OBSTETRICS & GYNECOLOGY

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

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

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

Date: Nov 05, 2021
To: "Aaron Lazorwitz" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1968

RE: Manuscript Number ONG-21-1968

Title : The effect of topiramate on serum etonogestrel concentrations among contraceptive implant users

Dear Dr. Lazorwitz:

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 14 days from the date of this letter. If we have not heard from you by Nov 19, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

1. Can you clarify that the subjects chosen were ENG implant users who agreed to take topiramate solely for the purpose of the study and were counselled on the risks of taking topiramate?

2. In lines 188-193, the description of pairwise comparisons of visits is a relatively complex way to show that ENG levels steadily went down with each successive study visit. You may reach more readers in this journal by reporting and explaining this data in a more straightforward manner - Table 3 is likewise a challenge to understand, for the same reason.

3. As this is a paper on pharmacokinetic outcomes rather than pharmacodynamic ones, it is difficult to draw clinical conclusions such as the vague suggestion that clinicians "discuss the potential risk of a drug interaction with the ENG contraceptive implant in a patient centered fashion." It would be clearer to focus in this paper on the pharmacokinetics, and just report that. The median percent changes fell within the pre-defined non-inferiority limit, which would lead the reader to assume that treatment with topiramate is not inferior to ENG implant use alone, but then the authors point out the outliers of levels less than 90 in 8 patients at visit four - it's hard to have it both ways - especially if ovulation suppression is potentially not the only mechanism of action, which seems likely. Of note, within the data set there is indeed one patient with a baseline lower than 90. Rather than counselling "all ENG contraceptive implant users on the potential drug-drug interaction with topiramate consistent with other EIAED's," this data seems to show that at least the "migraine dose" topiramate probably does not significantly affect the ENG level. If a level of <90 is something to prompt counselling about contraceptive failure, and that can occur with ENG implant alone, then all patients with implants must be counselled thusly, and if topiramate use plus ENG implant is non-inferior to ENG implant alone, the counselling is the same.

4. Along those same lines, it would be interesting to report each of the actual ENG levels in the 8 patients who fell below 90 pg/mL at visit four (in addition to the median). If those 8 levels are important it may be helpful to see the actual numbers.

Reviewer #2: The authors present a prospective, non-inferiority study evaluating topiramate and etonogestrel pharmacokinetics interactions. They enrolled 48 patients with a final discontinuation rate of 43.8%. Serum etonogestrel levels were determined in the setting of increasing doses of topiramate up to 400 mg daily (recommend seizure dosing).

The study was funded by an investigator grant from Merck as well as NIH grant funding. The authors conclude that there is a dose-dependent effect on changes in etonogestrel serum levels with increases in topiramate levels.

1. Methods, page 7, line 105: if duration of implant use was not available in the electronic health record, participant self-report of duration of use was allowed. Patients often mis-recall dates of procedures so this may be a confounder. This seems especially relevant given that there was a participant who was below to 90 pg/mL cut-off on the baseline sample as well as participants with "outlier" values that were much higher than other participants' levels. Please consider adding this as a limitation of the study.

2. Methods, page 8, line 144: The samples were de-identified at the completion of the study and given a random identification code. It is unclear from the manuscript if each participant's specimens were labelled together or if all the samples were labelled randomly and just kept with the same group (i.e. the correct associated visit-baseline, one, two, three, four). If the specimens were labelled randomly, can the authors comment on why each participants specimens were not kept together to evaluate for changes in an individual's etonogetrel serum level in the setting or rising topiramate concentrations. If the specimens were kept together by participant will the authors please clarify this within the body of the manuscript.

3. The p-values are written in various ways throughout the manuscript, including often in scientific notation. This is a non-standard way to notate p-values in a manuscript and quite difficult to read/interpret with a quick glance. Please note p-values in standard fashion throughout.

4. Results, page 10, line 184: The authors include a patient with a baseline serum etonogestrel concentration of 76.2 pg/mL. The authors excluded patients for numerous other reasons. Can they please comment on why a patient with a sub-therapeutic etonogestrel concentration at baseline would be included in the analysis. It seems difficult to say with certainty that the other low values (visit 3, visit 4) are not from the same patient.

5. Notable increases in serum etonogestrel concentrations were made for a subset of patients. Would like to see the authors comment on their hypothesis for why these huge increases (215%, 191% and 375%) were seen for some patients with a medication that is know to by a CYP3A P50 inducer.

6. Results, page 11, line 197: Only 52.1% of patients were therapeutic on their topiramate dosing. What was felt to by the likely reason why there was such a high rate of patients being non-therapeutic on the topirimate?

7. Discussion, page 12, line 218: What do the authors propose as a mechanism for a non-therapeutic patient falling below the 90 pg/mL level required for consistent ovulation suppression?

8. Table 1: Was any analysis done to determine initial and subsequent etonogestrel levels based on an individual participants BMI? Is there any thought that a patient's BMI and body fat composition may play any role in the pharmacokinetic interactions between the two medications as well as on overall levels of both etonogestrel and topiramate?

9. Table 2: Were participants confirmed to be a the a therapeutic topiramate concentration at each study visit or if they were sometimes therapeutic and sometimes not therapeutic were they still included in the "therapeutic group"? Depending on the answer to this question how does this potentially leading to confounding of the study results?

10. Table 3: This table is very difficult to read. As noted above, the p-values being expressed in a non-standard format in scientific notation make them difficult to read and quickly interpret. Consider removing Table 3 as it does not add significant information that was not already written in the manuscript.

Reviewer #3:

Overall Comments: The authors present the results of a pharmacokinetic study evaluating the steady state concentration of the long acting implant, etonogestrel (ENG), with increasing amounts of topiramate, an enzyme-inducing anti-epileptic drug (EIAED). This drug is used by women with partial-onset seizures, primary generalized tonic-clonic seizures and its primary use in migraine prophylaxis. As this medication has been found to be teratogenic, it is critical that its use is in the setting of adequate contraception in reproductive-aged women. Data from a study of the drug-drug interaction between topiramate and the ENG contraceptive implant in order to determine if toparimate is associated with a potentially clinically significant reduction in serum ENG concentrations are presented.

Specific Comments:

Title: Potentially add after current title: "a pharmacokinetic study" to clarify the study

Précis: Not sure if the word "clinically" should be there. Despite the fact that efficacy may be diminished with ENG levels

<90 pg/mL, this study only addresses the pharmacokinetics. Perhaps, Topiramate has a significant drug interaction…

Abstract: The first person nature of the writing is distracting. Ie Instead of , "We conducted a", please revise to, A prospective…was conducted.

Conclusions: as noted above, consider removing "clinically" significant

Introduction: Provides good rationale for the study. Could cut down by a paragraph. Is there any data regarding the proportion of reproductive-aged women using topiramate for a seizure disorder or migraine prophylaxis-would also inform to importance of the study. Please provide specific objective/hypothesis.

Methods: Oral titration of topirimate up to maximum dose and off of the drug is well described. Were the serum levels of ENG and topirimate performed in duplicate/triplicate and mean value used-please clarify? Please describe specifics of Bonferroni noted in footnote Table 3. Also note footnotes of Table 2 and Appendix 1 in the Methods.

Results: Are there other variables collected that could be placed in Table 1? Specifically, parity, medical comorbidities. Figure 2, would diminish the scale of the y-axis so that the values can be better appreciated ie maybe 0-300 and spread out.

Discussion: Results well discussed. Cannot really specifically state that the results are absolutely clinically significant as pregnancy rates are not addressed in this study. Because of inclusion criteria, the results lose a bit of external generalizability. Can specific recommendations be made?
Tables/Figures: As above.

STATISTICAL EDITOR COMMENTS:

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

lines 11-12, 162-168, Table 2: The study design was that of non-inferiority, based on a margin of 30% decrease in serum ENG from baseline to visit # 4. The abstract and results section and Table 2 should each conform to the language of a non-inferiority test, not on superiority or inferiority tests. Those are all secondary results and irrelevant to how the study was designed. Based on how the non-inferiority margin was stated, the actual decrease in serum ENG among all participants was -21% (lines 193). That is, non-inferiority was not proven and should be stated as not showing non-inferiority. Need to present the primary outcome in the usual format for non-inferiority testing.

General: The patients varied in terms of time since implant and BMI, neither of which were evaluated vs ENG levels. From the data presented, the reader cannot tell whether increasing BMI or time since implantation had any effect on decreasing the ENG serum level.

Table 2: The primary outcome only pertained to "all participants", not to its subsets. The "therapeutic" group did have a decrease outside the margin, but this group was not the primary outcome and if there were two primaries, then the sample size calculation would have to have been re-done to account for an alpha = 0.025. The "non-therapeutic" group had an increase in serum ENG, within the margin and was also underpowered.

EDITOR COMMENTS:

1. As the other reviewers point out, the study was designed as a non-inferiority trial and the median change in ENG levels fell within the non-inferiority range. While the substantial number of subjects whose ENG levels decline below 90 pg/mL is undoubtedly important and should be presented, the data should clearly be reported throughout that based on the study design ENG with topiramate was non-inferior to ENG alone.

2. Please clarify Table 3 and simplify the reporting.

3. 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.

4. 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.

5. 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.

6. 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, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/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. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

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 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.

8. 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.

9. 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.

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).
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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.

12. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

13. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

14. 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.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

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%").

15. 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.

16. 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.

17. Figures 1-3 may be resubmitted as-is.

18. 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.

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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 14 days from the date of this letter. If we have not heard from you by Nov 19, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason D. Wright, MD
Editor-in-Chief, Elect

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

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November 29th, 2021

Dear Editors and reviewers,

Thank you for the opportunity to submit a revised version of our original research article "The effect of topiramate on serum etonogestrel concentrations among contraceptive implant users: a pharmacokinetic study" for publication in *Obstetrics & Gynecology*. We have included the reviewers' and Editor's comments and our responses (in red) at the end of this cover letter.

We adhered to the GPP3 guideline for creation of this manuscript. 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). 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). 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). 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). All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation (TRUE).

This manuscript is not under consideration elsewhere and will not be submitted elsewhere until a final decision is made by the editors of *Obstetrics & Gynecology*. This work was presented as a poster presentation at the virtual 2021 Society of Family Planning Annual Meeting held virtually on October 1-2, 2021. **The lead author, [Dr. Aaron Lazorwitz], affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.** This study was approved by the Colorado Multiple Institutional Review Board and all participants gave written informed consent at enrollment. This study is registered on clinicaltrials.gov (ID: NCT03335163): https://clinicaltrials.gov/ct2/show/NCT03335163.

This study was primarily funded through an Investigator Initiated Study grant from Merck Sharp & Dohme Corp [MISP#57073] to Dr. Teal. The authors have maintained all ethical and transparent publication practices and all funding sources listed had no involvement in the study design, collection, analysis, interpretation of data, writing of this report, or decision to submit this article for publication. Dr. Teal serves on a Data Monitoring Board for a study funded by Merck and Co and has served as a consultant for Bayer Healthcare. The University of Colorado Department of Obstetrics and Gynecology has received research funding from Bayer, Agile Therapeutics, Merck and Co, Sebela, and Medicines360. The authors have no other conflicts of interest to disclose.

I appreciate the time and considerations invested into this review by the reviewers and Editor. All authors have fulfilled the requirements for authorship and confirmed submission.

Thank you,

Aaron Lazorwitz, MD, MSCS
Lead and Corresponding Author

Response to Reviewers' and Editor's Comments

Reviewer #1:

Thank you for your thoughtful review of our manuscript.

1. Can you clarify that the subjects chosen were ENG implant users who agreed to take topiramate solely for the purpose of the study and were counselled on the risks of taking topiramate?

This is correct that subjects were ENG implant users who agreed to take topiramate solely for the purpose of the study and were counselled on the risks of taking topiramate. We have added a line to the Methods to clarify this point:

Lines (141-143): "All participants were current ENG implant users who agree to take topiramate solely for the purposes of this study and were counseled on the risks of taking topiramate prior to initiating the study drug."

2. In lines 188-193, the description of pairwise comparisons of visits is a relatively complex way to show that ENG levels steadily went down with each successive study visit. You may reach more readers in this journal by reporting and explaining this data in a more straightforward manner - Table 3 is likewise a challenge to understand, for the same reason.

Thank you for this comment. We have revised this section of the Results to explain this data in a more straightforward manner. We have also removed the previous Table 3 to avoid unnecessary confusion among readers. This section of the Results now states:

Lines (241-245): "At Visit 2, median serum ENG concentrations decreased by only 10.2% (range -86% to +215%) from baseline. By Visit 3, median serum ENG concentrations had decreased by 20.1% (range -85% to +191%) from baseline. Finally, by Visit 4, median serum ENG concentrations had decreased by 21.0% (range -88% to +215%)."

Lines (253-255): "Serum ENG concentrations steadily decreased with each up-titration in topiramate therapy and corresponding successive study visit."

Similarly, we revised the next paragraph in the Results to replace the potentially confusing data with a simpler presentation. This line now states:

Lines (266-268): "Similarly to our analysis of all participants, median serum ENG concentrations for therapeutic participants steadily decreased with each up-titration in topiramate therapy."

Based on the comments from multiple reviewers, we have removed the previous Table 3 to avoid confusion.

3. As this is a paper on pharmacokinetic outcomes rather than pharmacodynamic ones, it is difficult to draw clinical conclusions such as the vague suggestion that clinicians "discuss the potential risk of a drug interaction with the ENG contraceptive implant in a patient centered fashion." It would be clearer to focus in this paper on the pharmacokinetics, and just report that. The median percent changes fell within the pre-defined non-inferiority limit, which would lead the reader to assume that treatment with topiramate is not inferior to ENG implant use alone, but then the authors point out the outliers of levels less than 90 in 8 patients at visit four - it's hard to have it both ways - especially if ovulation suppression is potentially not the only mechanism of action, which seems likely. Of note, within the data set there is indeed one patient with a baseline lower than 90. Rather than counselling "all ENG contraceptive implant users on the potential drug-drug interaction with topiramate consistent with other EIAED's," this data seems to show that at least the "migraine dose" topiramate probably does not significantly

affect the ENG level. If a level of <90 is something to prompt counselling about contraceptive failure, and that can occur with ENG implant alone, then all patients with implants must be counselled thusly, and if topiramate use plus ENG implant is non-inferior to ENG implant alone, the counselling is the same.

Thank you for your comment. We agree that this study was primarily designed around the pre-defined non-inferiority limit of 30%, as we initially suspected that topiramate would have a minimal CYP induction effect based on the previously published literature. After addressing the comments from the Statistical Editor, we have now included the 95% confidence intervals for mean percent change in serum ENG concentrations that clearly demonstrate that topiramate+ENG implant is inferior to ENG implant alone. We have revised the Discussion to highlight this primary finding regarding non-inferiority:

Lines (274-276): "In this pharmacokinetic drug-drug interaction study, we found that concomitant use of topiramate among ENG implant users led to inferior serum ENG concentrations based upon our pre-defined non-inferiority limit of 30%."

With these revised findings, our Discussion points regarding the counseling of patients on this potential drug-drug interaction are further supported. Even without the inferior pharmacokinetic outcome, we found a clinically significant increase in the number of participants that had serum ENG concentrations that fell below the threshold for ovulatory suppression by Visit 4, predominantly among those participants with therapeutic serum topiramate concentrations. As we currently do not know the minimum serum ENG concentration below which the ENG implant loses contraceptive efficacy, patients should be counseled that topiramate could interact with the ENG implant in such a way that could theoretically lead to an increased risk of unintended pregnancy. Some participants in our study experienced decreases in serum ENG concentrations greater than 80%, and we currently lack the means to identify patients at greatest risk of such clinically significant drug-drug interactions. Similarly, we lack the means to identify implant users with baseline serum ENG concentrations below 90pg/mL, though these users would theoretically be at even higher risk of contraceptive failure with taking drugs that further reduce serum ENG concentrations. We have revised the Discussion to explicitly state our new findings of inferiority and integrate the nuanced secondary findings in a tempered fashion. As topiramate is currently included in the CDC MEC's list of EIAEDs, our data support keeping it there until further research is available, particularly pharmacodynamic research.

Lines (276-278): "Topiramate demonstrated a clear dose-dependent effect on serum ENG concentrations causing an increasing number of ENG implant users to experience decreases in serum ENG concentrations beyond this non-inferiority limit."

Lines (291-293): "However, we currently have no means to predict which contraceptive implant users will experience a clinically significant drug-drug interaction with topiramate."

We agree that the dose of topiramate should be considered when counseling patients on this drug-drug interaction. We have revised this line to now state:

Lines (299-301): "Until those tools are available, healthcare providers should consider the dose of topiramate prescribed when counseling ENG contraceptive implant users on this potential drug-drug interaction (6)."

We further highlight the importance of considering the dose/indication for topiramate therapy later in our Discussion:

Lines (333-335): “Fortunately, given the dose dependent nature of this drug-drug interaction, contraceptive implant users prescribed topiramate for migraines likely face a much lower if any increased risk of contraceptive failure (2).”

Given the inter-individual variations noted in this data, and the preferences-sensitive nature of contraceptive provision, we believe in approaching clinical scenarios such as this in a patient-centered fashion. Consideration must be given to other medical conditions, medications, and personal preferences that patients may have when considering the best contraceptive option for that individual. As topiramate appropriately remains in the CDC MEC EIAED list, patients should be counseled on the available data (though limited) and what that might mean for their risk of unintended pregnancy. Thus, we have kept our final sentence unchanged to reflect the importance of patient-centered contraceptive provision.

4. Along those same lines, it would be interesting to report each of the actual ENG levels in the 8 patients who fell below 90 pg/mL at visit four (in addition to the median). If those 8 levels are important it may be helpful to see the actual numbers.

Thank you for your suggestion. We have replaced the previous Table 3 with a new Table 3 that presents the actual ENG levels for all 9 participants that had concentrations below 90pg/mL by the end of the study.

Reviewer #2: The authors present a prospective, non-inferiority study evaluating topiramate and etonogestrel pharmacokinetics interactions. They enrolled 48 patients with a final discontinuation rate of 43.8%. Serum etonogestrel levels were determined in the setting of increasing doses of topiramate up to 400 mg daily (recommend seizure dosing). The study was funded by an investigator grant from Merck as well as NIH grant funding. The authors conclude that there is a dose-dependent effect on changes in etonogestrel serum levels with increases in topiramate levels.

Thank you for your thoughtful review and comments.

1. Methods, page 7, line 105: if duration of implant use was not available in the electronic health record, participant self-report of duration of use was allowed. Patients often mis-recall dates of procedures so this may be a confounder. This seems especially relevant given that there was a participant who was below to 90 pg/mL cut-off on the baseline sample as well as participants with "outlier" values that were much higher than other participants' levels. Please consider adding this as a limitation of the study.

We agree that self-report of duration of use could be confounded by mis-recall. However, as we used a repeated measures design, we used each participant as their own control for comparison. Thus, this potential confounder would not affect our primary analyses. We have revised the Limitations section of our Discussion to identify this as a potential confounder and explain how the methodology selected controls for this confounder.

Lines (316-321): “When determining duration of implant use, we relied upon participant self-report when date of implant insertion was not available in the electronic health record, data which could have been confounded by participant mis-recall. However, the use of a repeated measures study design utilizes each participant as their own control for comparison, and thus would account for any potential confounding by participant characteristics such as duration of implant use.”

2. Methods, page 8, line 144: The samples were de-identified at the completion of the study and given a random identification code. It is unclear from the manuscript if each participant's specimens were

labelled together or if all the samples were labelled randomly and just kept with the same group (i.e. the correct associated visit-baseline, one, two, three, four). If the specimens were labelled randomly, can the authors comment on why each participants specimens were not kept together to evaluate for changes in an individual's etonogetrel serum level in the setting or rising topiramate concentrations. If the specimens were kept together by participant will the authors please clarify this within the body of the manuscript.

The specimens were all labeled randomly in terms of both which participant they came from and the specific visit they were obtained at. Each sample was given a randomly generated three letter code so that the analyzing laboratory was blinded to any relatedness (e.g. same participant) or timing (e.g. visit number) of the samples. This ensured that the analysis of the samples remained truly blinded. The samples were batched for analysis to ensure that any batch effects were consistent across all samples, thus reducing potential confounding from assay variability. We have revised this portion of the Methods to remove any confusion:

Lines (190-193): "At the conclusion of enrollment and all follow-up visits, we de-identified all stored serum samples and assigned all samples a randomly generated three letter identification code to remove any potential for bias in analysis based on samples from the same participant or based on timing of sample collection."

Lines (199-201): "We batched samples for analysis to reduce inter-assay variability and all laboratory personnel were blinded to sample relatedness and timing."

3. The p-values are written in various ways throughout the manuscript, including often in scientific notation. This is a non-standard way to notate p-values in a manuscript and quite difficult to read/interpret with a quick glance. Please note p-values in standard fashion throughout.

Thank you for your comment. We have removed all scientific notation to avoid confusion. All p-values have been changed to maintain consistent formatting. The following revisions have been made:

Line 253: "p= 1.7x10-5" replaced with "p<0.001"

P-values previously included in the Results pertinent to pairwise comparisons removed in response to Reviewer 1's comments

Line 266: "p= 1.5x10-5" replaced with "p<0.001"

The original Table 3 with p-value data has been replaced with a new Table 3.

4. Results, page 10, line 184: The authors include a patient with a baseline serum etonogestrel concentration of 76.2 pg/mL. The authors excluded patients for numerous other reasons. Can they please comment on why a patient with a sub-therapeutic etonogestrel concentration at baseline would be included in the analysis. It seems difficult to say with certainty that the other low values (visit 3, visit 4) are not from the same patient.

A serum ENG concentration <90pg/mL is not "sub-therapeutic." We currently do not have data on what minimum serum ENG concentration is necessary to maintain contraceptive efficacy with the contraceptive implant. The cut-off of <90pg/mL has clinical and research importance as the threshold to maintain ovulatory suppression with the contraceptive implant. There is known wide interindividual variability in serum ENG concentrations among implant users, and as this study used participants as their own control, we could control for this wide interindividual variability in individual baseline concentrations. Therefore, it was not necessary to have an exclusion criterion for this study based on baseline serum ENG concentration. Per Reviewer's 1 recommendation, Table 3 has now been replaced with a Table that shows the serum ENG concentrations across the study for the 9 participants with

concentrations <90pg/mL at Visit 4. This includes the participant with a baseline serum ENG concentration of 76.2pg/mL. With this new Table 3, readers can easily identify the serum ENG concentrations for this participant if desired.

5. Notable increases in serum etonogestrel concentrations were made for a subset of patients. Would like to see the authors comment on their hypothesis for why these huge increases (215%, 191% and 375%) were seen for some patients with a medication that is know to by a CYP3A P50 inducer.

We address these outliers in the Limitations section of the Manuscript:

Lines (312-316): "Our findings are also limited by the few outlier serum ENG concentrations (>600pg/mL) of unknown cause that occurred during the course of the study. However, the use of non-parametric statistical tests for our primary analyses controls for these outliers and prevents them from having a disproportionate effect on our results."

We are unsure as to the exact cause of these outlier values. We feel that any conjecture on our part regarding these outliers lies beyond the scope of this manuscript.

6. Results, page 11, line 197: Only 52.1% of patients were therapeutic on their topiramate dosing. What was felt to by the likely reason why there was such a high rate of patients being non-therapeutic on the topirimate?

We had 25 total participants reach a therapeutic topiramate level during the study, which accounts for 78.1% (25/32) of participants that completed Visit 2 of the study when the first serum topiramate level was measured. We suspect that the relatively low rate (21.9%) of being non-therapeutic on the topiramate was a combination of differential drug metabolism among participants, possible inaccuracy in timing of the topiramate level (beyond trough timing due to participant scheduling conflicts), and possibly study non-compliance. In clinical practice, some patients require higher doses of topiramate than what we achieved in this study to reach a therapeutic serum level for treatment of epilepsy disorders.

7. Discussion, page 12, line 218: What do the authors propose as a mechanism for a non-therapeutic patient falling below the 90 pg/mL level required for consistent ovulation suppression?

As now presented in the new Table 3, the only non-therapeutic participant who had a serum ENG concentration fall below 90pg/mL was Participant 31 who had an initial baseline serum ENG concentration below 90pg/mL. We have added a line to the Results section of the manuscript to highlight this finding:

Lines (269-271): "The single non-therapeutic participant that had a serum ENG concentration <90pg/mL at Visit 4 was the only participant who had a serum ENG concentration <90pg/mL at baseline (Table 3)."

8. Table 1: Was any analysis done to determine initial and subsequent etonogestrel levels based on an individual participants BMI? Is there any thought that a patient's BMI and body fat composition may play any role in the pharmacokinetic interactions between the two medications as well as on overall levels of both etonogestrel and topiramate?

As this study utilized a repeated measures design, participants served as their own control, thus controlling for any possible effects from individual characteristics such as BMI. From previously published work (citation 17 in the manuscript) that specifically evaluated the association between BMI and serum ENG concentrations, we know that increasing BMI has a small negative association with serum ENG concentrations among contraceptive implant users (average decrease in serum ENG concentrations of 3pg/mL for every 1kg/m^2 increase). We are not aware of any currently published literature that has found BMI or body fat composition to play a role in drug-drug interactions.

9. Table 2: Were participants confirmed to be a the a therapeutic topiramate concentration at each study visit or if they were sometimes therapeutic and sometimes not therapeutic were they still included in the "therapeutic group"? Depending on the answer to this question how does this potentially leading to confounding of the study results?

Serum topiramate concentrations were measured at study Visits 2, 3, and 4 regardless of prior values. The therapeutic group was defined as having a serum topiramate concentration >5.0ug/mL at any time during the study:

Lines 218-220: “We also performed a sub-group analysis (Friedman’s test) of only participants who reached a therapeutic topiramate concentration (≥5µg/mL) at any follow-up visit.”

Lines 424-425: “Therapeutic defined as reaching a serum topiramate concentrations of ≥5.0µg/mL at any visit during the study.”

Upon reviewing the raw data, there was only one participant that had a therapeutic topiramate concentration at Visit 3 but did not have a therapeutic topiramate concentration at Visit 4. This participant was still included in the sub-group analysis we performed for therapeutic participants based on the definition used for “therapeutic” in this study. As our primary analysis included all participants, regardless of their topiramate levels, this would not lead to any confounding for our primary analysis. Inclusion of this participant in the “therapeutic group” would have biased us towards not finding a difference in our sub-group analysis, if this participant had truly been non-compliant with the medication. This potential bias would only be relevant if we had not found a significant decrease in serum ENG concentrations in our sub-group analysis.

10. Table 3: This table is very difficult to read. As noted above, the p-values being expressed in a non-standard format in scientific notation make them difficult to read and quickly interpret. Consider removing Table 3 as it does not add significant information that was not already written in the manuscript.

Table 3 has been removed per Reviewer 1’s and 2’s recommendation to avoid confusion.

Reviewer #3:

Overall Comments: The authors present the results of a pharmacokinetic study evaluating the steady state concentration of the long acting implant, etonogestrel (ENG), with increasing amounts of topiramate, an enzyme-inducing anti-epileptic drug (EIAED). This drug is used by women with partial-onset seizures, primary generalized tonic-clonic seizures and its primary use in migraine prophylaxis. As this medication has been found to be teratogenic, it is critical that its use is in the setting of adequate contraception in reproductive-aged women. Data from a study of the drug-drug interaction between topiramate and the ENG contraceptive implant in order to determine if toparimate is associated with a potentially clinically significant reduction in serum ENG concentrations are presented.

Thank you for your thoughtful review and comments.

Specific Comments:

Title: Potentially add after current title: "a pharmacokinetic study" to clarify the study

Thank you for this suggestion. We have revised the title of the study as such:

Lines 1-1: “The effect of topiramate on serum etonogestrel concentrations among contraceptive implant users: a pharmacokinetic study”

Précis: Not sure if the word "clinically" should be there. Despite the fact that efficacy may be diminished with ENG levels <90 pg/mL, this study only addresses the pharmacokinetics. Perhaps, Topiramate has a significant drug interaction…

We have removed the word “clinically” from the Precis. The precis now states:

Lines 38-39: “Topiramate has a significant drug interaction with the etonogestrel contraceptive implant that may result in contraceptive failures at higher dosages.”

Abstract: The first person nature of the writing is distracting. Ie Instead of , "We conducted a", please revise to, A prospective…was conducted.

The Abstract and manuscript as a whole is written predominantly in the active voice per standards for scientific articles. This suggested revision would change a currently active voice sentence to a passive voice. We prefer to keep the Abstract in the active voice as much as possible and so will not make this revision unless it is desired by the Editor.

Conclusions: as noted above, consider removing "clinically" significant

We have removed “clinically” from the Conclusion of the Abstract per your recommendation. The Conclusion now states:

Lines 63-65: “Though only a mild EIAED, concomitant topiramate use led to inferior serum ENG concentrations among implant users, with a significant proportion reaching ENG concentrations below the threshold for ovulatory suppression when taking anti-epileptic dosages of topiramate.”

Introduction: Provides good rationale for the study. Could cut down by a paragraph. Is there any data regarding the proportion of reproductive-aged women using topiramate for a seizure disorder or migraine prophylaxis-would also inform to importance of the study. Please provide specific objective/hypothesis.

Thank you for your comment. We are not aware of reliable published data regarding the proportion of reproductive-aged women using topiramate for a seizure disorder or migraine prophylaxis. These data, if available, would likely be confounded by regional practice differences and so we have focused on the clinical recommendations/indications for topiramate use to highlight the importance of studying this specific drug-drug interaction.

We have revised the last line of the Introduction to provide a specific objective and hypothesis.

Lines 108-111: “We evaluated the drug-drug interaction between topiramate and the ENG contraceptive implant and hypothesized that topiramate would not cause a potentially clinically significant reduction in serum ENG concentrations.”

Methods: Oral titration of topirimate up to maximum dose and off of the drug is well described. Were the serum levels of ENG and topirimate performed in duplicate/triplicate and mean value used-please clarify? Please describe specifics of Bonferroni noted in footnote Table 3. Also note footnotes of Table 2 and Appendix 1 in the Methods.

The serum levels of ENG and topiramate were performed using single measurements per clinical and research standards. We have revised the methods to make the single-time nature of these measurements clear.

Lines 153-155: “Participants meeting all non-laboratory inclusion and exclusions criteria then underwent a single, baseline blood draw to obtain whole blood and serum.”

Lines 169-171: “All participants returned at the end of the third week of the topiramate titration schedule for Visit 2. At Visit 2, participants underwent a repeat single-time blood draw,…”

Lines 180-181: “We performed repeat single-time blood draws at these visits and again measured serum topiramate concentrations for compliance.”

The previous Table 3 has been removed from the manuscript and the noted footnote with Bonferroni corrections is no longer present to avoid confusion.

The footnote for Table 2 is described in the Methods as such:

Lines 218-220: “We also performed a sub-group analysis (Friedman’s test) of only participants who reached a therapeutic topiramate concentration (≥5µg/mL) at any follow-up visit.”

The footnote for Appendix 1 includes the specifics of our wash-out schedule for this study. We believe these specific details are not necessary to include in the Manuscript, as they relate to study procedures performed after all sample collection was already completed. Including these details in the manuscript may be confusing for some readers, and so we prefer to leave them in the Appendix for interested readers.

Results: Are there other variables collected that could be placed in Table 1? Specifically, parity, medical comorbidities. Figure 2, would diminish the scale of the y-axis so that the values can be better appreciated ie maybe 0-300 and spread out.

Table 1 presents the pertinent demographic and characteristic variables we collected for this study. We did not collect data on parity, as this was not pertinent for this study. We screened for medical comorbidities per the Inclusion/Exclusion criteria of this study, but did not collect data on medical comorbidities that were not pertinent to study inclusion.

For Figure 2, diminishing the scale of the y-axis to 300pg/mL would cause the majority of outlier values to not be represented. This could unintentionally bias readers by not displaying these outlier values. The y-axis scale was set based on the range of values in the data.

Discussion: Results well discussed. Cannot really specifically state that the results are absolutely clinically significant as pregnancy rates are not addressed in this study. Because of inclusion criteria, the results lose a bit of external generalizability. Can specific recommendations be made?

We have made revisions to the Discussion to place emphasis on the pharmacokinetic outcomes per comments from the other Reviewers. We agree that we cannot directly speak on absolute clinical significance based on the methodology of this study. We have tempered any statements in the Discussion relating to clinical significance. These revisions include:

Lines 281-283: Removal of “clinically” from this line. This line now states: “A significant proportion of participants reached serum ENG concentrations below the level needed to consistently suppress ovulation (90pg/mL) by the end of the study.”

Lines 335-337: “Further, pertinent clinical outcome data (e.g. pregnancy rates) are needed to determine the true clinical significance of topiramate’s effect on serum ENG concentrations.”

Lines 337-340: “Ultimately, more data are needed on the drug-drug interaction between topiramate and different hormonal contraceptive formulations to determine if this interaction remains consistent across different progestins and leads to actual effects on contraceptive efficacy.”

We are unsure what is exactly meant by how the inclusion criteria would cause the external generalizability to suffer. For this pharmacokinetic study, the inclusion criteria were designed to ensure

we were assessing this drug-drug interaction with as minimal confounding as possible. Our recommendations are based on the pharmacokinetic data obtained and have been tempered per the recommendations by the Reviewers.

Tables/Figures: As above.

Revisions described as above.

STATISTICAL EDITOR COMMENTS:

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

lines 11-12, 162-168, Table 2: The study design was that of non-inferiority, based on a margin of 30% decrease in serum ENG from baseline to visit # 4. The abstract and results section and Table 2 should each conform to the language of a non-inferiority test, not on superiority or inferiority tests. Those are all secondary results and irrelevant to how the study was designed. Based on how the non-inferiority margin was stated, the actual decrease in serum ENG among all participants was -21% (lines 193). That is, non-inferiority was not proven and should be stated as not showing non-inferiority. Need to present the primary outcome in the usual format for non-inferiority testing.

Thank you for your comments. As serum ENG concentrations are not normally distributed, the percent change in serum ENG concentrations are also not normally distributed, which we have confirmed via statistical testing. As such, it would not be appropriate to perform the standard non-inferiority testing procedure of calculating a 95% confidence interval on the raw percent change data. However, we are aware of a method developed by Hozo et al (citation 16) to convert median and range values to mean/SD for non-parametric data. In order to meet your request to present the primary outcome in the usual 95% CI format for non-inferiority testing, we have converted these data using that methodology. We then calculated 95% CI's for each time point for the mean percent change in serum ENG concentration. We actually found that the 95% CI for all follow-up visits crossed the -30% non-inferiority limit, thus serum ENG concentrations are inferior to baseline values with concomitant topiramate. In light of these findings, we have made revisions to the manuscript to appropriately highlight these primary findings of inferiority.

Lines 204-215: "To assess non-inferiority, we calculated percent changes in serum ENG concentrations from baseline to each subsequent visit for all participants. We then calculated the mean and range percent change in serum ENG concentrations among all participants with available data at each visit. As serum ENG concentrations are not normally distributed, we converted this median and range data to mean and standard deviation using the method developed by Hozo et al (16). We then calculated the 95% confidence interval for the mean percent change in serum ENG concentrations at each visit to determine non-inferiority. For this study, non-inferiority was defined as a change in serum ENG concentrations at the maximum dose of topiramate that would not result in concentrations below the threshold for ovulatory suppression (<90pg/mL) (12). We chose a non-inferiority limit of 30% because this level of decrease from the median published levels (137-207pg/mL) would not cross this threshold (17, 18)."

Lines 245-251: "After converting median/ranges to mean/standard deviations, the 95% confidence interval (CI) for mean percent change in serum ENG concentration was [-37.3%, +16.9%] for Visit 2, [-45.4%, +5.2%] for Visit 3, and [-66.8%, +24.8%] for Visit. Thus, the 95% CI's for mean percent change in serum ENG concentrations at all three visit timepoints crossed the -30% non-inferiority cut-off. Overall, 12.5% (8/32) of participants at Visit 2, 29.0% (9/31) at Visit 3, and 37.0% (10/27) at Visit 4 experienced a percent decrease in serum ENG concentrations greater than the non-inferiority limit for this study."

General: The patients varied in terms of time since implant and BMI, neither of which were evaluated vs ENG levels. From the data presented, the reader cannot tell whether increasing BMI or time since implantation had any effect on decreasing the ENG serum level.

As each participant served as their own control for this study, any effect of BMI or duration of implant use would be accounted for in our results. We have added these specific variables as examples of the potential confounders that our repeated measures design controlled for.

Lines 328-330: "Further, the repeated measures design of this study utilized each participant as their own control, which removes many potential confounders (e.g. BMI, duration of implant use)."

Table 2: The primary outcome only pertained to "all participants", not to its subsets. The "therapeutic" group did have a decrease outside the margin, but this group was not the primary outcome and if there were two primaries, then the sample size calculation would have to have been re-done to account for an alpha = 0.025. The "non-therapeutic" group had an increase in serum ENG, within the margin and was also underpowered.

Thank you for your comment. Table 2 presents the raw median/range data for all participants at each Visit and then the median/range data for "therapeutic" and "non-therapeutic" participants. These numbers are presented here for ease of visual interpretation by readers. We did not have two primary outcomes, only a planned sub-group analysis by "therapeutic" topiramate levels.

EDITOR COMMENTS:

1. As the other reviewers point out, the study was designed as a non-inferiority trial and the median change in ENG levels fell within the non-inferiority range. While the substantial number of subjects whose ENG levels decline below 90 pg/mL is undoubtedly important and should be presented, the data should clearly be reported throughout that based on the study design ENG with topiramate was non-inferior to ENG alone.

Thank you for you comments and feedback. As described above in response to the Statistical Editor's comments, we have added the 95% confidence intervals for the mean percent change in serum ENG concentrations to fit the primary non-inferiority analysis. As such, we now demonstrate that topiramate+ENG implant is actually inferior to ENG implant alone at all doses of topiramate evaluated based on these 95% confidence levels crossing the -30% threshold. As such, we have revised the manuscript to reflect this primary finding. We have made the following revisions to clearly highlight that topiramate+ENG implant is inferior:

Lines 50-52: "We measured ENG using a validated liquid chromatography-tandem mass-spectrometry assay and tested for non-inferiority (<30% decrease) in serum ENG concentrations from baseline."

Lines 58-60: "The 95% confidence intervals for mean percent change in serum ENG concentrations from baseline were [-37.3%, +16.9%], [-45.4%, +5.2%], and [-66.8%, +24.8%] at three weeks, four weeks, and six weeks, respectively."

Lines 63-65: "Though only a mild EIAED, concomitant topiramate use led to inferior serum ENG concentrations among implant users, with a significant proportion reaching ENG concentrations below the threshold for ovulatory suppression when taking anti-epileptic dosages of topiramate."

Lines 245-251: "After converting median/ranges to mean/standard deviations, the 95% confidence interval (CI) for mean percent change in serum ENG concentration was [-37.3%, +16.9%] for Visit 2, [-45.4%, +5.2%] for Visit 3, and [-66.8%, +24.8%] for Visit 4. Thus, the 95% CI's for mean percent change in

serum ENG concentrations at all three visit timepoints crossed the -30% non-inferiority cut-off. Overall, 12.5% (8/32) of participants at Visit 2, 29.0% (9/31) at Visit 3, and 37.0% (10/27) at Visit 4 experienced a percent decrease in serum ENG concentrations greater than the non-inferiority limit for this study."

Lines 274-276: "In this pharmacokinetic drug-drug interaction study, we found that concomitant use of topiramate among ENG implant users led to inferior serum ENG concentrations based upon our pre-defined non-inferiority limit of 30%."

2. Please clarify Table 3 and simplify the reporting.

Per the Reviewers' recommendations, we have removed the prior Table 3 from the manuscript and replaced it with the requested data by Reviewer 1 for the individual participant data from the 9 participants who reached serum ENG concentrations <90pg/mL by Visit 4. These data now appear in the new Table 3.

3. 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.

4. 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).

We have added the title page information to the main manuscript file.

* 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.

All funding information is disclosed on the title page and in the body text (Lines 14-21, Lines 67-70). The Role of the Funding Source section is included in the manuscript (Lines 113-125).

* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).

The clinical trial registration number is provided at the end of the abstract (Line 71).

* Name the IRB or Ethics Committee institution in the Methods section (if applicable).

The Colorado Multiple Institutional Review Board is named in the Methods (Lines 143-144).

* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

We have added "…in Denver, CO." to provide context for where participants were recruited from (Line 146).

5. 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.

I have confirmed with the co-authors that they received and completed this form and that all disclosures listed in the eCTA are included in the manuscript's title page.

6. 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, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/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. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

Upon consideration, the variables of race and ethnicity were not of vital importance to this study and were not used for any analyses. Therefore, we have omitted all race and ethnicity data from the revised manuscript.

We removed this date from Lines 233-235, which now state: "Participants were relatively young (median age of 25.3 years [range 18.3-37.2]), with a median BMI of 25.5kg/m2 (range 18.7-42.2) and median duration of implant use of 24 months (range 12-36)."

We have also removed these outcomes from Table 1.

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.

We have noted this 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:

We have included the following statements and our true/false response in the cover letter.

(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

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

The “Funding Source” heading and relevant information is included in the Abstract (Lines 67-70).

(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.

The “Role of the Funding Source” section can be found in Lines 113-125. This section contains a detailed description of the sponsor’s role as well as the above statement, as it is all true for this study.

8. 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.

We have no problems with use of the reVITALize definitions.

9. 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.

Our revised manuscript does not exceed 5,500 words.

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]."

Our Acknowledgment section adheres to these specific rules.

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.

The abstract does not contain information that does not appear in the body text and appropriately reflects the results found in the paper.

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 revised abstract is less than 300 words. Word count = 293.

12. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in

the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

Though not included in your list, ENG has become a standard abbreviation for etonogestrel and we feel it helps with the readability of the manuscript. If requested by the Editorial team, however, we will replace all instances of ENG used in this manuscript.

13. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

We have replaced all instances of “provider” throughout the manuscript. These have been replaced with “health care professional”.

14. 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.

With the revisions made to the manuscript per the Statistical Editor’s comments, we now primarily report effect sizes in the form of mean percent changes in serum ENG concentrations and the corresponding 95% confidence intervals. We still report p-values for the results of the Friedman’s test.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

A NNTb or NNTh is not appropriate for this manuscript.

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%").

We have revised the presented data so that all p-values do not exceed three decimal places and percentages do not exceed one decimal place.

15. 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 revised the Tables to conform to journal style.

16. 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.

We have reviewed the reference style and revised our references to meet journal requirements.

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.

We do not cite any ACOG documents for this manuscript.

17. Figures 1-3 may be resubmitted as-is.

These figures are resubmitted as-is.

18. 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.

We have only the one supplemental file: Appendix 1, which we have resubmitted as-is.

19. 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.

Thank you for this information. We will not be opting to publish open access if the manuscript is ultimately accepted for publication.

Date: Dec 06, 2021
To: "Aaron Lazorwitz" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1968R1

RE: Manuscript Number ONG-21-1968R1

The effect of topiramate on serum etonogestrel concentrations among contraceptive implant users: a pharmacokinetic study

Dear Dr. Lazorwitz:

Your revised manuscript has been evaluated by the Editors of Obstetrics & Gynecology. Additional concerns were raised regarding the revised statistical analysis and the non-inferiority trial design. Our Statistical Editor has provided additional comments below. We would be willing to further consider your manuscript if these comments can be adequately addressed.

Please note that the Editorial Office did a style review of your submitted R1. A copy of this file is uploaded to your submission's record in Editorial Manager as an Attachment. The file is also being sent in a separate email to you by Randi Zung (rzung@greenjournal.org). Please work off this version of the manuscript. Your Appendix file did not contain any edits.

STATISTICAL EDITOR COMMENTS:

The Authors state that the clinically relevant endpoint is ENG concentration < 90pg/mL and the use of 30% decrease from initial values was simply a way to allow statistical estimation of the needed sample size. Their summary in ClinicalTrials.gov does not specify a particular value or % decrease from baseline as the endpoint, but simply measurements at baseline, then at 3 times, up to 6 wks. Need to clarify which time point is the primary outcome (appears to be 6 weeks at the target dose, but the intermediate time points and the concentrations of topiramate are clinically relevant data.

Strongly suggest first presenting the n(%) of women who had ENG < 90pg/mL at 6 weeks, and then all intermediate time points. Those %s should include appropriate CIs. One individual (# 31) had a baseline assay < 90 pg/mL. That should be included in the the baseline %s and it is not logical to count that individual in subsequent assays as having a level < 90pg/mL that could be ascribed to topiramate, since (1) it occurred prior to topiramate and (2) that individual's topiramate concentration was sub-therapeutic. In other words, should not count that individual in subsequent times in either the numerator or denominator for determining rate of crossing the 90pg/mL threshold due to topiramate. Therefore the proportion at Visit #4 was 8/26 = 31%, 95% CIs = 13%-61%, while at Visit # 1 it was 1/32 = 3%, 95% CIs =1%-17%.

Table 3: Suggest showing similar Table for those that had assay < 90 pg/mL at visit # 2 and then for those with an assay < 90 pg/mL at visit # 3.

It would be more straightforward to simply report the changes in assay concentrations in terms of the actual measured means, SD and in terms of median (IQR)., rather than with estimated means and SD. An alternative would be to transform the ENG concentrations in order to emulate a normal distribution. Since they were so right skewed, perhaps converting to log [ENG], then converting the margin to a log scale would work. Then, one could back-transform those results to show whether the noninferiority was confirmed or refuted.

[END]

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.

Your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Dec 20, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason Wright, MD
Editor-in-Chief

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

University of Colorado
Anschutz Medical Campus

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Aurora, CO 80045
[redacted]

December 7th, 2021

Dear Editors,

Thank you for the opportunity to submit a second revised version of our original research article "The effect of topiramate on serum etonogestrel concentrations among contraceptive implant users" for publication in *Obstetrics & Gynecology*. We have included the Statistical Editor's comments and our responses (in red) at the end of this cover letter.

We adhered to the GPP3 guideline for creation of this manuscript. 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). 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). 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). 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). All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation (TRUE).

This manuscript is not under consideration elsewhere and will not be submitted elsewhere until a final decision is made by the editors of *Obstetrics & Gynecology*. This work was presented as a poster presentation at the virtual 2021 Society of Family Planning Annual Meeting held virtually on October 1-2, 2021. **The lead author, [Dr. Aaron Lazorwitz], affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.** This study was approved by the Colorado Multiple Institutional Review Board and all participants gave written informed consent at enrollment. This study is registered on clinicaltrials.gov (ID: NCT03335163): https://clinicaltrials.gov/ct2/show/NCT03335163.

This study was primarily funded through an Investigator Initiated Study grant from Merck Sharp & Dohme Corp [MISP#57073] to Dr. Teal. The authors have maintained all ethical and transparent publication practices and all funding sources listed had no involvement in the study design, collection, analysis, interpretation of data, writing of this report, or decision to submit this article for publication. Dr. Teal serves on a Data Monitoring Board for a study funded by Merck and Co and has served as a consultant for Bayer Healthcare. The University of Colorado Department of Obstetrics and Gynecology has received research funding from Bayer, Agile Therapeutics, Merck and Co, Sebela, and Medicines360. The authors have no other conflicts of interest to disclose.

I appreciate the time and considerations invested into this review by the Editors. All authors have fulfilled the requirements for authorship and confirmed submission.

Thank you,

Aaron Lazorwitz, MD, MSCS
Lead and Corresponding Author

STATISTICAL EDITOR COMMENTS:
The Authors state that the clinically relevant endpoint is ENG concentration < 90pg/mL and the use of 30% decrease from initial values was simply a way to allow statistical estimation of the needed sample size. Their summary in ClinicalTrials.gov does not specify a particular value or % decrease from baseline as the endpoint, but simply measurements at baseline, then at 3 times, up to 6 wks. Need to clarify which time point is the primary outcome (appears to be 6 weeks at the target dose, but the intermediate time points and the concentrations of topiramate are clinically relevant data.

Thank you for your additional comments. We powered this study for the primary outcome of comparing baseline measurements to those at the 6-week target dose. As you pointed out though, the intermediate time points still provide clinically relevant data, particularly as the sample size was greater for the intermediate time points due to study drop-out over the topiramate titration schedule. To clarify what the primary outcome of the study was, we have explicitly included this in the Methods section:

Lines 206-210: "We calculated that we would need a sample size of 27 participants for our selected non-inferiority limit of 30% with an alpha level of 0.05 and beta of 0.9 for our primary outcome of comparing baseline serum etonogestrel concentrations to etonogestrel concentrations at the end of the 6-week topiramate titration schedule (200mg twice a day dose)."

Strongly suggest first presenting the n(%) of women who had ENG < 90pg/mL at 6 weeks, and then all intermediate time points. Those %s should include appropriate CIs. One individual (# 31) had a baseline assay < 90 pg/mL. That should be included in the the baseline %s and it is not logical to count that individual in subsequent assays as having a level < 90pg/mL that could be ascribed to topiramate, since (1) it occurred prior to topiramate and (2) that individual's topiramate concentration was sub-therapeutic. In other words, should not count that individual in subsequent times in either the numerator or denominator for determining rate of crossing the 90pg/mL threshold due to topiramate. Therefore the proportion at Visit #4 was 8/26 = 31%, 95% CIs = 13%-61%, while at Visit # 1 it was 1/32 = 3%, 95% CIs =1%-17%.

Thank you for your suggestion. We agree with your assessment that the individual with a baseline level <90pg/mL was unlikely to have repeat measurements <90pg/mL due to topiramate, and so agree with your suggestion for how to present the n(%) of women who had ENG levels <90pg/mL. We have revised this portion of the results to include the updated n(%) and the corresponding 95% CI's.

Lines 257-264: "Only one participant at baseline (1/32 [3.1%], 95% CI 0.00-0.16) had a serum etonogestrel concentration <90pg/mL. Excluding the participant who had a serum etonogestrel concentration <90pg/mL at baseline, 30.8% of participants (8/26, 95% CI 0.14-0.52) reached a serum etonogestrel concentration <90pg/mL at the maximum topiramate dose (Visit 4) (Table 3). Also excluding the same participant, 16.7% of participants (5/30, 95% CI 0.06-0.35) reached a serum etonogestrel concentration <90pg/mL by Visit 3 (Table 4), and 9.7% of participants (3/31, 95% CI 0.02-0.26) reached a serum etonogestrel concentration <90pg/mL by Visit 2 (Table 5)."

We have also revised the Results section of the Abstract to correspond with the way the data are presented in the body of manuscript:

Lines 56-59: "Excluding one participant who had a serum etonogestrel concentration <90pg/mL at baseline, 30.8% of participants (8/26, 95% CI 0.14-0.52) reached a serum etonogestrel concentration <90pg/mL at six weeks."

Table 3: Suggest showing similar Table for those that had assay < 90 pg/mL at visit # 2 and then for those with an assay < 90 pg/mL at visit # 3.

Per your suggestion, we have added Tables 4 and 5 to the manuscript to present similar data as Table 3 for Visit #3 and Visit #2.

Table 4: Lines 439-444

Table 5: Lines 445-450

It would be more straightforward to simply report the changes in assay concentrations in terms of the actual measured means, SD and in terms of median (IQR)., rather than with estimated means and SD. An alternative would be to transform the ENG concentrations in order to emulate a normal distribution. Since they were so right skewed, perhaps converting to log [ENG], then converting the margin to a log scale would work. Then, one could back-transform those results to show whether the noninferiority was confirmed or refuted.

We are unclear what is meant by "straightforward" here, as the data are currently presented in the most appropriate form based on the qualities (e.g. normality) of the data. We present the changes in ENG concentrations in medians (ranges) given the non-normal distribution of the raw data.

Lines 243-247: "At Visit 2, median serum etonogestrel concentrations decreased by only 10.2% (range -86% to +215%) from baseline. By Visit 3, median serum etonogestrel concentrations had decreased by 20.1% (range -85% to +191%) from baseline. Finally, by Visit 4, median serum etonogestrel concentrations had decreased by 21.0% (range -88% to +215%)."

If we were to present means/SDs, these would be a biased descriptive presentation of the changes in ENG concentrations. Though log-transforming non-normally distributed data has been commonly done in the past, there are numerous statistical concerns with performing this as best described by Feng et al (https://doi.org/10.3969/j.issn.1002-0829.2014.02.009). Feng et al (2014) describe how log-transformation does not actually make data conform to a normal distribution, and thus statistical tests using log-transformed data still violate assumptions of normality. Thus, the method by Hozo et al (2005) to estimate means and SD are more appropriate for calculating the requested 95% CI's for non-inferiority testing than a log-transformation.