HOLOGIC®

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By Email (angela@dovepress.com)

Angela Jones
General Manager
Dove Medical Press Ltd
44 Corinthian Drive
PO Box 300-008
Albany, Auckland 0752
New Zealand

Re: Follow up regarding *Efficacy and patient satisfaction after NovaSure and Minerva endometrial ablation for treating abnormal uterine bleeding: a retrospective comparative study* (Manuscript ID 153699)

Dear Ms. Jones:

I am writing to update you regarding our review of the above-referenced study, sponsored by Hologic Inc. ("Hologic"), which was published in the International Journal of Women's Health ("IJWH") on April 18, 2018. As you are aware, in January 2018 Minerva Surgical ("Minerva") submitted a complaint to IJWH regarding this study, which included allegations that the study was conducted in a manner that did not comply with applicable research standards and was intentionally skewed to prejudice Minerva's product. IJWH conducted an independent investigation into these allegations, in which Hologic fully cooperated, and determined that such allegations had no merit.

Unfortunately, upon publication of the study, Minerva has continued to engage in a widespread, highly unethical campaign to discredit Hologic and the study investigators with these false allegations. We understand that Minerva has raised additional complaints to IJWH regarding the study as recently as yesterday. Minerva's fraudulent campaign directly questions the scientific integrity of IJWH, as well as Dove's adherence to medical journal publication standards. Once again, we intend to fully cooperate with IJWH in its review of Minerva's complaints, and we are confident that IJWH will again conclude that Minerva's allegations have no merit.

Because Hologic takes false and deceptive allegations very seriously, no matter the source or motivations, we engaged outside counsel to conduct a review of the study and Minerva's allegations. They concluded that the study was executed in compliance with all applicable laws and standards, including applicable Good Clinical Practices (GCPs) and publication standards. Moreover, the review showed the investigators carried out their duties in a manner that was fully consistent with the protocol approved by the institutional review board (IRB). Thus, we continue to fully defend the study as an important addition to the body of scientific literature supporting endometrial ablation as a treatment option for women suffering from abnormal uterine bleeding.

We are shocked and disturbed by Minerva's attempt to gain business advantage via its fraudulent campaign, threatening the health of women who rely on their physician's access to accurate scientific information in order to make critical clinical decisions. Hologic cannot be silent in the face of such willfully deceptive practices. As such, we are writing to report on our review of this matter and reiterate Hologic's unwavering commitment to scientific integrity and ethical, compliant, and high quality clinical research. Below are our responses to Minerva's false and unfounded allegations regarding the study, which we will be providing to Minerva and the relevant scientific/medical community.

1. **Minerva Allegation: Hologic and/or investigators skewed the results of the study by "hand picking" NovaSure patients, and failed to include certain Minerva patients.**

In conducting research, Hologic holds itself to the highest quality and ethical standards. All Hologic employees with roles or responsibilities in clinical affairs and research are well-trained and required to abide by GCPs in all aspects of their work. The IJWH study protocol was designed and executed consistent with GCPs and Hologic policies and procedures in a manner that strictly prohibited Hologic's selection of patients and ensured that the comparison of products was scientifically sound and in accordance with protocol.

Specifically, the study protocol required investigators to identify patients who had undergone ablation with the NovaSure or Minerva device whose procedure date was after July 2015. The protocol specified that up to 300 patients would be enrolled, and that there would be a similar number of Minerva and NovaSure cases at each clinical site. Consistent with the study protocol, investigators were first required to identify such patients and then obtain their informed consent. If consented, the investigator then screened the patients' medical records for eligibility for participation in the study using the inclusion and exclusion criteria in the study protocol approved by the IRB. After the investigators had a sufficient number of eligible patients for statistical analysis per the protocol, the retrospective study commenced.

During the informed consent and eligibility screening process, Hologic personnel never determined which specific patients to include in the study, and investigators were directed to utilize only neutral criteria, such as date of treatment. In fact, other than initial site qualification visits to certain sites, Hologic did not conduct any site visits or monitoring of the investigators, as required under the study protocol, until after the investigators had already selected all of their eligible patients. Notably, all Minerva patients that consented and met inclusion/exclusion criteria per the protocol were enrolled by the investigators. Thus, the allegation that Hologic skewed the results of the study by "hand picking" patients is simply false, and enrollment proceeded strictly in accordance with the IRB-approved protocol.

2. **Minerva Allegation: Hologic and/or investigators skewed the study results by "cherry picking" patients based on 2-3 month bleeding status, and omitted 2-3 months follow up visit data because it somehow showed bias toward the NovaSure group in the study.**

As noted above, Hologic personnel did not access 2-3 month post-procedure bleeding status information during the informed consent or screening process. Thus, any allegation that Hologic or the investigators skewed the results of the study by choosing patients based on such status is false. Moreover, Minerva's allegation that the exclusion of 2-3 month bleeding status data from the IJWH publication somehow skewed the publication against Minerva is scientifically misguided. Based on prior feedback on the manuscript, Hologic and the authors determined that that the focus in the IJWH publication should be

on the more meaningful 11-12 months postoperative time point. We believe the omission of the 2-3 month bleeding status data is consistent with the clear consensus in the medical community that such data is not clinically relevant or predictive of outcomes in endometrial ablation.

3. **Minerva Allegation: There were clinically significant differences in the patient groups in the study due to differences in uterine sound lengths and intra-cavitary pathology.**

Minerva's allegation about differences in uterine sound lengths is simply incorrect. Table 2 in the IJWH article, entitled "Diagnostic and operative parameters and observations" includes data for the various diagnostic assessments and procedural parameters captured in the study. Both the NovaSure and Minerva devices are only cleared by FDA for use in patients with a uterine sounding length equal to or less than 10cm. As expressly listed in Table 2, the mean uterine sounding length for the NovaSure and Minerva cohorts were 8.2±1.8 and 8.6±0.9, respectively; and the medians were 9 (6-10) and 8 (6-10), respectively. Thus, there were no clinically significant differences in the patient groups with respect to uterine sound lengths, which is the only measurement identified in the device instructions for use and relevant to this procedure.

Minerva erroneously cited to the *ultrasound* uterine length measure listed under the diagnostics assessments, which has no relevance or clinical significance to the study or use of either device. Such a mistake further underscores the reckless and unfounded nature of Minerva's allegations.

Moreover, there was no statistically significant differences in the patient groups with respect to intra-cavitary pathology, and thus those outcomes do not prejudice Minerva in any way. Further, as noted above, Hologic played no role in selecting specific patients in the study.

4. **Minerva Allegation: Important conflicts of interests were not disclosed in association with the publication of the IJWH study.**

This claim is false. The IJWH study expressly acknowledged that the study was "funded by Hologic Inc." and included a disclosure statement that expressly acknowledged the material fact that "All authors were principal investigators in the current study and received compensation from Hologic for participation." Other investigator financial interests were submitted by the investigators directly to the IJWH in accordance with the journal's guidelines. None were material to the study in question.[1]

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Given the above, it is clear that Minerva is engaging in a false and highly unethical marketing campaign based on an intentional mischaracterization of the actions of Hologic and the investigators. These findings confirm the findings of the IJWH that the study was conducted with integrity and was appropriate for publication.

[1] While the study's disclosure statement did not acknowledge Dr. Stankiewicz receiving speaker fees from Hologic, Dr. Stankiewicz disclosed these fees directly to IJWH on his ICMJE form, in compliance with the journal's policies. It is our understanding that Dove reviewed Dr. Stankiewicz's disclosure form upon initial submission, and again during its initial investigation, and found no impropriety. We also understand that Dove did not ask or require Dr. Stankiewicz to amend the disclosure statement at any time.

Thank you for your continued attention to this matter.

Sincerely,

Edward Evantash, MD
Medical Director
Vice President, Global Medical Affairs

cc: Shay O'Neill
Constantine Scordalakes, MD
Robert delRosario, MD
Andrew Shimer, MD
Russell Stankiewicz, MD
Matthew Silverman