECONNECT stands for should be stated along with the mnemonic.

6. Role of the funding source does not need to be stated in the actual Introduction.

7. At least a sentence or two on the results of the phase II studies should be included.

Methods

8. As above, rationale for conducting and combining two studies should be included.

9. What were the diagnostic criteria for HSDD.

10. What are the actual estimates of efficacy in placebo and treatment arms for sample size calculation? It is unclear from the description.

11. Some description of the setting in which patients were recruited should be included.

Results

12. Anchored responder analysis should be defined.

13. What is the time frame for SSE's described, is this entire study period?

14. Only standard abbreviaitons should be used, TEAE's, etc.

15. The nature of the severe AE's should be noted in the Results.

16. If the studies are the same design with similar populations why are the curves for outcomes so different between the two studies (Figures)?

17. 95% confidence intervals should be included when appropriate (Figure 2).

18. Additional demographics including race, comorbidity, etc, should be included in the demographics table

19. While discussed briefly in the Discussion, some indication of the magnitude of the effect for the drug would be helpful.

Discussion

20. Paragraph recognizing limitations of the study should be included.

21. Similarly, some sort or conclusion paragraph would be useful.

Reviewer #2: This manuscript, submitted under the category of Original Research represents the findings of 2 identical phase 3 trials of a novel on demand injectable medication for the treatment of premenopausal hypoactive sexual desire disorder. The authors acknowledge support and sponsorship of the studies by the drug developer, as well as editorial support. The study drug demonstrated efficacy and a favorable safety profile.

LINES:

44 What does RECONNECT stand for?
45 Does 1:1 mean for every study subject that there is a placebo subject?
46 2 Primary endpoints?
50 The 1267 women randomized is confusing because the following 2 populations are far greater. Maybe this is just the wording but I got caught up on it.
51 Some clarification on these groups: Safety and Efficacy would be helpful
106 Were the 1500 planned subjects representative of the 2 studies or for each one?
125 Were the mechanics of a planned dose that was observed as well as BP assessments to do at all conflicting with the planned sexual activity to occur in 45 minutes? What setting was this in? And how could they have BP checks done at intervals following this if they were meant to be having a sexual encounter???
129 What was assessed in the Safety Evaluation?
132 In what kind of settings were these patients recruited and were they from many centers/clinics?
137 Were postpartum patients excluded?
144-7 It would be helpful to see the detail of these described questions rather than simply a reference to the scales
148 Was there any assessment of the # of doses of the study drug plotted against # of SSE's?
166 This number remains confusing, and does state it represents both studies. Also, how many were excluded after screening for the criteria
176 What is meant by the efficacy endpoints were met? Is that just saying the hoped for results were achieved?
201-5 What is the key difference between # of SSE's and percentage?
209 Isn't overall sexual function similar to the primary endpoint of FSFI?
237 Did all SAE's occur in Study 301?
249 The number of subjects that completed the 24 week initial phase is 856?
262 What is dynamic anchor assessment?
264 Is 35% unusually high?
283 But not the key secondary endpoints?
287 Did patients keep diaries?
293 Is this the first mention of tertiary efficacy endpoints?
310 How does this study shield speculation?

Reviewer #3: The authors present the results of two clinical trials of a novel pharmaceutical agent for the treatment of

hypoactive sexual desire disorder. The design of the trials is sound, and for the most part the methodology is described well. There are a few issues that need to be addressed regarding the study description and interpretation of results that are specified below:

Methods:

1. Sample size was calculated for 90% power to describe "the change" in number of SSEs. How much of a change was anticipated to be adequate for demonstration of efficacy, and how was this determined? And how is "satisfying" sexual event defined?

2. How was HSDD diagnosed? Was there a diagnostic interview, and if so was this administered by the research team?

3. Blood pressure measurements were an outcome, but exclusion criteria did not include women with hypertension or using antihypertensives. Was an effect on this subset examined?

4. Also were subjects excluded who concurrently used other agents for treatment of sexual dysfunction (testosterone, flibanserin, herbals)? Was any analysis made of women concurrently using hormonal contraception? If so, please specify.

Results:

5. Patient disposition: Appendix 2 does not clearly show the disposition of the women who were randomized but not included in the safety population or mITT population. A flow chart may be easier to show this information.
Baseline characteristics: Table 1 only shows age and weight (not really a demographic). Were the study populations similar in terms of ethnicity, marital status, education, sexual orientation, etc?

6. The study population is described as being predominantly white and non-Hispanic. Was this because of an inherent racial/ethnic tendency for this disease state, or a lack of diversity/ inclusion in recruitment strategies? Please include ramifications in the discussion section for generalizing the results to other segments of the population.

7. Statistical analysis: Primary endpoints are compared between baseline and end of study. How do the end of study effects compare between the study population and control groups? Cumulative distribution is given, but this does not seem to be the same thing.

8. Secondary endpoints: Line 201 states that the difference in SSEs did not reach statistical significance. Please provide the numbers to illustrate that fact.

9. Lines 205-206 are misleading in describing the data shown in Figure 2. It is not the percentage of SSEs that increased 2-fold in the treatment group, it is the difference in percentages. It would be more straightforward to provide the statistical analysis for the absolute differences between the two groups.

10. Safety: In describing the results on BP measurements, it would be helpful to know the effects in the subset of patients with hypertension. Also, what data was gathered in the open-label extension? Is safety data provided only for the core phase?

Discussion:

11. Lines 293-297 describe tertiary endpoints that were not discussed in the results. If they are not addressed previously, they shouldn't be included here.

12. In addition to discussing the acceptability of the side effects discovered in this trial, it would be helpful to discuss the acceptability in general of using a self-injected medication for sexual dysfunction. Did women in this trial express any reservations about the method of administration?

STATISTICAL EDITOR'S COMMENTS:

1. Abstract and Methods sections: Need to provide a clearer, more complete expression for the sample size/power calculation. Including: there were two co-primary endpoints, so the inference threshold should be .025. Need to specify the expected change from baseline (compared to the placebo control group) for each of the co-primary endpoints.

2. A significant potential problem with the determination of the endpoint scores is on lines 156-158. That is, to be considered as endpoint, a minimum of 1 dose during the treatment vs placebo phase was all that was required to determine the endpoint, since the LOCF method was employed. The Authors need to give a full accounting of how many patients completed the 4, 8, 12,16,20 and 24 week evaluations and what the results were if only those actually completing each interval (ie, not using LOCF) were evaluated.

3. Fig 1: The explanation of how p-values were calculated describes a method that does not compare the beginning vs

endpoints, but rather repeated measures using the change from baseline to all data during wks 4-24. That does not seem to be how the sample-size/power analysis was set up and increases the effective sample sizes.

4. Fig 2: It seems worthwhile to point out for the reader that in the placebo group, the proportion increased 25% from baseline, while in the treatment group, the proportion increased by 63%. In other words, ~ 40% of the relative increase among the treatment group could be attributed to a placebo effect. Also, regarding the earlier queries, how were the endpoint proportions calculated? Wer they also LOCF? If so, what were the proportions without LOCF?

5. Fig 3: Need to clearly separate the co-primary from the secondary outcomes and again, need to address the issue of LOCF.

6. Appendix 2: The withdrew from double blind period was higher for the treatment than the placebo cohorts (42 vs 16% and 44 vs 28% in the two studies. That would seem to have biased the LOCF method. This differential loss to follow-up should be included among limitations.

ASSOCIATE EDITOR - GYN

It is not clear within the text why the authors conducted 2 separate identical RCTs. Reviewer #1 points out it is also unclear why these 2 trials are being published together. We do not have a known precedent to accepting a paper in the original research category wherein 2 trials are combined for publication. We would favor rewriting this manuscript with responses to Reviewer comments on study 301 and separately submitting 302 as a stand-alone manuscript.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
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B. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

3. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the Methods section.

4. Obstetrics & Gynecology follows the Good Publication Practice (GPP3)* guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.

(1) Adherence to the GPP3 guideline should be noted in the cover letter.

(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:
(2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.
(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.
(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.

(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.
(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s).

(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:
"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above).

*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med 2015;163:461-4.

5. Was this study presented as a poster at the 2018 Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists? If so, please note the name, dates, and location of the meeting in your cover letter.

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and print appendixes) but exclude references.

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* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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11. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com

/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

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If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jun 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

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2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

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