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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*
- Email correspondence between the editorial office and the authors*

**The corresponding author has opted to make this information publicly available.*

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

Date: Nov 01, 2018
To: "Andrea S Lukes" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1857

RE: Manuscript Number ONG-18-1857

Health-Related Quality of Life Improvement with Ulipristal Acetate for Treatment of Uterine Fibroids

Dear Dr. Lukes:

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 Nov 22, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors present a randomized trial of UPA versus placebo for improvement in QOL in women with symptomatic uterine fibroids. Given the need for non-surgical options for the treatment of fibroids this is an important intervention. Overall this is a well done RCT which answers an important clinical question. Specific comments:

1) Lines 89-91; Given the importance of this work I would add two sentences to summarize the results of the Venus 1 study here.

2) How did you determine if a difference existed between the three interventions? Did you consider utilizing a reliable change statistic?

3) Lines 135-138; How did you determine the 20 point difference as being statistically significant? This is important to assess the validity of your study.

4) Line 155: Your methods section states that the ratio was 1:1:1 for your groups. But this does not appear to be the case if 169 patients were in the placebo group and 215 in the UPA 5 mg group. What is the reason for the difference? This would change some of your statistical analysis as the lack of a true 1:1:1 ratio unbalances your groups.

5) The results section is written in a confusing manner; It would be better to present the data as simply showing the improvement in QOL over placebo and presenting the P value.

6) The limitations of this study should be expounded upon further commenting on the expanded discussion from the Venus trials.

Reviewer #2: Lukes and colleagues present a pooled analysis of 2 multicenter randomized controlled trials evaluating the effects of ulipristal acetate on patient scores on quality of life assessment tools. This is an interesting study that deals with a common gynecologic diagnosis. I have the following questions/comments for the authors:

1- The abstract is succinct and clear.

2- The introduction is well-written. References germane to the topic are included though not exhaustive. The use of the "personal communication" reference seemed strange when Dr. Liu was not included on the referenced paper. As he is on

other papers regarding VENUS I and II, it can be assumed that he is involved. Consider further clarification of involved parties and time line. In addition, when referring people to previous work to outline inclusion/exclusion criteria, study design, etc., make the referenced work clear.

3- Line 89: The confirmation of efficacy is stated but not explained. What metrics were used in the prior iteration?

4- Methods and statistical analyses are appropriate.

5- Table 1: Consider inclusion of p values to reinforce the similarity across groups.

6- The use of validated assessment tools is noted and appreciated.

7- Line 223-230: This seems to be a repeat presentation of results without additional insight or discussion presented. Consider removal or editing to be in line with the discussion section purpose.

8- Strengths and weakness are presented.

9- Line 242: Amenorrhea is mentioned here for the first time in the paper. I could not find data presented regarding this finding in this work in the text or tables. It has been discussed in prior work/reviews but with mixed results. If amenorrhea results available, please present. If not, then consider not bringing it up at this late place in the paper.

10- Table 2 and 3 give a nice overview of the results.

11- Figures 2 and 3 - These are visually helpful. However, including the responder vs non-responder definitions in the legends but nowhere else was a bit surprising. Consider describing this in the body of the paper as well.

Reviewer #3: Thank you for this opportunity to review this manuscript entitled "Health-Related Quality of Life Improvement with Ulipristal Acetate for Treatment of Uterine Fibroids.

This is a pooled analysis to further investigate the effects of Ulipristal Acetate (UPA) on health related quality of life (HRQoL) and symptom severity for patients in the VENUS I and VENUS II studies (phase 3 multicenter, double-blind, placebo-controlled industry sponsored trials).
The manuscript is very well written, and the role of the sponsor was elaborated clearly during the process of the study design, conduct, analysis, interpretation, writing of the report, and decision to publish.

Abstract: well written. It would be great if (meaningful change in the Symptom Severity) would be defined in the abstract.

Introduction: Concise, well written.

Methods: Clear and well written, please explain what is meant by (observed cases were also used) in line 140.

Results/Discussion: well written, well supported with the data.

Reviewer #4: This is a secondary analysis of pooled data from two randomized controlled trials which analyzed the effectiveness of two different treatment doses of Ulipristal Acetate (UPA) for symptoms associated with uterine fibroids. The objective of the current study is to further evaluate the quality of life for women treated with UPA. The authors pooled results from both studies and used a validated measure, the Uterine Fibroid Symptom and Health Related Quality of Life Survey.

1. When establishing responder thresholds, please give more detail on how the different cut-points for "meaningful improvement" were set (i.e. ≥ 20 point for Symptom Severity and Total, and ≥ 30 point for the revised activities scale)?

2. Line 139-140 states that intention to treat (ITT) was used, but that "observed cases" were also included. Please clarify.

3. From Figure 2 it appears that there are approximately 10% of patients in the UPA treatment groups who had a worsening of symptoms (negative change from baseline). It would be interesting to have the authors speculate on reasons for this finding.

4. Reference for Liu et.al should be updated to reflect publication.

STATISTICAL EDITOR COMMENTS:

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

Table 2: It is not clear which of the outcomes is meant to be the primary vs secondary ones. If all are considered as primary, then there are a total of 18 comparisons, so the inference threshold is not strict enough. Also, about 10-15% of data is missing for the 3 cohorts (placebo, 5 mg, 10 mg). What were the baseline characteristics (Table 1) of the missing vs the analyzed data sets?

Table 3: Again, issue of missing data. I presume these are all secondary outcomes, but should be made clearer.

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 Randi Zung and she will send it by email - rzung@greenjournal.org.

- Please consult the Instructions for Authors regarding the use of abbreviations, and what constitutes an acceptable abbreviation. This is not an acceptable abbreviation. Please spell the words out throughout the manuscript.

- Define "longer term".

- You will also need to spell this out throughout the paper.

- Haven't both of these been published? Please reference the papers.

- Given that the HRQOL results were reported in the prior studies, its important in the introduction to tell us why this pooled analysis is important. What will this add?

- is this a planned secondary analysis?

- for clarity, these are the cycle lengths?

- what about liver disease?

- How large is the scale? (ie, what is the range? Is a 20 point difference 20%? Do you have reference for deciding these values were clinically significant? If not, how were they chosen?

- what does this mean? What are 'Observed cases"?

- This methodology will be somewhat opaque to most readers. Can you provide some explanation so people know how to interpret the results?

- For data presented in the text, please provide the raw numbers as well as data such as percentages, effect size (OR, RR, etc) as appropriate and 95% CI's.

- Can you also point out how many women in the different treatment groups reported a stable, or worsening QOL and symptoms?

- So in discussion, it looks like it will be important to note that about 1/2 of the improvement was perhaps placebo related, if I'm reading this correctly.

- Important not to repeat information from introduction in the discussion, unless for specific reason. Ideally, would be in one or the other.

- the tested treatment regimens are for 12 weeks. How does this relate to your comment on line 208 and earlier

about looking for "longer term". Is this longer than off label uses of TXA and GRH agonists?

2. 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:
1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

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. 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.

(b) 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.

(c) 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.

(d) 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.

(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.

5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), and quality improvement in health care (ie, SQUIRE 2.0). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, or SQUIRE 2.0 guidelines, as appropriate.

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 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.

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

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

8. Title: Please delete "Improvement" from the title.

9. Please include the following on your title page: "Presented in part as an oral presentation at The American Society for Reproductive Medicine Annual Meeting in Denver, Colorado, October 6–10, 2018."

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

* All financial support of the study must be acknowledged.
* 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.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal's author agreement form verifies that permission has been obtained from all named persons.
* 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).

11. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

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.

12. 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.

13. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

14. Please round all p-values to a maximum of three decimal places.

15. Please express outcome data as both absolute and relative effects since information presented this way is much more useful for clinicians. In both the Abstract and the Results section of the manuscript, please give actual numbers and percentages in addition to odds ratios (OR) or relative risk (RR). If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in dollar amounts.

16. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

17. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly. If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at http://www.acog.org/Resources-And-Publications.

18. Figures 1–3: All figures are okay to resubmit as-is; however, they might be easier to read in color (especially Figure 3).

19. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response

to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 Nov 22, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

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In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.

[redacted]

Nancy C. Chescheir, MD

Editor-in-Chief, *Obstetrics & Gynecology*

409 12th Street, SW

Washington DC 20024

December 20, 2018

Dear Dr. Chescheir,

Thank you for your consideration of our manuscript – "Health-Related Quality of Life with Ulipristal Acetate for Treatment of Uterine Fibroids" – and for the thorough review comments from you, the statistical editor, and reviewers. We have listed our responses to these comments in the following table.

As the lead author, I affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. We have followed the CONSORT guidelines within this manuscript, as appropriate.

We hope that you will find our revised manuscript suitable for publication by *Obstetrics & Gynecology*. Many thanks for your time and consideration.

Yours sincerely,

Andrea S. Lukes, MD, MHSc, FACOG

Women's Wellness Clinic

[redacted]

ONG-18-1857: Health-Related Quality of Life ~~Improvement~~ with Ulipristal Acetate for Treatment of Uterine Fibroids

We would like to thank the reviewers and editors for their time in reviewing our manuscript and for the insightful comments provided. We have addressed the comments as detailed in the table below, with revisions in blue text, and have provided a "track changes" version of the manuscript. We thank you for your consideration of our manuscript for publication and look forward to your response.

Reviewers' comments	**Response**
Reviewer #1: The authors present a randomized trial of UPA versus placebo for improvement in QOL in women with symptomatic uterine fibroids. Given the need for non-surgical options for the treatment of fibroids this is an important intervention. Overall this is a well done RCT which answers an important clinical question. Specific comments:	
Lines 89-91; Given the importance of this work I would add two sentences to summarize the results of the Venus 1 study here.	We have briefly summarized the co-primary endpoint findings from VENUS I and II, in order to remain within the Introduction limit of 250 words, as follows: "Two pivotal phase 3 studies – VENUS I and VENUS II – confirmed the efficacy of ulipristal for the treatment of women with symptomatic uterine fibroids: in both studies, rate of and time to amenorrhea was superior for ulipristal 5 mg or 10 mg compared to placebo (P<.001)."

[redacted]

2) How did you determine if a difference existed between the three interventions? Did you consider utilizing a reliable change statistic?	The pooled analysis conducted was consistent with the pooled analyses that were part of the pre-specified analyses for the VENUS I and II trials. We have included clarification of the significance threshold in the Methods section on page 10: "All statistical tests were two-sided hypothesis tests performed at the 2.5% level of significance, ie, an *a priori P* value of .05 was set, unless otherwise mentioned." In the Results section, we explain that there were significantly greater improvements from baseline in UFS-QOL scale scores with ulipristal 5 mg and 10 mg vs placebo, as evidenced by significant least-square mean differences vs placebo ($P<.001$). Furthermore, significantly more patients treated with ulipristal vs placebo achieved a meaningful response on the Symptom Severity scale, HRQoL Total scale, and Revised Activities subscale ($P<.001$).
3) Lines 135-138; How did you determine the 20 point difference as being statistically significant? This is important to assess the validity of your study.	The results of a responsiveness analysis of the UFS-QOL form part of a separate study by Dr. Coyne and colleagues, which has recently been submitted to *Obstetrics & Gynecology*. The ≥20-point and ≥30-point responder thresholds were determined using a triangulation approach considering distribution-based, clinical

[redacted]

	relevancy-based, and anchor-based analyses, as noted on page 10. We have clarified that this was a separate study and have included reference to an abstract published in *Fertil Steril* describing the results of the responsiveness analysis, rather than personal communication with Dr. Coyne.
4) Line 155: Your methods section states that the ratio was 1:1:1 for your groups. But this does not appear to be the case if 169 patients were in the placebo group and 215 in the UPA 5 mg group. What is the reason for the difference? This would change some of your statistical analysis as the lack of a true 1:1:1 ratio unbalances your groups.	The randomization ratio in VENUS I was 1:1:1. In VENUS II the ratio was 1:1:2:1:2:1, as depicted in Fig. 1; therefore, more patients were randomized to ulipristal than to placebo. We have amended the Methods on page 8 to provide clarification: "In VENUS II, patients were randomized to one of six treatment arms in a 1:1:2:1:2:1 ratio, with course 1, course 2 dosing of placebo, ulipristal 5 mg; placebo, ulipristal 10 mg; ulipristal 5 mg, 5 mg; ulipristal 5 mg, placebo; ulipristal 10 mg, 10 mg; ulipristal 10 mg, placebo (Fig. 1B)."
5) The results section is written in a confusing manner; It would be better to present the data as simply showing the improvement in QOL over placebo and presenting the P value.	In the Results section, on pages 11–13, we have decribed the improvements in quality of life, as measured by the UFS-QOL scales and subscales, with ulipristal compared to placebo and have presented *P* values. For example: "The least-square mean differences on the UFS-QOL Revised Activities subscale score in the ulipristal 5 and 10 mg groups vs placebo (97.5% CI) were

	34.0 (27.6–40.4) and 42.2 (35.6–48.7) (both *P*<.001)". We, therefore, feel that no revisions are required in this regard.
6) The limitations of this study should be expounded upon further commenting on the expanded discussion from the Venus trials.	The scope of this analysis is the UFS-QOL, and the limitations in relation to this questionnaire and the pooled analyses employed in this study are described in the Discussion.
Reviewer #2: Lukes and colleagues present a pooled analysis of 2 multicenter randomized controlled trials evaluating the effects of ulipristal acetate on patient scores on quality of life assessment tools. This is an interesting study that deals with a common gynecologic diagnosis. I have the following questions/comments for the authors:	
1- The abstract is succinct and clear.	No revisions required.
2- The introduction is well-written. References germane to the topic are included though not exhaustive. The use of the "personal communication" reference seemed strange when Dr. Liu was not included on the referenced paper. As he is on other papers regarding VENUS I and II, it can be assumed that he is involved. Consider further clarification of involved parties and time line. In addition, when referring people to previous work to outline inclusion/exclusion criteria, study design, etc., make the referenced work clear.	At the time of manuscript submission, the VENUS II primary manuscript by Dr. James Liu and colleagues had not been published. We have now been able to update the "Dr. James Liu, personal communication" statement to the published manuscript: Liu JH et al. Ulipristal acetate for treatment of uterine leiomyomas. A randomized controlled trial. Obstet Gynecol 2018;132:1241–51. This appears as reference number 25 throughout the manuscript and in the references list.

	We have also included additional references to the VENUS I and II primary manuscripts within the Methods when describing the study design.
3- Line 89: The confirmation of efficacy is stated but not explained. What metrics were used in the prior iteration?	We have provided further explanation of the efficacy demonstrated by ulipristal, as follows: "Two pivotal phase 3 studies – VENUS I and VENUS II – confirmed the efficacy of ulipristal for the treatment of women with symptomatic uterine fibroids: in both studies, rate of and time to amenorrhea was superior for ulipristal 5 mg or 10 mg compared to placebo (*P*<.001)."
4- Methods and statistical analyses are appropriate.	No revisions required.
5- Table 1: Consider inclusion of p values to reinforce the similarity across groups.	Baseline demographic and clinical characteristics for the pooled data sets were analyzed using descriptive statistics; therefore, no *P* values are available to present in Table 1. However, Table 1 demonstrates that baseline values were very similar across the three groups.
6- The use of validated assessment tools is noted and appreciated.	No revisions required.

7- Line 223-230: This seems to be a repeat presentation of results without additional insight or discussion presented. Consider removal or editing to be in line with the discussion section purpose.	We have deleted this paragraph from the Discussion as advised.
8- Strengths and weakness are presented.	No revisions required.
9- Line 242: Amenorrhea is mentioned here for the first time in the paper. I could not find data presented regarding this finding in this work in the text or tables. It has been discussed in prior work/reviews but with mixed results. If amenorrhea results available, please present. If not, then consider not bringing it up at this late place in the paper.	As above, in response to the comment from Reviewer #1, we have now included reference to amenorrhea in the Introduction of the manuscript, as the rate of and time to amenorrhea were co-primary efficacy endpoints in VENUS I and II. Therefore, we have not revised the mention of amenorrhea in the Discussion.
10- Table 2 and 3 give a nice overview of the results.	No revisions required.
11- Figures 2 and 3 - These are visually helpful. However, including the responder vs non-responder definitions in the legends but nowhere else was a bit surprising. Consider describing this in the body of the paper as well.	We had provided some explanation of the responder thresholds, in the Methods of the manuscript on page 10, and have included reference to an abstract published in *Fertil Steril* describing the results of the responsiveness analysis.
Reviewer #3: Thank you for this opportunity to review this manuscript entitled "Health-Related Quality of Life Improvement with Ulipristal Acetate for Treatment of Uterine Fibroids.	

This is a pooled analysis to further investigate the effects of Ulipristal Acetate (UPA) on health related quality of life (HRQoL) and symptom severity for patients in the VENUS I and VENUS II studies (phase 3 multicenter, double-blind, placebo-controlled industry sponsored trials). The manuscript is very well written, and the role of the sponsor was elaborated clearly during the process of the study design, conduct, analysis, interpretation, writing of the report, and decision to publish.	
Abstract: well written. It would be great if (meaningful change in the Symptom Severity) would be defined in the abstract.	We have included the definitions of meaningful change within the abstract: "The proportion of women achieving meaningful change in the Symptom Severity (≥20-points), HRQoL Total (≥20-points), and Revised Activities (≥30-points) scales was also calculated."
Introduction: Concise, well written.	No revisions required.
Methods: Clear and well written, please explain what is meant by (observed cases were also used) in line 140.	We have provided an explanation of "observed cases", as follows: "The intent-to-treat population, which included all randomized patients, was the primary population for all analyses. Observed cases were also used, including assessments collected at each scheduled visit; this visit type was used in by-visit analyses of the UFS-QOL data."

Results/Discussion: well written, well supported with the data.	No revisions required.
Reviewer #4: This is a secondary analysis of pooled data from two randomized controlled trials which analyzed the effectiveness of two different treatment doses of Ulipristal Acetate (UPA) for symptoms associated with uterine fibroids. The objective of the current study is to further evaluate the quality of life for women treated with UPA. The authors pooled results from both studies and used a validated measure, the Uterine Fibroid Symptom and Health Related Quality of Life Survey.	
1. When establishing responder thresholds, please give more detail on how the different cut-points for "meaningful improvement" were set (i.e. ≥ 20 point for Symptom Severity and Total, and ≥ 30 point for the revised activities scale)?	As noted in response to other reviewers, the results of a responsiveness analysis of the UFS-QOL form part of a separate study by Dr. Coyne and colleagues, which has recently been submitted to *Obstetrics & Gynecology*. The ≥20-point and ≥30-point responder thresholds were determined using a triangulation approach considering distribution-based, clinical relevancy-based, and anchor-based analyses, as noted on page 10. We have clarified that this was a separate study and have included reference to an abstract published in *Fertil Steril* describing the results of the responsiveness analysis, rather than personal communication with Dr. Coyne.
2. Line 139-140 states that intention to treat (ITT) was used, but that "observed cases" were also included. Please clarify.	We have provided an explanation of “observed cases”, as follows: “The intent-to-treat population, which included all randomized patients, was the primary population for all analyses. Observed

	cases were also used, including assessments collected at each scheduled visit; this visit type was used in by-visit analyses of the UFS-QOL data."
3. From Figure 2 it appears that there are approximately 10% of patients in the UPA treatment groups who had a worsening of symptoms (negative change from baseline). It would be interesting to have the authors speculate on reasons for this finding.	The goal of the analyses described within our manuscript was to identify statistically significant differences in HRQoL and symptom severity between ulipristal and placebo. As would be expected in any study of treatment effect, there will always be a proportion of patients who demonstrate non-response or a placebo response. Change from baseline in physical and social activities, as measured by the Revised Activities subscale, will also be influenced by a variety of factors other than the disease itself (eg limitations in social activities due to work or family situations); therefore the key difference is that between ulipristal and placebo. In the primary VENUS I (Simon et al. Obstet Gynecol 2018) and VENUS II (Liu et al. Obstet Gynecol 2018) manuscripts, not all patients receiving ulipristal achieved absence of bleeding or controlled bleeding. In this group of patients, it may be speculated that the lack of treatment effect carried over to the patients' HRQoL and led to a decline from baseline in their physical and social activities. Although the focus of this

	manuscript is improvement in HRQoL and symptom severity, it would be of interest to investigate worsening of these outcomes in patients with symptomatic fibroids in future studies. Also worthwhile would be an investigation in to whether those patients who did not respond to ulipristal had clinical or demographic characteristics that influenced their response (eg, very small or large fibroids, submucosal fibroids, adenomyosis, genetic factors that may affect ulipristal metabolism, very high or low BMI). We have included a short statement in the Discussion on page 14, in response to the reviewer's comment: "Although a small proportion of patients experienced no change or some worsening in these outcomes, the majority of women reported clear improvements, eg, over 70% of patients in the ulipristal treatment arms achieved a meaningful improvement of ≥30 points on the Revised Activities subscale (a 0–100 scale)."
4. Reference for Liu et.al should be updated to reflect publication.	We have now updated the "Dr. James Liu, personal communication" statement to the published manuscript: Liu JH et al. Ulipristal acetate for treatment of uterine leiomyomas. A randomized controlled trial. Obstet Gynecol 2018;132:1241–51. This appears as reference number 25 in the references list.

Statistical editor comments:	
Table 2: It is not clear which of the outcomes is meant to be the primary vs secondary ones. If all are considered as primary, then there are a total of 18 comparisons, so the inference threshold is not strict enough. Also, about 10-15% of data is missing for the 3 cohorts (placebo, 5 mg, 10 mg). What were the baseline characteristics (Table 1) of the missing vs the analyzed data sets?	Information explaining the specific endpoints is provided on page 9 in the Methods, as follows: "Mean change from baseline at the end of treatment course 1 on the Revised Activities subscale score of the UFS-QOL was a pre-specified secondary endpoint in VENUS I and II. Mean change from baseline at end of treatment (VENUS I) or end of treatment courses 1 and 2 (VENUS II) on the UFS-QOL Symptom Severity, HRQoL Total scale, and the other HRQoL subscale scores were other efficacy measurements." We have amended the title of Table 2 to provide clarification: "Table 2. Secondary and Other Efficacy Endpoints: Baseline, End of Treatment, and LS Mean Difference in Change from Baseline in UFS-QOL Scale Scores (Pooled VENUS I and VENUS II)." Unfortunately, baseline characteristics are not available for the missing vs the analyzed data set. All the analyses conducted were based on observed cases with no imputation of missing data; this is the same approach as was used in the primary VENUS I and II trials.

Table 3: Again, issue of missing data. I presume these are all secondary outcomes, but should be made clearer.	As for Table 2, only observed cases were used and data were not imputed, as per the analysis approach employed by the VENUS I and II trials. We have amended the text on page 11 in the Methods to explain that the responder analyses were performed *post hoc*: "Responder analyses for the Symptom Severity and HRQoL Total scales, and the Revised Activities subscale, were performed *post hoc* in the pooled VENUS I and II population (treatment course 1 only)." We have also amended the title of Table 3 as follows: "Table 2. *Post Hoc* Analysis: Meaningful Improvements in UFS-QOL Symptom Severity (≥20-Point), HRQoL Total (≥20-Point), and Revised Activities (≥30-Point) Scale Scores (Pooled VENUS I and VENUS II)."
Editor comments:	
- Please consult the Instructions for Authors regarding the use of abbreviations, and what constitutes an acceptable abbreviation. This is not an acceptable abbreviation. Please spell the words out throughout the manuscript.	Thank you; we have amended "UF" to "uterine fibroids" throughout the manuscript. We note that "UFS-QOL" and "HRQoL" are not in the approved abbreviations list; however, we feel that to spell these in full throughout would considerably detract from the readability of

	the manuscript, since they have long definitions and appear very frequently.
- Define "longer term".	We have revised this sentence so that it is more accurate: “There are no pharmacologic treatments indicated outside of pre-operative use for women with symptomatic uterine fibroids.”
- You will also need to spell this out throughout the paper.	We have amended “UPA” to “ulipristal” throughout the manuscript.
- Haven't both of these been published? Please reference the papers.	We have now updated the “Dr. James Liu, personal communication” statement to the published manuscript: Liu JH et al. Ulipristal acetate for treatment of uterine leiomyomas. A randomized controlled trial. Obstet Gynecol 2018;132:1241–51. This reference appears as number 25 in the references list.
- Given that the HRQOL results were reported in the prior studies, its important in the introduction to tell us why this pooled analysis is important. What will this add?	We have amended the objective in the Introduction as follows: “The objective of this analysis was to provide a more robust and in-depth investigation of the effects of ulipristal on HRQoL and symptom severity for patients in the VENUS I and VENUS II studies.”
- is this a planned secondary analysis?	The pooled analysis was a planned, secondary analysis. The change from baseline to the end of treatment course 1 compared to change from baseline to end of treatment course 2 was a *post*

[redacted]

	hoc analysis; these analyses were important to understand the beneficial effect of ulipristal treatment when moving from placebo, and also to understand the decline in treatment effect when moving from ulipristal to placebo. The responder analyses were also *post hoc* and give context to meaningful improvements in scale change scores, providing tangibility to the HRQoL results from the clinician's perspective. We have provided clarification of the planned, secondary, pooled analysis, as follows: "VENUS I and VENUS II were considered suitable for pooling based on similarities in study design, treatment, study population, and endpoints; the pooled analysis was a planned secondary analysis agreed with the Food and Drug Administration in June 2016."
- for clarity, these are the cycle lengths?	That is correct; we have clarified this by amending the text to read: "(≥22 and ≤35 menstrual cycle length days)."
- what about liver disease?	We have included information on the liver-related exclusion criteria, as follows: "Patients with alanine transaminase, aspartate transaminase, alkaline phosphatase, or total bilirubin ≥2 × the upper limit of normal at screening were excluded."

- How large is the scale? (ie, what is the range? Is a 20 point difference 20%? Do you have reference for deciding these values were clinically significant? If not, how were they chosen?	The UFS-QOL scales (and subscales) range from 0–100 (page 9 of the manuscript). The results of a responsiveness analysis of the UFS-QOL form part of a separate study by Dr. Coyne and colleagues, which has recently been submitted to *Obstetrics & Gynecology*. The ≥20-point and ≥30-point responder thresholds were determined using a triangulation approach considering distribution-based, clinical relevancy-based, and anchor-based analyses, as noted on page 10. We have clarified that this was a separate study and have included reference to an abstract published in *Fertil Steril* describing the results of the responsiveness analysis. The analytic approaches taken are robust and are in line with the FDA's guidance on patient-reported outcomes.
- what does this mean? What are 'Observed cases"?	We have provided an explanation of "observed cases", as follows: "The intent-to-treat population, which included all randomized patients, was the primary population for all analyses. Observed cases were also used, including assessments collected at each scheduled visit; this visit type was used in by-visit analyses of the UFS-QOL data."

- This methodology will be somewhat opaque to most readers. Can you provide some explanation so people know how to interpret the results?	We have provided the following explanation of least-square means on page 10: "Least-square means are adjusted for the terms in the model (study, baseline value, and pooled center) and are less sensitive to missing data."
- For data presented in the text, please provide the raw numbers as well as data such as percentages, effect size (OR, RR, etc) as appropriate and 95% CI's.	In the Results on page 11, we have added the raw number for black or African-American women: "67.4% of women (n=397) were black or African American." On page 12, we have included n values, ORs, and CIs for the percentages of women achieving responder thresholds, as follows: "A ≥20-point improvement for Symptom Severity was achieved by 35.2% of patients (n=51) in the placebo group, 71.4% (n=140) in the ulipristal 5 mg group (OR 4.7; 97.5% CI 2.7–8.2), and 79.6% (n=140) in the ulipristal 10 mg group (OR 7.8; 97.5% CI 4.3–14.2) (Table 3). A ≥20-point improvement for HRQoL Total score was achieved by 35.9% of patients (n=51) in the placebo group, 77.4% (n=151) in the ulipristal 5 mg group (OR 5.8; 97.5% CI 3.3–10.2), and 86.8% (n=151) in the ulipristal 10 mg group (OR 12.5; 97.5% CI 6.5–24.2) (Table 3). A ≥30-point improvement for the Revised Activities subscale was achieved by 34.9% of patients (n=51) in the placebo group,

	73.5% (n=144) in the ulipristal 5 mg group (OR 5.0; 97.5% CI 2.9–8.6), and 80.6% (n=141) in the ulipristal 10 mg group (OR 7.9; 97.5% CI 4.3–14.6) (Table 3 and Fig. 2)."
- Can you also point out how many women in the different treatment groups reported a stable, or worsening QOL and symptoms?	With regard to the pre-specified secondary endpoint, the Revised Activities subscale, the proportion of patients with no change from baseline was approximately 25%, 8%, and 5% in the placebo, ulipristal 5 mg, and ulipristal 10 mg groups, respectively. The proportion of patients with worsening (a score of -10) was approximately 13%, 2%, and 4% in the placebo, ulipristal 5 mg, and ulipristal 10 mg groups, respectively. Similar analyses for the other UFS-QOL scores would be an excellent future research endeavor. We have included additional information about the proportion of women whose Revised Activities score remained stable, on page 12: "A lack of improvement in the Revised Activities subscale was reported by approximately 25%, 8%, and 5% of patients in the placebo, ulipristal 5 mg, and ulipristal 10 mg groups, respectively (Fig. 2)."

- So in discussion, it looks like it will be important to note that about 1/2 of the improvement was perhaps placebo related, if I'm reading this correctly.	The focus of our manuscript is the magnitude of change and to report the significantly greater number of patients in the ulipristal treatment groups compared to the placebo group who achieved a meaningful change in the the Revised Activities subscale. Therefore, we have included a short statement in the Discussion on page 14: "Although a small proportion of patients experienced no change or some worsening in these outcomes, the majority of women reported clear improvements, eg, over 70% of patients in the ulipristal treatment arms achieved a meaningful improvement of ≥30 points on the Revised Activities subscale (a 0–100 scale)."
- Important not to repeat information from introduction in the discussion, unless for specific reason. Ideally, would be in one or the other.	We have deleted the second part of this section sentence so that it now reads: "Hysterectomy continues to be the most common surgical treatment for uterine fibroids, with rates of 21–53% in the United States."
- the tested treatment regimens are for 12 weeks. How does this relate to your comment on line 208 and earlier about looking for "longer term". Is this longer than off label uses of TXA and GRH agonists?	Gonadotropin-releasing hormone agonists, such as leuprolide acetate, are indicated for 3-month administration before uterine fibroid surgery to improve anemia, but are often used for longer, while tranexamic acid is not indicated for the treatment of uterine fibroids yet is still used in its management. We have amended the text to highlight that there are no pharmacologic

[redacted]

	therapies indicated for the treatment of uterine fibroids outside of pre-operative use; therefore, treatments are often used off-label: "With no pharmacologic treatments indicated other than for pre-operative therapy for women with symptomatic uterine fibroids, many are used off-label, including gonadotropin-releasing hormone agonists and tranexamic acid,[33-35] non-steroidal anti-inflammatories, levonorgestrel intrauterine devices, and oral and non-oral combination contraceptives.[34-37] Thus, there is a significant unmet need for oral therapy for the treatment of uterine fibroids that is effective and safe, and can be used both pre- and post-surgery."
2. 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	We would like to OPT-IN, publishing our responses to the revision letter and subsequent email correspondence.

[redacted]

posted. Please reply to this letter with one of two responses: 1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries. 2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.	
3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor. If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.	We had previously included part of this statement and have now included it in full in the cover letter: "As the lead author, I affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."
4. Obstetrics & Gynecology follows the Good Publication Practice (GPP3) guideline for manuscripts that report results that	We can confirm that each of these GPP3 statements is true.

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. (b) 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. (c) 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. (d) 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. (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.	
5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health	We have submitted a completed CONSORT checklist alongside the revised manuscript, and have indicated this in the cover letter.

interventions (ie, CHEERS), and quality improvement in health care (ie, SQUIRE 2.0). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, or SQUIRE 2.0 guidelines, as appropriate.	
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 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.	Thank you; we do not believe any revisions are required based on these definitions.
7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by	The entire manuscript is now 5330 words in length.

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.	The revised Introduction is now 250 words; the revised Discussion is 509 words.
8. Title: Please delete "Improvement" from the title.	As requested, we have deleted “Improvement” from the title.
9. Please include the following on your title page: "Presented in part as an oral presentation at The American Society for Reproductive Medicine Annual Meeting in Denver, Colorado, October 6–10, 2018."	We have included this statement on the title page.
10. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with the following guidelines: * All financial support of the study must be acknowledged. * 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	As above, we have updated the Acknowledgments to include the following statement: “Presented in part as an oral presentation at The American Society for Reproductive Medicine Annual Meeting in Denver, Colorado, October 6–10, 2018.”

directly or indirectly. * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal's author agreement form verifies that permission has been obtained from all named persons. * 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).	
11. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully. In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows:	We can confirm that we have checked the Abstract for inconsistencies against the body of the manuscript. The abstract has a clear conclusion statement. Following the requested revisions, we have made minor amends to the Abstract to limit it to 300 words. The word count is stated on page 6.

Original Research articles, 300 words. Please provide a word count.	
12. 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.	We have amended "UF" to "uterine fibroids" and "UPA" to "ulipristal" throughout the manuscript. We note that "UFS-QOL" and "HRQoL" are not in the approved abbreviations list; however, we feel that to spell these in full throughout would considerably detract from the readability of the manuscript, since they have long definitions and appear very frequently.
13. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.	We have included an updated data-sharing statement on the title page, which does include "and/or". With regard to "Energy/Mood" in the Methods, Tables 2 and 3, and Figs. 2 and 3, we have not amended "Energy/Mood" since this is the specific language of the UFS-QOL questionnaire.
14. Please round all p-values to a maximum of three decimal places.	We have amended all *P* values to three decimal places.
15. Please express outcome data as both absolute and relative effects since information presented this way is much more useful for clinicians. In both the Abstract and the Results section of the manuscript, please give actual numbers and percentages in	In the Abstract, we have included n values and odds ratios for the Revised Activities meaningful change data: "A meaningful change in Revised Activities was achieved by 34.9% (n=51), 73.5% (n=144; odds ratio 5.0), and 80.6% (n=141; odds ratio

addition to odds ratios (OR) or relative risk (RR). If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in dollar amounts.	7.9) of patients receiving placebo, ulipristal 5 mg, and 10 mg, respectively." In the Results section, as noted in response to comment 1, we have added the n value for black or African-American women on page 11, and have included n values, ORs, and CIs for the percentages of women achieving responder thresholds on page 12.
16. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.	We have referred to the Table checklist and amended "(SD)" to "±SD" and included an en-dash instead of comma for CIs.
17. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly. If the reference you are citing has been withdrawn with no clear replacement, please	We have checked the Resources and Publications page and we believe that no update is required to reference number 34: American College of Obstetricians and Gynecologists. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol 2008;112:387–400. This practice bulletin was reaffirmed in 2016.

contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at http://www.acog.org/Resources-And-Publications.	
18. Figures 1–3: All figures are okay to resubmit as-is; however, they might be easier to read in color (especially Figure 3).	Figs. 1–3 have been amended from black and white to color.
19. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.	

Randi Zung

From: Gibbons, Laura (MAN-CHV) [redacted]
Sent: Tuesday, February 5, 2019 12:29 PM
To: Randi Zung
Cc: Andrea Lukes; Loh, Tamalette (CHI-CHV); Blair, Cara (CHI-CHV); Allison, Stephen (MAN-CHV); 91126
Subject: RE: Your Revised Manuscript 18-1857R1

Dear Randi

Many thanks for sharing Dr Chescheir's minor changes to the manuscript 18-1857R1.

On behalf of Dr Lukes, please accept this approval of the amends.

With many thanks and kind regards
Laura

LAURA GIBBONS PhD, ISMPP CMPP™ | SENIOR MEDICAL WRITER | COMPLETE HEALTHVIZION
[redacted]

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www.complete-hv.com

From: Randi Zung <RZung@greenjournal.org>
Sent: 05 February 2019 15:17
To: Gibbons, Laura (MAN-CHV) [redacted]
Cc: Andrea Lukes [redacted] Loh, Tamalette (CHI-CHV) [redacted]; Blair, Cara (CHI-CHV) [redacted]>; Allison, Stephen (MAN-CHV) [redacted]>; 91126 [redacted]
Subject: [EXTERNAL] RE: Your Revised Manuscript 18-1857R1

Dear Dr. Gibbons:

Dr. Chescheir has reviewed your edited version. She has a few minor changes, which are highlighted in green in the attached file (v5).

They are:

- In the Financial Disclosure, Dr. Chescheir says you do not need to state "beyond study sponsorship, or employment, by Allergan" because that information is already captured in the Acknowledgments.
- In the Abstract-Results: She says the data that has been added is okay as-is now. No further edits are needed, but we are making a minor edit to abbreviate "odds ratio" to "OR."

Please let me know if you approve.

Thanks,
Randi

From: Gibbons, Laura (MAN-CHV) [redacted]
Sent: Tuesday, February 5, 2019 9:25 AM
To: Randi Zung <RZung@greenjournal.org>
Cc: Andrea Lukes [redacted] Loh, Tamalette (CHI-CHV) [redacted]; Blair, Cara (CHI-CHV) [redacted]; Allison, Stephen (MAN-CHV) [redacted]>; 91126 [redacted]
Subject: FW: Your Revised Manuscript 18-1857R1
Importance: High

Dear Randi

On behalf of Dr Lukes, please find attached the amended Pooled UFS-QOL manuscript (18-1857R1). We have included the revisions as track changes within the document (in purple) and note the responses to the individual queries below, as requested.

We look forward to hearing from you regarding the journal's decision.

With many thanks and kind regards
Laura

1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.
   - Thank you; we have reviewed and these are correct.

2. eCTA: All authors except Dr. Lukes will need to complete our electronic Copyright Transfer Agreement, which was sent to them from Editorial Manager. The two authors who need to complete the new electronic form are David Soper and Amanda Harrington.
   - We understand that all authors have now completed the electronic Copyright Transfer Agreements

3. Financial Disclosure: Please note the edit to this section. Is this correct?
   - We would like to suggest the following, slightly amended statement: "*The authors did not report any potential conflicts of interest beyond study sponsorship, or employment, by Allergan*"

4. Starting at Line 62: TC is not an acceptable abbreviation. Please eliminate throughout the abstract and paper.
   - We have now removed the abbreviation 'TC' throughout the manuscript

5. Line 74: In the abstract, please provide absolute numbers as well as whichever effect size you are reporting + Confidence intervals. P values may be omitted for space concerns. By absolute values, I mean something like: "xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI=). An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4).
   - We have revised the sentence in the abstract to read: "A meaningful change in Revised Activities was achieved by 51 patients receiving placebo (34.9%), compared with 144 (73.5%; odds ratio 5.0 [97.5% 2.9–8.6]) and 141 (80.6%; odds ratio 7.9 [97.5% 4.3–14.6]) patients receiving ulipristal 5 mg, and 10 mg, respectively."
   - With this change and the other amends within the abstract, the abstract word count is 316 words. To add absolute numbers, effect sizes and confidence intervals for all data presented in the abstract would take it significantly over the word limit.

6. Line 122-123: Please disclose the role of Allergan in the design, execution, and analysis. Answer each part of the question separately. Referencing a prior publication is not appropriate.
   - We have revised this sentence to read: "Allergan (the sponsor) played a role in the design, execution, analysis, reporting, and funding of these studies."

7. Line 128 and elsewhere: The Journal style doesn't not use the virgule (/) except in numeric expressions. Please edit here and in all instances. Should this be "and" or "or"?
   - We have amended to read: "...United States or the European Union..."

8. Line 126-132: This highlighted information is now in the data sharing table. Please add information for last question there re: data use agreement, non-commercial purposes and the website for further information.

- We have added the following information for the last question: "To request access to the data, the researcher must sign a data-use agreement and any shared data are to be used for non-commercial purposes. More information can be found at http://www.allerganclinicaltrials.com/."

9. Line 206: For articles submitted to O&G after July 1, 2018, we require a data sharing statement indicating what we've listed here. Your answers may be different from what I've listed here. If so, please edit the responses accordingly.

- We have amended the response to the last question, as above.

10. Line 206 (Authors' Data Sharing Statement box): Please clarify: Earlier you describe which data and requirements needed to obtain shared data. The statement about data sharing goes here, rather than earlier, and needs to reflect that actual data sharing plan. Perhaps the confusion, and why you indicate different things, is that the questions in the gray box do not all related to Individual participant data, just the first question.

- We have amended the response to the last question, as above.

LAURA GIBBONS PhD, ISMPP CMPP™ | SENIOR MEDICAL WRITER | COMPLETE HEALTHVIZION
[redacted]

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From: Randi Zung
Sent: Wednesday, January 9, 2019 3:40 PM
To: 'andrealukes@cwrwc.com' <[redacted]
Subject: Your Revised Manuscript 18-1857R1

Dear Dr. Lukes:

Your revised manuscript is being reviewed by the Editors. Before a final decision can be made, we need you to address the following queries. Please make the requested changes to the latest version of your manuscript that is attached to this email. **Please track your changes and leave the ones made by the Editorial Office.** Please also note your responses to the author queries in your email message back to me.

1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.

2. eCTA: All authors except Dr. Lukes will need to complete our electronic Copyright Transfer Agreement, which was sent to them from Editorial Manager. The two authors who need to complete the new electronic form are David Soper and Amanda Harrington.

3. Financial Disclosure: Please note the edit to this section. Is this correct?

4. Starting at Line 62: TC is not an acceptable abbreviation. Please eliminate throughout the abstract and paper.

5. Line 74: In the abstract, please provide absolute numbers as well as whichever effect size you are reporting + Confidence intervals. P values may be omitted for space concerns. By absolute values, I mean something like: "xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI=). An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4).

6. Line 122-123: Please disclose the role of Allergan in the design, execution, and analysis. Answer each part of the question separately. Referencing a prior publication is not appropriate.

7. Line 128 and elsewhere: The Journal style doesn't not use the virgule (/) except in numeric expressions. Please edit here and in all instances. Should this be "and" or "or"?

8. Line 126-132: This highlighted information is now in the data sharing table. Please add information for last question there re: data use agreement, non-commercial purposes and the website for further information.

9. Line 206: For articles submitted to O&G after July 1, 2018, we require a data sharing statement indicating what we've listed here. Your answers may be different from what I've listed here. If so, please edit the responses accordingly.

10. Line 206 (Authors' Data Sharing Statement box): Please clarify: Earlier you describe which data and requirements needed to obtain shared data. The statement about data sharing goes here, rather than earlier, and needs to reflect that actual data sharing plan. Perhaps the confusion, and why you indicate different things, is that the questions in the gray box do not all related to Individual participant data, just the first question.

To facilitate the review process, we would appreciate receiving a response within 48 hours.

Best,
Randi Zung

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Randi Zung (Ms.)
Editorial Administrator | *Obstetrics & Gynecology*
American College of Obstetricians and Gynecologists
409 12th Street, SW
Washington, DC 20024-2188
T: 202-314-2341 | F: 202-479-0830
http://www.greenjournal.org

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From: [redacted]
To: Stephanie Casway
Cc: [redacted]
Subject: RE: O&G Figure Revision: 18-1857
Date: Tuesday, January 8, 2019 12:55:10 PM
Attachments: image001.png
18-1857 Legend - amends.pdf

Dear Stephanie

We have been assisting Dr Lukes with the submission of the 18-1857 manuscript to which you refer below.

Many thanks for sharing the edited figures and legend. We request some amends to the legend, as detailed in the attached.

Please let us know if you have any questions at all.

With thanks and kind regards
Laura

LAURA GIBBONS PhD, ISMPP CMPP™ | SENIOR MEDICAL WRITER | COMPLETE HEALTHVIZION
[redacted]

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From: Stephanie Casway <SCasway@greenjournal.org>
Date: January 4, 2019 at 1:16:51 PM EST
To: [redacted]
Subject: O&G Figure Revision: 18-1857

Good Afternoon Dr. Lukes,

Your figures and legend have been edited, and PDFs of the figures and legend are attached for your review. Please review the figures CAREFULLY for any mistakes.

PLEASE NOTE: Any changes to the figures must be made now. Changes at later stages are expensive and time-consuming and may result in the delay of your article's publication.

To avoid a delay, I would be grateful to receive a reply no later than Tuesday, 1/8. Thank you for your help.

Best wishes,

Stephanie Casway, MA
Production Editor
Obstetrics & Gynecology
American College of Obstetricians and Gynecologists
409 12th St, SW
Washington, DC 20024
Ph: (202) 314-2339
Fax: (202) 479-0830
scasway@greenjournal.org

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