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.
RE: Manuscript Number ONG-22-1202

Relugolix Combination Therapy in Women with Symptomatic Uterine Fibroids: Results from the LIBERTY Long-Term Extension Study

Dear Dr. Al-Hendy:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 19, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The manuscript presents the results of a long-term extension study evaluating the outcome of treatment with 52 total weeks of Relugolix combination therapy (Relugolix + estradiol + NEA) for treatment of bleeding due to uterine fibroids. Patients who completed the original Phase 3 Liberty 1 and 2 studies were offered 28 weeks of Relugolix CT treatment (no matter their original treatment arm: placebo, Relugolix-Relugolix CT or Relugolix CT). The primary outcome was the proportion who achieved or maintained a mean blood loss volume <80mL and more than a 50% reduction in MBL from original study baseline to the last 35 days of treatment. Safety was evaluated through adverse events, blood work and bone mineral density monitoring.

The trial was registered at ClinicalTrials.gov.

1. Lines 34-40, Abstract: Please clarify that this data is ONLY the group treated continuously with Relugolix CT for the entire 52 weeks and not for the entire study cohort.

2. Line 57, Introduction: What were the differences between Liberty 1 and 2?

3. Lines 89-90, Methods: Was there any lapse or wash-out period or did treatment continue without lapse between Liberty 1 or 2 and the extension study?

4. Line 97 and 115, Methods: I recommend re-stating for clarity that pivotal study baseline means the original Liberty 1 or 2 study baseline.

5. Line 98, Methods: Please briefly describe the alkaline hematin method.

6. Line 100, Methods: Please spell out NRS.
7. Lines 141-144, Results and Table 1: Please specify if these were baseline characteristics from the pivotal study or from start of the long-term extension study. If these are from extension study baseline, why would there be a higher MBL at baseline in the Relugolix-CT group?

8. Line 166, Results: Please spell out LS.

9. Line 195, Results: Please specify what some of the serious adverse events were.

10. Lines 264-265, Discussion: This sentence seems fragmentary and out of place.

11. Table 2 is very busy. Consider simplifying if no internal statistical comparisons were made or move to supplemental data.

12. Figure 1: Under "Relugolix-Relugolix CT" the % completed looks incorrect.

13. Consider moving figure 7 to supplemental.

Reviewer #2:

Description of Study:
This study is an extension of LIBERTY 1 and 2 wherein relugolix combination therapy (CT) was initiated or extended past the initial study of 24 weeks to 52 weeks. LIBERTY 1 and 2 demonstrated improvement in symptoms related to uterine fibroids including quantitative menstrual blood loss. Relugolix acts as a GnRH antagonist and initial studies of monotherapy demonstrated adverse effects including bone loss, but combination therapy with an estrogen and progestin demonstrated preserved bone mineral density and decreased vasomotor symptoms. For this trial, LIBERTY participants who met inclusion criteria were offered extension on relugolix CT for a total of 52 weeks. All three groups showed improvement in uterine fibroid related symptoms including heavy menstrual bleeding and decreased fibroid disease burden. The group who received relugolix CT for the full 52 weeks (n=163) demonstrated sustained improvement in symptomatic uterine fibroids and preserved bone mineral density without added safety concerns or significant untoward events.

Abstract
In discussing enrollment, consider clarifying there were 3 groups of women who participated in the extension: placebo > relugolix CT, relugolix > relugolix CT, and relugolix CT.

Results
For the paragraph starting on line 170, comparisons between placebo > relugolix CT and relugolix> relugolix CT are not in parallel. Meaning, the first comparison has placebo first then relugolix group (lines 171-172), the second has relugolix first then placebo (lines 172-174), etc. It is easier to follow if the comparison groups are in the same order throughout the paragraph.

Discussion
Line 237-242- the data on decreased uterine/fibroid volume size could be included in the results section. The figures are helpful, but a brief statement in the body of text could help providers consider relugolix for decreasing fibroid size prior to definitive surgical management- myomectomy or hysterectomy- to improve the likelihood of a minimally invasive surgical approach.

Reviewer #3: In the manuscript under review: Relugolix Combination Therapy in Women with Symptomatic Uterine Fibroids: Results from the 3 LIBERTY Long-Term Extension Study- report the long-term efficacy and safety of relugolix CT treatment for 25 up to 52 week

1. A clear objective is stated, no issues noted
2. Very well written study, has clearly elicited long term efficacy and safety
3. Questions for author did any patient received iron therapy while on study?
4. Add on extension trial showed additional decrease in bone density but minimal to have significant effect. Overall the extension of the treatment is safe.
STATISTICAL EDITOR COMMENTS:

Fig 1: The third arm of the flow diagram (Relugolix -> Relugolix CT) completed 108 should be 72% of n = 150, not 99.3%.

Moreover, of the aggregate of the original randomized (n = 760), then completed (n = 610), then enrolled in LTE (n = 477), the completed cohort has n = 363. That is, only ~ 1/2 of the original cohort is represented in the 52-week final analyzed cohort. Need to demonstrate that this cohort is representative of the original randomized cohort in baseline demographic and clinical characteristics. This would allow for generalization of these conclusions to the original population. Without that analysis, there is potential for selection bias, since ~ 1/2 of cohort was absent from analysis. Table 1 simply compares the baseline variables of the treated tier in Fig 1, not a comparison of all treated vs the others in the original trials.

Table 2: This is important but does not address the responder rates compared to the original trials.

Fig 2A, 2B, 2C; 4A, 4B: Should state in figure legends whether there is any statistical difference in the three proportions.

Fig 3, 5, 6, 7, 8, 9: Should state in figure legend any statistical differences by time epoch and cohort.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

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:
   * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
   * 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’s Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/Junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals’ race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories.

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts /Race_and_Ethnicity.pdf.

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled
"women"; "women with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

6. The journal follows ACOG's Statement of Policy on Inclusive Language (https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language). When possible, please avoid using gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;" "patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."

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

(4) The title page should describe how the funder was or was not involved in the manuscript.

8. 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.

9. Please add whether you received IRB or Ethics Committee approval or exemption to your Methods. Include the name of the IRB or Ethics Committee. If you received an exemption, explain why in this section.

10. 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.

11. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

12. For your title, please note the following style points and make edits as needed:
* 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 should not be used.
* Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," "A Systematic Review," or "A Cost-Effectiveness Analysis" as appropriate, in the subtitle. If your manuscript is not one of these four types, do not specify the type of manuscript in the title.

13. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:
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 or indicate whether the meeting was held virtually).

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]."

Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

Was this presented at a meeting? If so, please disclose it on the title page.

Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

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.

The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

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").

Express all percentages to one decimal place (for example, 11.1"). Do not use whole numbers for percentages.

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

Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. 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 formal reference list. Please cite them on the line in parentheses.

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. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

Figures: Please upload all figures as figure files on Editorial Manager.

Figure 1: In the discontinued box for placebo to Relugolix CT, should withdrawal by patient be 11?
21. 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.

22. 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 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 a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

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

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 19, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason D. Wright, MD
Editor-in-Chief

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.
Dear Professor Wright,

Thank you for your consideration of our manuscript entitled "Relugolix Combination Therapy in Women with Symptomatic Uterine Fibroids: Results from the LIBERTY Long-Term Extension Study" (Manuscript Number ONG-22-1202) and for the opportunity to respond to the reviewer comments.

Per your request, we have provided a point-by-point response in the table below addressing each reviewer comment. We have also included a revised manuscript for your consideration (both ‘track changes’ and ‘clean’ versions of the manuscript are included). We include all the reviewers’ comments in the table below and respond to them. Below our responses to reviewers’ comments, we included a point-by-point response to the ‘Editorial points’ and confirm we have adhered to the guidance provided.

Per your letter, we also wish to confirm that this manuscript was prepared in adherence to the GPP3 guideline. As you have requested, we would also like to indicate whether the following statements are true or false (answer in bold text):

(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. **TRUE**

(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. **TRUE**

(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. **TRUE**

(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. **TRUE**

(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation. **TRUE**
Please note we did update the primary endpoint data in Figure 2 (and corresponding text) in the revised manuscript to reflect the final clinical study report data. The changes did not impact the interpretation of the study results and no other data was changed in the manuscript.

Please let us know if there is any additional information that would be helpful to facilitate the review process. The reviewer comments are very helpful and have provided us an opportunity to improve the quality of the manuscript. We look forward to addressing any further comments or providing additional information as needed.

Thank you in advance for your consideration.

Kind regards,

Ayman Al-Hendy
Department of Obstetrics and Gynecology
University of Chicago,
5841 S Maryland Avenue
Chicago, IL 60637
### Table: Response review comments

<table>
<thead>
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<td><strong>Reviewer #1:</strong>&lt;br&gt;The manuscript presents the results of a long-term extension study evaluating the outcome of treatment with 52 total weeks of Relugolix combination therapy (Relugolix + estradiol + NEA) for treatment of bleeding due to uterine fibroids. Patients who completed the original Phase 3 Liberta 1 and 2 studies were offered 28 weeks of Relugolix CT treatment (no matter their original treatment arm: placebo, Relugolix-Relugolix CT or Relugolix CT). The primary outcome was the proportion who achieved or maintained a mean blood loss volume &lt;80mL and more than a 50% reduction in MBL from original study baseline to the last 35 days of treatment. Safety was evaluated through adverse events, blood work and bone mineral density monitoring.&lt;br&gt;&lt;br&gt;The trial was registered at ClinicalTrials.gov.</td>
<td></td>
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<tr>
<td>1. Lines 34-40, Abstract: Please clarify that this data is ONLY the group treated continuously with Relugolix CT for the entire 52 weeks and not for the entire study cohort.</td>
<td>Manuscript is focused on women who were continuously treated up to 52 weeks with relugolix-CT, however, it also includes results in patients who were transitioned to Relugolix-CT from placebo, or were initiated with Relugolix monotherapy over the first 12 weeks in the pivotal studies and then transitioned to Relugolix CT.</td>
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<td>2. Line 57, Introduction: What were the differences between Liberta 1 and 2?</td>
<td>LIBERTY 1 and 2 are replicate studies, identical in study designs features, with minor differences in PK and PD sampling and endometriosis biopsies. The decision to conduct two replicate studies is based on FDA Guidance, “Demonstrating Substantial Evidence of Effectiveness for”</td>
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Human Drug and Biological Products.” Two adequate and well-controlled trials help to establish effectiveness by demonstrating reproducibility of the findings. While one large trial could have been conducted to demonstrate effectiveness, concerns about introduction of bias could limit generalizability in that a positive finding could be attributed to a chance occurrence. Therefore, two trials were conducted to confirm the clinical outcomes. A similar approach was followed for the endometriosis program with relugolix combination therapy.

We added some brief text to note that the two studies were replicate, independent, and run in parallel.

References

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, US Department of Health and Human Services, Food and Drug Administration. https://www.fda.gov/media/133660/download

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<td>3. Lines 89-90, Methods: Was there any lapse or wash-out period or did treatment continue without lapse between Liberty 1 or 2 and the extension study?</td>
<td>LIBERTY 1 and 2 were separate studies. Patients who completed LIBERTY 1 and 2 and were eligible for the 28-week extension study and interested women were enrolled into the extension study where all participants received open-label Relugolix-CT. We added some brief text to indicate that there were not any treatment breaks between the pivotal studies and the LTE.</td>
<td>142-144</td>
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<td>4. Line 97 and 115, Methods: I recommend re-stating for clarity that pivotal study baseline means the original Liberty 1 or 2 study baseline.</td>
<td>We have added 'Liberty 1 &amp; 2' for clarity in the manuscript by the pivotal study baseline.</td>
<td>133</td>
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<td>5. Line 98, Methods: Please briefly describe the alkaline hematin method.</td>
<td>We have added a brief description of this method in the Methods section</td>
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<td>We have now spelled out NRS</td>
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<td>7. Lines 141-144, Results and Table 1: Please specify if these were baseline characteristics from the pivotal study or from start of the long-term extension study. If these are from extension study baseline, why would there be a higher MBL at baseline in the Relugolix-CT group?</td>
<td>We state in the table 1 data are from LIBERTY 1 and 2 baseline. Therefore, all baseline characteristics reflect the status prior to treatment initiation. Only patients included who entered in the LTE as reflected in the Title: Baseline Characteristics for Long Term Extension Population by LIBERTY 1 and LIBERTY Randomized Treatment Assignment (data are from LIBERTY 1 and 2 baseline)</td>
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<td>8. Line 166, Results: Please spell out LS</td>
<td>We have now spelled out LS</td>
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<td>9. Line 195, Results: Please specify what some of the serious adverse events were.</td>
<td>In the long-term extension, there was a single report of uterine hemorrhage in the relugolix-CT group, five events in the delayed relugolix-CT group including bone fracture, events of cholecystitis/cholelithiasis, and worsening uterine leiomyoma, and 11 events in the placebo → relugolix CT group including menorrhagia, appendicitis, cholelithiasis, atrial fibrillation, blood pressure increased, and intervertebral disc protrusion. The disproportionately greater incidence of serious adverse events in the placebo → relugolix CT group during the long-term extension study is mainly driven by serious adverse events across multiple system organ classes that are reflective of general conditions and unlikely to be related to treatment.</td>
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10. Lines 264-265, Discussion: This sentence seems fragmentary and out of place

**Comment:** We have reworded this sentence for better readability. The new sentence is: Therefore, a therapeutic agent that is well-tolerated and provides effective long-term management of symptoms associated with uterine fibroids may help address a significant medical need as well as help support patient demands and choice for new uterus-preserving treatments.¹⁹

**Location of edits in track changes revision:** 355-359

11. Table 2 is very busy. Consider simplifying if no internal statistical comparisons were made or move to supplemental data.

**Response:** Per your suggestion, we have moved Table 2 to the supplemental appendix.

12. Figure 1: Under "Relugolix-Relugolix CT" the % completed looks incorrect.

**Response:** This value has been updated to 72.0%.

13. Consider moving figure 7 to supplemental.

**Response:** Per your suggestion, we have moved Figure 7 to the supplement.

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**Reviewer #2**

*Description of Study:*

This study is an extension of LIBERTY 1 and 2 wherein relugolix combination therapy (CT) was initiated or extended past the initial study of 24 weeks to 52 weeks. LIBERTY 1 and 2 demonstrated improvement in symptoms related to uterine fibroids including quantitative menstrual blood loss. Relugolix acts as a GnRH antagonist and initial studies of monotherapy demonstrated adverse effects including bone loss, but combination therapy with an estrogen and progestin demonstrated preserved bone mineral density and decreased vasomotor symptoms. For this trial, LIBERTY participants who met inclusion criteria were offered extension on relugolix CT for a total of 52 weeks. All three groups showed improvement in uterine fibroid related symptoms including heavy menstrual bleeding and decreased fibroid disease burden. The group who received relugolix CT for the full 52 weeks (n=163) demonstrated sustained improvement in symptomatic uterine fibroids and preserved bone mineral density without added safety concerns or significant untoward events.
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<td><strong>Abstract</strong>&lt;br&gt;In discussing enrollment, consider clarifying there were 3 groups of women who participated in the extension: placebo &gt; relugolix CT, relugolix &gt; relugolix CT, and relugolix CT.</td>
<td>We added a sentence in the abstract to indicate the analyses were conducted by the randomized treatment groups in the pivotal studies</td>
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<td><strong>Results</strong>&lt;br&gt;For the paragraph starting on line 170, comparisons between placebo &gt; relugolix CT and relugolix&gt; relugolix CT are not in parallel. Meaning, the first comparison has placebo first then relugolix group (lines 171-172), the second has relugolix first then placebo (lines 172-174), etc. It is easier to follow if the comparison groups are in the same order throughout the paragraph.</td>
<td>The ordering has been addressed for consistency in the presentation of the data, per your suggestion.</td>
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<td><strong>Discussion</strong>&lt;br&gt;Line 237-242- the data on decreased uterine/fibroid volume size could be included in the results section. The figures are helpful, but a brief statement in the body of text could help providers consider relugolix for decreasing fibroid size prior to definitive surgical management- myomectomy or hysterectomy- to improve the likelihood of a minimally invasive surgical approach.</td>
<td>Per your suggestion, data have been added for relugolix CT in the results section and referenced Figure 6 for the placebo → relugolix CT and relugolix → relugolix CT groups. &lt;br&gt;We have also added a sentence on this point in the same paragraph in the Discussion section.</td>
<td>332-334</td>
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The sentence reads: In addition, the modest reduction of UF and uterine volumes, it may be beneficial in patients who still may need a surgical intervention.
In the manuscript under review: Relugolix Combination Therapy in Women with Symptomatic Uterine Fibroids: Results from the 3 LIBERTY Long-Term Extension Study- report the long-term efficacy and safety of relugolix CT treatment for 25 up to 52 weeks.

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<td>1. A clear objective is stated, no issues noted</td>
<td>Iron therapy was a part of the study protocol:</td>
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<td>2. Very well written study, has clearly elicited long term efficacy and safety</td>
<td>Women who entered the extension study on iron therapy were allowed to continue iron treatment during the study. Women who developed new microcytic iron deficiency anemia during the study, defined as a hemoglobin concentration ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, had to be started on iron therapy, either oral or parenteral. Iron deficiency anemia was reported in 13% of patients at pivotal studies baseline (LTE population)</td>
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<tr>
<td>3. Questions for author did any patient received iron therapy while on study?</td>
<td>In the relugolix + E2/NETA group, the most frequently reported concomitant medications included also iron products: with 30.1% reporting use of ferrous sulfate, 17.2% reporting use of iron.</td>
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4. Add on extension trial showed additional decrease in bone density but minimal to have significant effect. Overall the extension of the treatment is safe.

In the relugolix + delayed E2/NETA group: 31.5% reporting use of ferrous sulfate, 17.4% reporting use of iron.

In the placebo group: 30.5% reporting use of ferrous sulfate, 17.1% reporting use of iron.

Since the BMD changes are consistent with an observational study of women with uterine fibroids for one year, it would be misleading to state that the effect of relugolix CT is significant. These data were presented at the ACOG 2021 clinical and scientific annual meeting. A sentence has been added to address comparability with the untreated group of women.

Reference
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<td><strong>Fig 1:</strong> The third arm of the flow diagram (Relugolix -&gt; Relugolix CT) completed 108 should be 72% of n = 150, not 99.3%.</td>
<td>We have updated Figure 1 to reflect this comment</td>
<td>206-208</td>
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<td>Moreover, of the aggregate of the original randomized (n = 760), then completed (n = 610), then enrolled in LTE (n = 477), the completed cohort has n = 363. That is, only ~ 1/2 of the original cohort is represented in the 52-week final analyzed cohort. Need to demonstrate that this cohort is representative of the original randomized cohort in baseline demographic and clinical characteristics. This would allow for generalization of these conclusions to the original population. Without that analysis, there is potential for selection bias, since ~ 1/2 of cohort was absent from analysis. Table 1 simply compares the baseline variables of the treated tier in Fig 1, not a comparison of all treated vs the others in the original trials.</td>
<td>We have added a statement to the manuscript noting that the baseline characteristics of the completers was generally similar to those of the pivotal studies. We also added a baseline characteristics table of the completers to the supplement, per your suggestion.</td>
<td></td>
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<td>Table 2: This is important but does not address the responder rates compared to the original trials.</td>
<td>We have moved Table 2 to the supplemental appendix.</td>
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<td>The purpose was not to make a comparison with the original studies but to make an analysis by subgroups and demonstrate that different factors do not impact significantly the outcomes, or to show whether the responder rate observed on the overall patients is comparable among the subgroups.</td>
<td>The purpose was not to make a comparison with the original studies but to make an analysis by subgroups and demonstrate that different factors do not impact significantly the outcomes, or to show whether the responder rate observed on the overall patients is comparable among the subgroups.</td>
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<td>Fig 2A, 2B, 2C; 4A, 4B: Should state in figure legends whether there is any statistical difference in the three proportions.</td>
<td>Statistical comparison was not done because it was open label study where all patients received the same product and had received different durations of antecedent relugolix-CT.</td>
<td>178</td>
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### Editorial Office Comments

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

   Noted

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:

   * Funding information (i.e., grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
   * 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 (i.e., city, state, or country), if necessary for context.

   Funding information and a description of the funder involvement has been added to the title page
   The clinical trial registration numbers are included at the end of the abstract
   For this study, there was a central IRB for the US and country-level EC for the other participating countries. We have added a supplemental table with the information for all IRB/ECs.
   We have indicated that it is a multinational study in the Methods section

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

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<td>4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race. Use &quot;Black&quot; and &quot;White&quot; (capitalized) when used to refer to racial categories. List racial and ethnic categories in tables in alphabetic order. Do not use &quot;Other&quot; as a category; use &quot;None of the above&quot; instead. Please refer to &quot;Reporting Race and Ethnicity in Obstetrics &amp; Gynecology&quot; at <a href="https://urldefense.com/v3/__https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf__;!!MvNZe7V6M35izPbIbgg-hfU12VWkGGfBz56Cfm58MFh9uFaHs9h55rwEW_rzLk7Wl9uPhewMGVxKgQlehnh1h1pSxp5ypNUuPBIBgtoenMlk$">https://urldefense.com/v3/__https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf__;!!MvNZe7V6M35izPbIbgg-hfU12VWkGGfBz56Cfm58MFh9uFaHs9h55rwEW_rzLk7Wl9uPhewMGVxKgQlehnh1h1pSxp5ypNUuPBIBgtoenMlk$</a></td>
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<td>5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: “People with disabilities” or “women with disabilities” instead of “disabled people” or “disabled women”; “patients with HIV” or “women with HIV” instead of “HIV-positive patients” or “HIV-positive women”; and “people who are blind” or “women who are blind” instead of “blind people” or “blind women.”</td>
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<td>6. The journal follows ACOG’s Statement of Policy on Inclusive Language [<a href="https://urldefense.com/v3/__https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language">https://urldefense.com/v3/__https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language</a> ;!!MvNZe7V6M35izPbIbgg-hfU12VWkGGfBz56Cfm58MFh9uFaHs9h55rwEW_rzLk7Wl9uPhewMGVxKgQlehnh1h1pSxp5ypNUuPBIBgtoenMlk$](<a href="https://urldefense.com/v3/__https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language">https://urldefense.com/v3/__https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language</a> ;!!MvNZe7V6M35izPbIbgg-hfU12VWkGGfBz56Cfm58MFh9uFaHs9h55rwEW_rzLk7Wl9uPhewMGVxKgQlehnh1h1pSxp5ypNUuPBIBgtoenMlk$). When possible, please avoid using gendered descriptors in your manuscript. Instead of &quot;women&quot; and “females,” consider using the following: “individuals,” “patients,” “participants,” “people” (not “persons”), “women and transgender men,” “women and gender-expansive patients,” or “women and all those seeking gynecologic care.”</td>
<td>We believe it is appropriate to use ‘women’ to describe the individuals in our study based on the patient population</td>
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7. 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 end of the abstract should contain the heading, "Funding Source," and should provide an abbreviated listing of the funder(s).

(4) The title page should describe how the funder was or was not involved in the manuscript.

8. 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.
9. Please add whether you received IRB or Ethics Committee approval or exemption to your Methods. Include the name of the IRB or Ethics Committee. If you received an exemption, explain why in this section.

**Response:** For this study, there was a central IRB for the US and country-level EC for the other participating countries. We have added a supplemental table with the information for all IRB/ECs.

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**Response:** noted

11. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

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**Response:** After incorporating the feedback from the reviewers and editors, our word count is now approximately 3400 words. Although this is over the 3000 word limit, we hope this will be acceptable since the extra word count was to satisfactorily address the reviewers/editors comments

12. For your title, please note the following style points and make edits as needed:

* 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.

**Response:** We have confirmed that our current title conforms to these style points
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| * Abbreviations, jargon, trade names, formulas, and obsolete terminology should not be used.  
* Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," "A Systematic Review," or "A Cost-Effectiveness Analysis" as appropriate, in the subtitle. If your manuscript is not one of these four types, do not specify the type of manuscript in the title.  
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* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.  
* 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.  
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Was this presented at a meeting? If so, please disclose it on the title page. | We have confirmed compliance with this rule.  
We have also added a sentence in the acknowledgements stating that parts of this paper were presented at 2020 ASRM Scientific Congress.  
We have also added the disclosure of previous presentation to the title page, as requested. |
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<td>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 manuscript.</td>
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<td>In addition, the abstract length should follow journal guidelines. Please provide a word count. Original Research: 300 words</td>
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<td>15. Only standard abbreviations and acronyms are allowed. A selected list is available online at <a href="https://urldefense.com/v3/__http://edmgr.ovid.com/ong/accounts/abbreviations.pdf__;!!MvNZe7V6M35iZPbgng-hfuU2VWkGf8z56Cm58MfH9uFaHeHs9h55rwEW_ruzLk7Dlr9uPheMeWGVxKqQlehn1h1pSxp5ypNUuPBlGbt7CKHDxwS">https://urldefense.com/v3/__http://edmgr.ovid.com/ong/accounts/abbreviations.pdf__;!!MvNZe7V6M35iZPbgng-hfuU2VWkGf8z56Cm58MfH9uFaHeHs9h55rwEW_ruzLk7Dlr9uPheMeWGVxKqQlehn1h1pSxp5ypNUuPBlGbt7CKHDxwS</a>_. 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>
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<td>16. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. Please rephrase your text to avoid using &quot;and/or,&quot; 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 have removed 3 '/' in the paper and edited using different text as needed, per your request</td>
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| 17. 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.  
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Express all percentages to one decimal place (for example, 11.1%). Do not use whole numbers for percentages. | The comments are for comparative studies and are not applicable to the LTE study. There are no formal statistical between treatment comparisons in the extension study since the study was a open label, single arm study, descriptive statistics were provided for each pivotal study treatment group, there were no treatment comparison. Where needed, we updated percentages to one decimal place. |
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Please make sure your references are numbered in order of appearance in the text.

20. Figures: Please upload all figures as figure files on Editorial Manager.

**Figure 1:** In the discontinued box for placebo to Relugolix CT, should withdrawal by patient be 11?  

**Correct:** In Figure 1, should be 11 pts who were withdrawn for placebo to relugolix CT.
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<td>21. Each supplemental file in your manuscript should be named an &quot;Appendix,&quot; 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.</td>
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