

OBSTETRICS & GYNECOLOGY



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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:
obgyn@greenjournal.org.

Date: Aug 13, 2018
To: "Kazuaki Enya" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1223

RE: Manuscript Number ONG-18-1223

Oral Gonadotropin Releasing Hormone Antagonist Relugolix Versus Leuporelin Injections: A Randomized, Controlled, Phase 3 Study in Uterine Fibroids

Dear Dr. Enya:

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 Sep 03, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is an interesting manuscript with a purpose to "investigate the noninferiority of relugolix versus leuporelin acetate in reducing heavy menstrual bleeding (HMB) associated with uterine fibroids (UF). This is a multicenter, prospective, double-blind, double-dummy, noninferiority study conducted for 24 weeks and follow-up of 4 weeks.

1. Why did the authors evaluate their primary objective of noninferiority at 12 weeks instead of at completion of the treatment at 24 weeks? At 24 weeks of treatment was relugolix still noninferior to leuporelin acetate?
2. The authors note that "myoma and uterine volumes measured by transvaginal ultrasound". What type of ultrasound machine and vaginal probe was used to conduct the ultrasounds? Who performed the ultrasounds? Who interpreted and recorded the dimensions of the fibroids? Were the ultrasounds and measurements performed one time or replicates? What formulas were used to calculate volume?
3. Could the authors expand on the discussion of Numerical Rating Scale? How is the NRS administered? Who administered the NRS?
4. Could the authors expand on the mechanism of action of GnRH agonists? How does the elevated GnRH levels induce the "negative feedback loop"?
5. The authors note that relugolix 40 mg was administered daily. How did they measure compliance (which they noted was >99%) with taking the daily relugolix? The authors note that most of the non-responders in the relugolix group who completed week 24 had at least one estradiol level of >20 pg/mL. What were the FSH and LH levels in these patients with elevated estradiol? Had the subjects with elevated estradiol missed any relugolix doses?
6. Could the patients use tranexamic acid during the study? Is tranexamic acid over-the-counter or prescription in Japan?
7. The authors note that "Menstruation was recovered in almost all patients in both groups." How many subjects did not menstruate after completing treatment? How long were these individuals followed-up? Why did they not have restoration of menstrual function after stopping therapy?

Reviewer #2:

Thank you for the opportunity to review this study of oral relugolix compared to IM Leuporelin in a randomized, double-blinded fashion.

The study is well done. The submission is well written. I only have a few comments.

Line 177: What is "severe" interstitial cystitis? Is there a scale used and thus some of these patients were mild or moderate? May be better to say "abdominal pain not related to the female reproductive tract" or just remove the word severe.

Line 295: I would think a paragraph devoted to amenorrhea would be good. Not only is the oral medicine faster to PBAC<10 but faster to a PBAC=0. Keep the data reporting in chronological order--that is useful (i.e., write about the first study period first and the last study period last).

Line 388-389: Would also affect the route of the hysterectomy as well.

Line 401: Is there a way to measure the non-compliance? Can you determine how much of the drug is in the system? Did the non-responders have low levels of estradiol at some points in the study (like the beginning) but then have them go up in the 18-24 week period? Maybe there are some fast metabolizers? Was there a correlation with those who had higher estradiol levels to any complications--liver enzymes, etc.? I agree that it is probably non-compliance but it could also be shorter half life in some patients.

Line 424 and 426: I would choose one name for the White/Caucasian ethnic group, not both.

The tables have no p-values. I'm not a statistician, but I like seeing p-values as they tell me whether the difference is statistically significant or not. Also, the tables list the confidence intervals to the hundredth decimal point but the data only to the tenth. Is the hundredth decimal point significant or even relevant? Listing that extra column just bogs down the table and makes it harder to read.

Figure 3: If you could put on the figure y-axis the 20 pg/mL number, that would make the table a bit friendlier to read.

Thank you again for the opportunity to review this submission.

Reviewer #3:

General Comments:

This study presents the results of a randomized, double blinded, placebo-controlled trial comparing oral relugolix and a monthly leuporelin acetate injection. It is a well-designed and executed study and the results are presented in a clear and effective manner. It is important in that it tests the effectiveness (non-inferiority) of an alternative therapy for heavy menstrual bleeding associated with uterine fibroids.

Specific comments:

Line 132 - Should be stressed that GnRH agonists are not considered first line treatments for this problem.

Line 142 - Need to provide a reference for this statement ("without the clinical flare of symptoms associated with...").

Line 143-144 - same as above. Needs reference.

Line 159 - I do not agree that this is "a standard of care". It is more a treatment option for recalcitrant symptoms - not a standard of care. In fact, this would be a non-FDA approved treatment, as the only currently FDA approved use is for: "the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata."

Table I: BMI is lower than might be expected in a randomized group of US women. Any impact of weight on treatment efficacy? You comment on the generalizability based on race, but this could be another important variable (BMI) that could impact results.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 191-192: This use of two dose form for the leuporelin requires more elaboration. Giving a higher dose of leuporelin

based on larger body wgt, if established a priori, is OK, but the second criteria, "symptoms of individual women" needs further explanation. How many women had a dose increase based on symptoms and was the body wgt threshold uniformly adhered to? What symptoms were the basis for a larger dose? If the symptoms included PBAC or related issues of volume or frequency of bleeding, then it would seem that this change could bias the results by ensuring that a subset of women with worse symptoms received a higher dose, and presumably a larger effect. What were the results of the analysis if only the 124 women with the lower dose were evaluated for the primary outcome?

lines 251-253: Need to give further explanation for choice of non-inferiority margin of 15%. What was the basis for stating that this was "considered smaller than the expected smallest effect size of leuporelin"? Need to reference studies, or preferably, a meta analysis or synthesis of several studies to justify this margin. Nowhere in the sample size analysis is there discussion of using 2 dosages for leuporelin, yet the results are aggregated into comparison of leuporelin vs relugolix.

Table 2: Since the primary endpoint (lines 91-92) was the proportion of women with PBAC score < 10 at 6-12 weeks, that should be clearly separated from the other outcomes cited in Table 2. They may be of interest, may be statistically significant, but they were not the basis for the sample size calculation and the primary hypothesis, so they should not be given same degree of emphasis as the primary.

Table 3: The symptom scores and volume scores on Table 3 appear to be highly skewed. If so, (ie, not normally distributed), then should cite as median (IQR or range) and test non-parametrically.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Katie McDermott and she will send it by email – kmcdermott@greenjournal.org.

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3. 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. For publication purposes, the portions of particular importance to industry-sponsored research are below.* Please indicate whether the following statements are true or false, and provide an explanation if necessary:

(a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.

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(e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

*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.

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

5. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

6. 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, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

7. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with the following guidelines:

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- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.

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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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In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

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15. Figure 1: Please upload a new version where the key is not blocking the figure.

Figure 2: Please consider adding exclusion information between screened and randomized and adding a final box to the end (ie, analyzed or completed).

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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 Sep 03, 2018, we will assume you wish to withdraw the manuscript from further consideration.

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Nancy C. Chescheir
Editor in Chief of Obstetrics & Gynecology

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