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**Laser versus Sham for Genitourinary Syndrome of Menopause: a Randomised Controlled Trial.**

**Our reply to letter by S Salvatore, L Cardozo, A Ruffolo and S Athanasiou.**

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**Running title:** Letter to the Editor

**LETTER TO THE EDITOR**

Dear Editor,

We read with interest the comments on our study “Laser versus Sham for Genitourinary Syndrome of Menopause: a Randomised Controlled Trial.” We thank the authors for their comments and are glad to provide additional clarification.

As to the laser settings in the treatment group, they were as provided by the manufacturer, also used by others, hence would be what the average user would use. This makes our observations probably widely generalizable. We agree that operators very familiar with laser application may want to optimize settings according to the individual patient and clinical presentation, but such variation cannot be part of a double blind study design and its results would not apply to a general population.

Indeed, for an as close as possible simulation of the laser treatment procedure, the *placebo* procedure was done with the same device, yet using the minimum of energy the machine can deliver. We assume this is also what was done in other studies in an effort to blind patients and operators. According to the machine the energy generated was 15mJ.

As to the sample size and statistical analyses, we want to emphasize that our sample size was *not* based on the hypothesis that sham application *would not be effective*, yet on a sham-effect of 45%, as has been earlier reported for this condition.1 Neither did this trial have a *non-inferiority design*; conversely it was adequately powered for equality or superiority. We are sorry if that was not clear in our manuscript.

Last, we indeed report on the changes in the *most bothersome symptom* (MBS; i.e. a participant-selected single symptom) in the *entire* population, categorized as either moderate or severe. The VAS scores are secondary outcomes, for which the study was not powered, hence reported with descriptive statistics. Our conclusions were for obvious reasons not based on these.

We agree that missing information on exact numbers of sexually active participants is one of the shortcomings of our report.

Finally, we do not agree that reporting the 18-months follow up is meaningless. First, this was one aim of the study and is exactly what regulators have been asking.2-4 Long term documentation of the safety of laser therapy is an additional strength of our study, which is relevant for any patient choosing for this treatment modality. Apart from that, participants at every follow-up visit were offered either repetitive laser or alternative treatments for GSM-symptoms. Using identical assessment methods at all time points, as many as 64.4% (35/57) eventually reported their symptoms as insufficiently improved. Of those, only five asked for additional laser treatment, whereas the others preferred alternatives.

Therefore, our findings add to the growing experience within the rigorous context of well designed, appropriately powered randomized clinical trials, of which one is ours, reporting apparently opposing results. For patients and physicians alike, it would be good that individual data from those studies are pooled whenever possible, resulting by the additional power of a meta-analysis into a more robust evaluation of this new technology.

**AUTHOR CONTRIBUTIONS**

ASP, JV and JDP conceptualized, drafted and approved this manuscript.

**ACKNOWLEDGEMENT**

None.

**FUNDING INFORMATION**

None.

**CONFLICT OF INTERESTS**

None.

**DATA AVAILABILITY STATEMENT**

Not applicable.

**ETHICS APPROVAL**

Not applicable.

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