OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

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

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Jan 04, 2022
To: "Elizabeth A. Stewart" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-2361

RE: Manuscript Number ONG-21-2361

Relugolix Combination Therapy for Uterine Fibroid–Associated Pain in the LIBERTY Randomized Trials

Dear Dr. Stewart:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

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 Jan 25, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This article's data derives from the double-blinded, randomized LIBERTY 1 and 2 trials. These assessed the oral gonadotropin-releasing hormone antagonist relugolix, alone or in combination with add-back therapy (estradiol plus norethindrone), compared against placebo. Data regarding efficacy for heavy menstrual bleeding (HMB) was published in 2021 in the NEJM (PMID: 33596357).

One limitation is the study's requirement that participants have pain and HMB. Thus, conclusions for those with pain alone cannot be drawn. The authors specify this in their Precis.

Line 41: Uterine volume can contribute to pain symptoms. In describing the findings of the LIBERTY 1 and 2 trials in the Introduction, it might be valuable to add a sentence that also describes the changes in uterine volume with treatment (Table 2 of the NEJM article).

Line 102: For some women, baseline data was gathered over a 7-day time period. This seems to be a short window to establish a baseline pain value. Moreover, data from this short-window would likely reflect menstrual pain or nonmenstrual pain but not both.

Line 157: The read of this sentence was a bit confusing. Are the authors meaning to say: Of these, 277 were compliant with eDiary completion and thus met study pain-evaluation requirements? The current read suggests to me that there were other "pain-evaluation requirements" in addition to a score ≥4 and 80% compliance. Later, the discussion might benefit from author insight as to why 90 of 367 (177 + 190) women (25%) with moderate-to-severe pain were excluded from the pain subpopulation. I am assuming because of not reaching 80% compliance in eDiary entry? The reader may benefit from spelling this out.

Table 1: Again, pain and bulk symptoms are often associated with large uterine volume. In the NEJM's LIBERTY 1 and 2 trial article, uterine volume data is presented in its Table 1. Adding this patient data to your Table 1 would be valuable. Currently, only the "index uterine fibroid (UF)" data is listed.

Line 207: The author's discussion at times presupposes that readers have already read their NEJM article. For our audience, many of whom are busy clinicians, a summary statement that encapsulates the lack of differences found in study arms regarding adverse events, bone mineral density, vital signs, and laboratory tests could be added.

Reviewer #2:

Review of Manuscript ONG-21-2361 "Relugolix combination therapy for uterine fibroid-associated pain in the LIBERTY randomized trials"

A manuscript combining the results of two similar designed and performed randomized controlled trials, the LIBERTY 1 and LIBERTY 2 trials, whose primary objective was to evaluate the interventional therapy on menstrual bleeding symptoms, has been submitted and reports on what appears to be a secondary endpoint of the trial. I have the following questions and comments. Although the authors have appropriately included a CONSORT checklist, a CONSORT flow diagram was not included and may be helpful. Accordingly, this is a summary of a subset of the total trial population of 277 women (54% of the study) that met the pain eligibility inclusion criteria. I have the following questions and comments.

Title - Consideration should be made to note this is a secondary endpoint.

Précis - As this is a secondary endpoint of the RCTs, note this in the precis.

Abstract -
Line 8 - If space allows consider listing clinicaltrials.gov NCT number.

Line 10 - Pain was a secondary objective per the primary manuscript so should be identified as such.

Lines 18-21 - Can you add the 95% CIs here to the reported point estimates?

Introduction -
Line 30 - From these references is there an estimate on the proportion of women with myomas reporting these symptoms?

Line 37 - Considering adding a comment on the rationale of adding hormonal therapy to the GNRH antagonist. Also, as noted later consider noting limitations on the length of time the drug may be used and/or comparisons with other agents that may have a limitation on length of time used.

Methods -
Line 57 - If NCT numbers not listed above could list here.

Line 103 - Perhaps an example of why a flow diagram is helpful as the phrase "…eligible to enroll" was used.

Line 123 - Should this data be presented as supplementary since it supports how you reported the pain outcome(s)?

Results -
Line 182 - Table 2 appears to be duplicated in this sentence and bolded in one instance as well.

Line 204 - Secondary to absence of differences noted here, the referenced figure could be supplementary

Discussion -
Line 208 - I would disagree that pain is underappreciated. It may be undertreated but certainly in my experience not underappreciated.

Line 250 - Consider noting that per the FDA label that this therapy is limited to 24 months and so effective, may be a temporary management.

Tables -
Table 1 - Consider adding the total N in the top row for the 4 list categories / columns.

Table 2 - Again consider adding the total N to the top row for each of the two columns

Figures -
Figure 1 - No comment although I think this should be supplementary and a CONSORT flow diagram should be used in its place.

Figure 2 - No comments

Figure 3 - No comments

Figure 4 - No comments

Figure 5 - As noted above as all favored the intervention, other than age < 40 which was a very small subset, this could be

supplementary

STATISTICAL EDITOR COMMENTS:

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

lines 155-159: Need to include a flow diagram that clearly shows the reader (1) the N enrolled in each trial (2) the N treated in each trial (3) the N with moderate to severe pain at baseline in each trial and (4) the N included in this study's analysis of those with moderate to severe pain. Need to separately show the N for the placebo and treatment groups at each step for each cohort. For those that did not meet the study pain evaluation requirements and were not compliant with eDiary completion (lines 157-159), Need to compare the subset analyzed (in Table 1) vs those excluded (comprised of 177-126 = 51, or 29% of treatment and 190-151= 41, 22% of the placebo group). That comparison is not provided in Table 1. Need to address any issues of selection bias.

lines 98-103 and 124-126: How many (n and %) of women had 7 days of baseline pain scores vs higher number of days in relevant categories? Were women in the latter categories different in demographic or clinical characteristics which may have affected their baseline pain scores? It would seem that the number of days included in baseline pain score would influence the precision of those estimates, not to mention whether a shorter number of days might bias the estimate. More generally, how complete were the data (in terms of eDiary entries) for the women in the placebo vs treatment groups and in various subsets? Were only actual entries included in the estimation of scores or was "Last observation carried forward" used? If so, how often in the various subsets? Again, is there an issue of potential selection bias?

lines 122-124: Need to include this analysis in supplemental material.

lines 155-159, 165-167: If the pain subpopulation included only those with moderate to severe pain, then why were the proportions in the treatment and placebo cohorts reported as 92.9% and 96.0%, respectively, rather than each = 100%? If they did not have moderate to severe pain at baseline, then why were they included in the pain subset for analysis?

Fig 1: Need to define for the reader the "Week 24 Primary endpoint" in figure legend.

Fig 2 legend: What is the distinction between (LIBERTY pooled subpopulations) and "pooled from LIBERTY 1 and 2". If they are the same, then should use same nomenclature.

Fig 2: Since the Non-menstrual pain subpopulation has denominators = 85 and 74, need to round their respective %s to nearest integer %, not cite to 0.1% precision.

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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. 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:

A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

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. Your submission indicates that one or more of the authors is employed by a pharmaceutical company, device company, or other commercial entity. This must be included as a statement in the Financial Disclosure section on the title page.

6. 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 Methods section of the body text, 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 website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the 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.

7. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

8. 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 5,500 words. Stated word limits include the title page,

précis, abstract, text, tables, boxes, and figure legends, but exclude references.

9. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

10. Specific rules govern the use of acknowledgments in the journal. Please note 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 response in the journal's electronic author 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).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

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 limit for Original Research articles is 300 words. Please provide a word count.

12. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

13. 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.

14. 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.

15. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

16. Line 209: Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

17. 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.

18. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting

presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and 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 (exceptions could include manuscripts that address items of historical interest). 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 an ACOG document has been withdrawn, it should not be referenced in your manuscript.

19. Figures 1-5: Please upload as figure files on Editorial Manager.

20. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

21. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at https://wkauthorservices.editage.com/open-access/hybrid.html.

If your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

If you choose open access, you will receive an Open Access Publication Charge letter from the Journal's Publisher, Wolters Kluwer, and instructions on how to submit any open access charges. The email will be from publicationservices@copyright.com with the subject line, "Please Submit Your Open Access Article Publication Charge(s)." Please complete payment of the Open Access charges within 48 hours of receipt.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

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 Jan 25, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason D. Wright, MD
Editor-in-Chief

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

Table: Response to ONG-21-2361 comments

Comment	Response	Location of edits in track-changes revision
Reviewer 1		
1. Line 41: Uterine volume can contribute to pain symptoms. In describing the findings of the LIBERTY 1 and 2 trials in the Introduction, it might be valuable to add a sentence that also describes the changes in uterine volume with treatment (Table 2 of the NEJM article).	We thank the reviewer for raising this point and agree that this result is important for our current analysis. However, since HMB was the primary endpoint of the studies, this measure is retained in the introduction. We have however, included a separate sentence that speaks to the uterine volume result in the Discussion section.	Lines 291-293
2. Line 102: For some women, baseline data was gathered over a 7-day time period. This seems to be a short window to establish a baseline pain value. Moreover, data from this short-window would likely reflect menstrual pain or nonmenstrual pain but not both.	We thank the reviewer for this request for clarification and have added a phrase to the manuscript that clarifies that less than 4% of subjects had less than a week of baseline pain scores and most women had in excess of a month of baseline. Moreover, all women with the week or less of baseline had a menses during that window.	Lines 142-144
3. Line 157: The read of this sentence was a bit confusing. Are the authors meaning to say: Of these, 277 were compliant with eDiary completion and thus met study pain-evaluation requirements? The current read suggests to me that there were other "pain-evaluation requirements" in addition to a score ≥4 and 80% compliance. Later, the discussion might benefit from author insight as to why 90 of 367 (177 + 190) women (25%) with moderate-to-severe pain were excluded from the pain subpopulation. I am assuming because of not reaching 80% compliance in eDiary entry? The reader may benefit from spelling this out.	We thank the reviewer for this recommendation. We have reworded this sentence for clarity and added a flow diagram (Fig. 1) within the manuscript that confirms the exclusions were for < 80% compliance.	Lines 206-208; Fig. 1
4. Table 1: Again, pain and bulk symptoms are often associated with large uterine volume. In the NEJM's LIBERTY 1 and 2 trial article, uterine volume data is presented in its Table 1. Adding this patient data to your Table 1 would be valuable. Currently, only the "index uterine fibroid (UF)" data is listed.	Thank you. We agree that this endpoint is important for the present analyses and have added Uterine Volume in Table 1 as requested.	Table 1

Table: Response to ONG-21-2361 comments

5. Line 207: The author's discussion at times presupposes that readers have already read their NEJM article. For our audience, many of whom are busy clinicians, a summary statement that encapsulates the lack of differences found in study arms regarding adverse events, bone mineral density, vital signs, and laboratory tests could be added.	We thank the reviewer for this suggestion. We expanded the discussion of the findings of the initial NEJM report in the introduction rather than the results section of this study which might be confusing.	Lines 78-82
Reviewer 2		
1. Title - Consideration should be made to note this is a secondary endpoint.	We thank the reviewer for their suggestion, but based on our review of articles published in Obstetrics and Gynecology to date, this does not appear to be journal style (we found no instances of "secondary endpoint" called out in titles). However, our manuscript highlights at several points that pain is a secondary endpoint in the LIBERTY trials: abstract Line 45-49, introduction Line 82, methods Lines 126, 149-153, 164, and 197, results Line 234-237, and discussion section Lines 262-264 and 265-267.	Line 1
2. Précis - As this is a secondary endpoint of the RCTs, note this in the precis.	We have reviewed the possibilities of adding this to the precis. Since we are already at the maximal word limit and consider that all the elements or the current sentence are required for clarity, we propose to retain the precis as-is.	Lines 37-38
3. Abstract - Line 8 - If space allows consider listing clinicaltrials.gov NCT number.	The NCT number was originally excluded to align with the journal's double-blind review requirements. It has now been reinstated at the end of the abstract.	Line 61
4. Line 10 - Pain was a secondary objective per the primary manuscript so should be identified as such.	Thank you, the description of the secondary endpoint has been added as requested on Lines 45-49.	Lines 45-49
5. Lines 18-21 - Can you add the 95% CIs here to the reported point estimates?	Confidence intervals have been added as requested, both to the abstract (Lines 53-57) and to the appropriate results sections (Lines 222-230; 232-235; 252-254) as well as to Fig. 2 and 3.	Lines 53-57; 222-230; 232-235; 252-254
6. Introduction - Line 30 - From these references is there an estimate on the proportion of women with myomas reporting these symptoms?	We thank the reviewer for this question. The epidemiological study conducted in Spain reported that HMB was experienced by 86.6% of women and pain by 49.0% (Monleon J et al. Eur J Obstet Gynecol Reprod Biol 2018 Jul;226:59-65). We have added this point and the accompanying reference to this sentence in the introduction.	Lines 67-68
7. Line 37 - Considering adding a comment on the rationale of adding hormonal therapy to the GNRH antagonist. Also, as noted later consider noting limitations on the length of	Given the limitation of 250 words to the introduction, we have decided to include the rationale for the addition of hormonal therapy in the discussion: "…relugolix monotherapy is associated with a hypoestrogenic state[24] with declines in bone mineral density and vasomotor symptoms, including hot	Lines 288-291 Lines 75-78

Table: Response to ONG-21-2361 comments

time the drug may be used and/or comparisons with other agents that may have a limitation on length of time used.	flashes.[25] The combination of relugolix, estradiol, and NETA was designed to reduce fibroid symptoms while minimizing hypoestrogenic side effects.[14]" Please see Lines 288-291. Regarding the length of time the drug may be used, the 24-month limitation applies to US label only; EU label does not have this restriction. A statement to this effect has been added in the Introduction section, please see Lines 75-78.	
8. Methods - Line 57 - If NCT numbers not listed above could list here.	Thank you, as discussed in point 3 above, the NCT number was originally omitted to align with the journal's double-blind review requirements. It has now been reinstated, please see Lines 61 and 97.	Lines 61 and 97
9. Line 103 - Perhaps an example of why a flow diagram is helpful as the phrase "…eligible to enroll" was used.	Thank you, we have created a flow diagram that outlines how many women met these criteria, please see the updated Fig. 1.	Fig. 1
10. Line 123 – Should this data be presented as supplementary since it supports how you reported the pain outcome(s)?	Thank you, we have included these data into the supplement, please see Appendix 4.	Line 165; Appendix 4
11. Results – Line 182 – Table 2 appears to be duplicated in this sentence and bolded in one instance as well.	Thank you. While our original Word document was correct, when the file was converted to PDF format the duplication appeared. We have ensured that the resubmitted Microsoft Word document does not have this duplication and will double check this after PDF conversion.	–
12. Line 204 – Secondary to absence of differences noted here, the referenced figure could be supplementary	We respectfully disagree and consider, that in this specific manuscript, this is an important subgroup analysis. For clinicians, differences between these subgroups are important and common inquiries. Given that we are not going to publish another manuscript for the subgroups, we propose to retain Fig. 5 within the main text.	–
13. Discussion – Line 208 – I would disagree that pain is underappreciated. It may be undertreated but certainly in my experience not underappreciated.	We thank the reviewer for this insight; we have revised the sentence accordingly, please see Lines 261-262.	Lines 261-262
14. Line 250 – Consider noting that per the FDA label that this therapy is limited to 24 months and so effective, may be a temporary management.	As mentioned in comment 7, the 24-month limitation applies to US label only; the EU label does not have this restriction. We have added a statement to this effect above (Lines 75-78).	Lines 75-78
15. Tables – Table 1 – Consider adding the total N in the top row for the 4 list categories / columns.	We have added the total Ns in the top row of Table 1 as requested.	Table 1

Table: Response to ONG-21-2361 comments

16. Table 2 – Again consider adding the total N to the top row for each of the two columns	We thank the reviewer for this recommendation. For clarity, we have split Table 2 into two tables: 1) for the types of medications used [Table 2] and 2) for the proportion of days of medication use of uterine fibroid-associated pain [Table 3].	Table 2 and Table 3
17. Figures – Figure 1 – No comment although I think this should be supplementary and a CONSORT flow diagram should be used in its place.	Thank you, we have replaced the Study Design figure with a flow diagram (Fig. 1) to show the numbers of patients included in the current analysis and moved the Study Design figure to the supplementary section, as Appendix 1.	Fig. 1; Appendix 1
18. Figure 5 – As noted above as all favored the intervention, other than age < 40 which was a very small subset, this could be supplementary	As discussed in #12 above, we consider this is an important subgroup analysis and we propose to retain this figure within the main text.	Fig. 5
Statistical reviewer		
1. Lines 155-159: Need to include a flow diagram that clearly shows the reader (1) the N enrolled in each trial (2) the N treated in each trial (3) the N with moderate to severe pain at baseline in each trial and (4) the N included in this study's analysis of those with moderate to severe pain. Need to separately show the N for the placebo and treatment groups at each step for each cohort.	We thank the reviewer for this recommendation. We have developed a flow diagram outlining the N enrolled in each trial, the N treated in each trial, the N with moderate-to-severe pain in each trial, and the N included in this analysis of those with moderate-to-severe pain (Fig. 1). In the flow diagram, separate ns are presented for the treatment and placebo group arms.	Fig. 1
2. For those that did not meet the study pain evaluation requirements and were not compliant with eDiary completion (lines 157-159), Need to compare the subset analyzed (in Table 1) vs those excluded (comprised of 177-126 = 51, or 29% of treatment and 190-151= 41, 22% of the placebo group). That comparison is not provided in Table 1. Need to address any issues of selection bias	We thank the reviewer for this recommendation. We have created a flow diagram to illustrate the total number of participants that were eligible for inclusion into these analyses, please see Fig. 1 in the manuscript. We also compared baseline and demographic characteristics of these groups and found no differences.	Fig. 1 Lines 232-234
3. Lines 98-103 and 124-126: How many (n and %) of women had 7 days of baseline pain scores vs higher number of days in relevant categories? Were women in the latter categories different in demographic or clinical characteristics which may have affected their baseline pain scores? It would seem that the number of days included in baseline pain score would influence the precision of those estimates, not to mention whether a shorter number of days might bias the estimate.	As outlined in response for Reviewer 1, Question 2, among the pain evaluable subpopulation (N=277 patients), the number of patients who had 7 or fewer days of baseline pain scores was very low (11/277 or < 4%). Additionally, even when a 7-day window was used, the patient had at least one day of moderate-to-severe pain that made her eligible to be part of the analysis. Since most of the patients (>90%) had 10 or more days of baseline pain scores, there is less issue of potential selection bias and the impact of including such patients in the analysis.	–
4. More generally, how complete were the data (in terms of eDiary entries) for the women in the placebo vs treatment groups and in various subsets? Were only actual entries	We thank the reviewer for this comment, which we interpret as a request for clarification rather than a point to be incorporated in the manuscript.	206-208; 181-185

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included in the estimation of scores or was "Last observation carried forward" used? If so, how often in the various subsets? Again, is there an issue of potential selection bias?	Compliance rates of e-Diary entries were high and similar between the treatment groups in both LIBERTY studies with mean (SD) rate of ~90% (~15%). The median compliance rate was ≥90% across the treatment groups in both studies. Given the high compliance rates observed in the treatment groups on the overall study populations, similar observations were expected in the various subsets. For the key secondary pain endpoint (defined as proportion of patients who had maximum NRS ≤1 during the last 35 days of treatment), the analysis population used to assess the pain-reduction endpoint was the pain-evaluable subpopulation defined as the subgroup of patients who had moderate-to-severe pain at baseline and who had at least 80% compliance with daily electronic diary (eDiary) entry (ie, recording pain scores in at least 28 days) during the last 35 days of treatment. For this analysis, the "Last observation carried forward" approach was used to derive the maximum NRS score among the pain scores recorded during the last 35 days of treatment (ie, either using the Week 24 scores for Week 24 completers or using the scores recorded over the last 35 days of treatment prior to discontinuation of treatment for early terminated patients) to determine their responder status (maximum NRS ≤1), please see Lines 181-185. Since the majority (≥90%) of patients in the pain evaluable subpopulation and its subpopulations (menstrual and non-menstrual) have completed Week 24 visits, there is less issue of potential selection bias in the analyses conducted in these subpopulations.	
5. Lines 122-124: Need to include this analysis in supplemental material.	A demographic table has been included for comparative purposes in Appendix 4, showing baseline characteristics of participants in the pain subpopulation for LIBERTY 1 and LIBERTY 2 separately.	Line 165; Appendix 4
6. Lines 155-159, 165-167: If the pain subpopulation included only those with moderate to severe pain, then why were the proportions in the treatment and placebo cohorts reported as 92.9% and 96.0%, respectively, rather than each = 100%? If they did not have moderate to severe pain at baseline, then why were they included in the pain subset for analysis?	This is a misunderstanding. We refer to 92.9% and 96.0% of patients who reported moderate-to-severe pain on menstrual days, 51.6% and 49.0% reported moderate-to-severe pain on non-menstrual days; and 44.4% and 45.0% of women reported moderate-to-severe pain on both menstrual and non-menstrual days.	Lines 215-217
7. Fig 1: Need to define for the reader the "Week 24 Primary endpoint" in figure legend	Thank you for highlighting this point. As mentioned above, the Study Design figure has been moved from Fig. 1 to Appendix 1.	Appendix 1

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	We have included the definition of the primary endpoint of the LIBERTY studies (defined as proportion of women who had menstrual blood loss volume < 80mL and had at least 50% reduction in MBL at Week 24) in the footnote of Appendix 1 as requested.	
8. Fig 2 legend: What is the distinction between (LIBERTY pooled subpopulations) and "pooled from LIBERTY 1 and 2". If they are the same, then should use same nomenclature.	We thank the reviewer for highlighting this discrepancy. There is no difference between these two phrases. The text has been revised to use the same nomenclature throughout.	Fig. 2
9. Fig 2: Since the Non-menstrual pain subpopulation has denominators = 85 and 74, need to round their respective %s to nearest integer %, not cite to 0.1% precision.	We thank the reviewer for this revision request. For the non-menstrual pain subpopulation, the respective rates have been rounded to the nearest integer in Fig. 2 as requested.	Fig. 2
Editorial comments		
1. The Editors of Obstetrics & Gynecology have increased 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. 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: A. OPT-IN: Yes, please publish my point-by-point response letter. B. OPT-OUT: No, please do not publish my point-by-point response letter.	OPT-IN: Yes, please publish our point-by-point response letter.	–
2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review: * Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).	*Title page information has been included into the main manuscript file. *Funding information has been included on Lines 8-10, 16-17, and 21-33. The Role of the Funding Source section is included after the Introduction and before the Methods section, on Lines 84-94. *Trial registration numbers have been included in the Abstract on Line 61 and in the Methods section on Line 97. *The names of all independent Ethics Committees and Institutional Review Boards are presented in Appendix 2. *The LIBERTY studies were conducted internationally, and the countries are specified in the Methods section, on Line 106 and in Appendix 2.	*– *Lines 8-10, 16-17, 21-33; 84-94 *Lines 61 and 97 *Appendix 2

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* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript. * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable). * Name the IRB or Ethics Committee institution in the Methods section (if applicable). * Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.		*Line 106Appendix 2
3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.	We have checked with the author group and can confirm that all authors have received and completed this form, and that disclosures listed in their eCTA are included on the manuscript's title page.	–
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.	(1) Thank you, we have noted this in the updated cover letter. (2) We attest that all components of this section are accurate. (2a) Accurate (2b) Accurate (2c) Accurate (2d) Accurate (2e) Accurate (3) Included in the abstract, Line 62. (4) Included in the Methods section, Lines 84-94.	(3) Line 62 (4) Lines 84-94

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(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		

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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. Your submission indicates that one or more of the authors is employed by a pharmaceutical company, device company, or other commercial entity. This must be included as a statement in the Financial Disclosure section on the title page.	This disclosure has been included on the title page on Lines 21-33.	Lines 21-33
6. 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 Methods section of the body text, 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 website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the 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.	We have added a sentence stating the study was approved by international review boards as requested and included the comprehensive list of IRBs in supplementary content (Appendix 2).	Lines 100-102; Appendix 2
7. 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 data definitions at https://www.acog.org/practice-	We thank the editor for providing these resources. We have accessed both links and can assert that definitions that fall outside those developed through the reVITALize initiative have not been used in this manuscript.	–

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management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.		
8. 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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.	We thank the editor for his leniency with respect to the word count, especially to the Abstract, Introduction, and Discussion sections. We have been mindful of this word restriction when revising the Abstract Introduction, and Discussion sections, and all-inclusive, the word count is at 5667.	–
9. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.	The title is currently 98 character long, including spaces, and adheres to all of the specified requirements.	Line 1
10. Specific rules govern the use of acknowledgments in the journal. Please note 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 response in the journal's electronic author form verifies that permission has been obtained from all named persons.	We attest that all rules for the acknowledgements section have been satisfied, with no contribution omitted. *All partial presentations of this data have been disclosed on the title page on Lines 11-15. *This manuscript has not been uploaded to a preprint server prior to submitting to *Obstetrics & Gynecology*.	Lines 16-17 *Lines 11-15

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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 limit for Original Research articles is 300 words. Please provide a word count.	The abstract has been revised to take into account the comments put forth by Reviewers 1, 2, and the Statistical editor. The manuscript has been checked thoroughly to avoid inconsistencies of reporting and to ensure that no data included in the abstract is not present in the manuscript proper. We have included 95% confidence intervals to the Results section of the abstract to satisfy the requests of the Reviewer 2, please see Lines 52-57. The abstract is currently 316 words. Again, we are grateful to the editor for the leniency granted to this word count to accommodate the additions as mentioned.	Lines 52-57
12. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.	The abstract has been structured according to the journal's standard format. Given that this manuscript reports on a key secondary outcome of the LIBERTY 1 and 2 studies, the relevant secondary endpoints have been described in detail in the Methods section of the abstract (Lines 43-51). The Methods section describes the primary outcome reported in the primary manuscript with a citation to this publication (Al-Hendy A, et al. N Engl J Med 2021;384(7):630-42). These secondary endpoint analyses, of women with moderate-to-severe UF-associated pain are described in detail and a flow diagram has been created (Fig. 1) to illustrate the number of participants included in each trial arm. For your information, sample size estimation for the primary endpoint of each LIBERTY study is provided at the end of the response (Part I). Given the planned 130 patients per treatment group, assuming about 50% of the patients would be in the pain evaluable subpopulation, responder rates of 10% for placebo and 40% for relugolix-CT, the study would have about 65 patients per group with approximately 90% power to detect a treatment difference of 30%.	Abstract methods: Lines 43-51 Abstract results: Lines 52-57

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	The Results section begins with the dates of enrollment and is followed by a description of patient demographics and the secondary outcome analysis (Lines 52-57) **Part I: Sample Size Estimation for Primary Efficacy Endpoint of LIBERTY Studies** The following assumptions were used to determine the sample size for each LIBERTY study: • 2-sided type I error rate: 0.05 • Randomization: 1:1:1 • Responder rate for placebo group: 25% • Difference in responder rates between the relugolix + E2/NETA group and the placebo group: 30% • Dropout rate: ~20% With the assumption of a dropout rate of 20%, approximately 130 women in the relugolix + E2/NETA group and 130 women in the placebo group will provide at least 99% power at a 2-sided 0.05 significance level to detect a 30% difference in responder rates between relugolix + E2/NETA group and the placebo group for the primary endpoint. With an additional 130 women in the relugolix + delayed E2/NETA group, the total sample size will be approximately 390 women. The assumed responder rate of 25% for the placebo group is within the range of responder rates observed from similar phase 3 trials in uterine fibroids (Gordon et al, 2017). The sample size and power calculations are based on a chi-squared test. **Part II: Projected probability of success for key secondary endpoints in LIBERTY studies**	

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<table>
<tr><td></td><td>
<table>
<tr><th colspan="2" rowspan="2">Key secondary efficacy endpoints</th><th rowspan="2">Analysis population</th><th colspan="2">Hypothesized Treatment Effect Size</th><th rowspan="2">POS[b]</th></tr>
<tr><th>Placebo[a] (N = 130)</th><th>Relugolix + E2/NETA[a] (N = 130)</th></tr>
<tr><td>1.</td><td>Amenorrhea rate</td><td>mITT</td><td>0%</td><td>50%</td><td>99.9%</td></tr>
<tr><td>2.</td><td>% change in MBL</td><td>mITT</td><td>-25% (SD = 85)</td><td>-80% (SD = 85)</td><td>91.1%</td></tr>
<tr><td>3.</td><td>Change in BPD scale</td><td>mITT</td><td>-10 point (SD = 35)</td><td>-30 point (SD = 35)</td><td>85.7%</td></tr>
<tr><td>4.</td><td>Hemoglobin > 2 g/dL</td><td>Subset (~30% of mITT)</td><td>10%</td><td>50%</td><td>80.2%</td></tr>
<tr><td>5.</td><td>Maximum NRS ≤ 1</td><td>Subset (~50% of mITT)</td><td>10%</td><td>40%</td><td>88.7%</td></tr>
<tr><td>6.</td><td>% change in uterine volume</td><td>mITT</td><td>2% (SD = 50)</td><td>-15% (SD = 50)</td><td>63%</td></tr>
<tr><td>7.</td><td>% change in uterine fibroid volume</td><td>mITT</td><td>-5% (SD = 50)</td><td>-20% (SD = 50)</td><td>56.4%</td></tr>
</table>
Abbreviations: BPD = bleeding and pelvic discomfort; E2 = estradiol; MBL = menstrual blood loss; mITT = modified intent-to-treat; N = number of patients; NETA = norethindrone acetate; NRS = numerical rating scale; POS = probability of success; SD = standard deviation.
[a] Based on Takeda relugolix or elagolix phase 2/3 head-to-head comparative data.
[b]For proportion endpoints, considered excluding difference of 10% as a conservative estimate of POS.
</td><td></td></tr>
<tr><td>13. 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.</td><td>We thank the editor for highlighting the journal's requirements regarding abbreviations. We have limited these in the revised manuscript to only those abbreviations appearing in the selected list and published Obstetrics & Gynecology articles. This use of accepted abbreviations has helped us to limit the manuscript word count.</td><td>–</td></tr>
<tr><td>14. 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.</td><td>We thank the editor for highlighting the journal's requirements regarding the use of the virgule symbol. To align with the editorial review and for simplification purposes in the context of the abstract since the full definition is provided in the main text, "week 24/end of treatment" has been revised to "week 24".</td><td>–</td></tr>
<tr><td>15. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the</td><td>We thank the editor for this request. As mentioned above, we have included 95% confidence intervals as requested, both to the abstract (Lines 53-57) and to the appropriate results sections (Lines 222-230; 234-235; 252-254) as well as to Fig. 2 and 3.</td><td>Lines 53-57; 222-230; 234-235; 252-254.

Fig. 5</td></tr>
</table>

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form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone. Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").	Presentation of data has been standardized throughout: P values do not exceed 3 decimal places and Fig. 5 has been revised to align with the percentage decimal point maximum as requested.	
16. Line 209: Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.	We thank the editor for highlighting this point. This claim has been removed.	Line 262
17. 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 reviewed the table checklist and can confirm that all criteria have been satisfied.	–
18. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list. In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.	We thank the editor for providing this resource. Digital identifiers (DOIs) have been included for all cited publications. No ACOG documents were used as citations in the development of this manuscript. All references cited within the body of the manuscript are the updated versions available.	–

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If the reference you are citing has been updated and 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 (exceptions could include manuscripts that address items of historical interest). 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 an ACOG document has been withdrawn, it should not be referenced in your manuscript.		
19. Figures 1-5: Please upload as figure files on Editorial Manager.	We thank the reviewer for this recommendation. All figures have been uploaded individually in the Editorial Manager.	Fig. 1 Fig. 2 Fig. 3 Fig. 4 Fig. 5
20. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.	All supplemental tables and figures have been numbered in the order they are referenced within the text and uploaded individually in the Editorial Manager.	Appendix 1 Appendix 2 Appendix 3 Appendix 4

References

Monleon J et al. Epidemiology of uterine myomas and clinical practice in Spain: An observational study. Eur J Obstet Gynecol Reprod Biol 2018 Jul;226:59-65.

Al-Hendy A, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. N Engl J Med 2021;384(7):630-42.

Gordon K et al. Effective and rapid control of bleeding with elagolix with or without add-back therapy in women with heavy menstrual bleeding associated with uterine fibroids. SEUD 3rd Annual Congress; Abstract 2410; 2017.