Author’s response to reviews

Title: Safety and efficacy of a standardized intracameral combination of mydriatics and anesthetic for cataract surgery in type-2 diabetic patients.

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BOPH-D-19-01108R1

Safety and efficacy of a standardized intracameral combination of mydriatics and anesthetic for cataract surgery in type-2 diabetic patients.

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BMC Ophthalmology
Dear Dr. Crnej,

Thank you for providing the Editor and Reviewer comments for our manuscript "Safety and efficacy of a standardized intracameral combination of mydriatics and anesthetic for cataract surgery in type-2 diabetic patients." (BOPH-D-19-01108R1). Please find below our point-by-point response to the comments. We thank the Editor and the Reviewers for helping us refine this manuscript.

We remain, at your disposal for any further queries.

Sincerely,

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Editor Comments:

Dear authors, nice work and a lot of data gathered initially for an important product on the market.

Response: Thank you very much for the encouraging comment

Please see my comments below:
1. You are not mentioning the seniority of the surgeon, which is very important. Surgeons with more experience are happy with smaller mydriasis, so they decide for additional "help" at the later stage or not at all. Surgeons seniority has to be comparable between the groups. Please add this info.

Response: We have added the following as the first 2 sentences in the Administration of Study Medications subsection of the Methods section (page 6, lines 130-136): “All investigators involved in this study had been selected on the basis of their experience (high volume cataract surgeries for several years) and their acceptance of being videorecorded for the purpose of masked analysis of the pupil size and other endpoints. Additionally, the randomization (ICMA vs. topical eye drops) was performed just before the surgery in order to keep the groups comparable (no possibility of changing the surgeon at the last moment), which was verified (comparable numbers of patients randomized in each group for a given investigator).”

Additionally in page 19, lines 569-572 of the Discussion section we have added the following sentence: “Surgeon experience was likely not a factor in the outcomes as the same surgeons performed surgery in diabetics and non-diabetic patients, hence surgeon seniority, experience and skill should affect both groups equally”.

2. Please add which viscoelastic was used. Again - certain viscoelastics keep the pupil open, the others do not. In order for the groups to be comparable, the viscoelastics used must be similar between the groups.

Response: We have added the following as the last sentence in the Administration of Study Medications subsection of the Methods section (page 7, lines 147-148): Duovisc (Alcon Inc., Fort Worth, TX, USA) viscoelastic was used for all surgeries.

3. Results line 285 - 289 - these are the results of one group. Either you already mentioned them before, then delete; or you add the information about the second group.

Response: We added the information for the second group (Topical Group) in this paragraph in the Discussion section, page 15, lines 394-395
4. The sequence of the two groups is not the same throughout the paper (for example icma first and topical second). Please correct.

Response:

The order has been corrected throughout the paper including the tables.

5. Please shorten discussion significantly (remove all results). Results found in lines: 302-309, 313-317, 331-335, 358-371, 375-381.

Response: We have shortened the Discussion. Original lines 302-309, 330-338, 359-362 have been deleted.

Original lines 313-317 have been changed as follows (page 16, lines 431-436): “We found that the change in intraoperative pupil size in diabetics in the ICMA Group was smaller than in the Topical Group of diabetics. These outcomes for diabetics are comparable to previous experience with ICMA in non-diabetics and studies20 of a topical regimen on non-diabetics.”

Original lines 358-371 have been changed as follows (Last paragraph of page 17, lines 491-495 and page 18, lines 537-540): “Surgeons graded surgery as mostly uncomplicated in both diabetic groups. In the current study, there were no safety concerns regarding the use of ICMA in diabetics. For example, there were no ocular or systemic events related to the study medications. The ocular AEs that occurred in the two diabetics in the ICMA Group were mild and resolved with observation without further sequelae. One serious case of transient ischemic attack occurred in one diabetic patient in the ICMA Group that was deemed by the investigator as unrelated to the study medication (occurred 6 days postoperatively and was more likely due to a history of vascular disorders, including high blood pressure and a stroke 4 years previously). Endothelial cell loss was similar in diabetics and non-diabetics.”
Original lines 375-381 - We believe that the effect of multiple injections of ICMA requires documentation and discussion as it is a common question that we, the authors, are often asked. Hence, we request the Reviewers to keep most of this section and we have modified the sentences as follows (page 18, lines 545-548): “Endothelial cell loss was greater in patients who received 2 or more injections of ICMA in both diabetics and non-diabetics. During the phase 3 study, surgeons were allowed to deliver more than one injection of ICMA if they deemed the pupil size was inadequate.”

Reviewer reports:

Mercè Morral (Reviewer 1):

Dear authors, this is a post-hoc subgroup analysis of a previous phase 3 study that shares interesting data on diabetic patients. Authors have adequately described the limitations of the study (small sample size not adequately powered for subgroup analysis). In this context, I would encourage you to add the following data:

1. Page 8: efficacy variables: "Additional mydriatic treatments were, pupillary expansion device and/or instillation of extra medication(s) for mydriasis that were not included in the clinical trial protocol" Describe which type of "additional medications for mydriasis" were used.

Response:

We have included a description on page 7/8, lines 163-171 as follows : “Additional mydriatic treatments were pupillary expansion device and/or instillation of extra medication(s) for mydriasis (for example, extra drops of phenylephrine, cyclopentolate, and/or tropicamide) that were not included in the clinical trial protocol, between the initial delivery of the intracameral or topical regimen and capsulorhexis.”

2. Results: add standard deviation and range to all variables (pupil size, duration of surgery, etc..)

Response:

The manuscript has been revised to include standard deviation and range to all variables, including in the tables.
3. Authors describe adverse events as mild or moderate: could you define the following? These are not standard terms. How were they determined?

Response: We have used the Medical Dictionary for Regulatory Activities (MedDRA) definitions. MedDRA is a standard used in clinical trials worldwide and this was defined in the clinical study protocol.

We have included the following descriptions page 8, 180-188:

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA)12 (as defined in the clinical study protocol) and their severity graded using the following scale: mild - visible to the subject, but did not need any additional treatment and did not interfere with the subject’s daily activities; moderate - troublesome, could require an additional treatment, but did not interfere with the subject’s daily activities; severe - intolerable, could require an additional treatment or a modification of this treatment, could interfere with the subject’s daily activities.

4. Why was ECC not measured in all patients?

Response: At the time of the study, specular microscopes were not available at all the sites, and asking patients to travel for endothelial microscopy measurement would have induced a selection bias (e.g. towards younger patients, more prone to accept additional steps in the procedure and more mobile). Hence, for immediate feasibility and mitigating bias, we selected some centers with specular microscopes and these centers included a representative proportion of the whole study population, which allowed a reliable analysis of the data.

We have thus included the following on page 8, line 180: … and endothelial cell counts (ECC; at designated study sites based on availability of a specular microscope).

Thiemo Rudolph, M.D. (Reviewer 2):

Dear Author, in my opinion your subgroup analysis of a well documented, large randomized study is a valid and worthwhile approach. However, I would recommend a few clarifications and some shortening of the manuscript text. Specifically, I would like to address the following issues:
Abstract: when reading the abstract, it is confusing that the ICMA group is said to consist of 24/57 patients, followed by the statement that 24\%(96\%) patients had successful capsulorhexis, when you actually refer to 24/25 patients. This is later explained by the differences between ITT and mITT set in lines 178ff. and the switch of one patient from topical to ICMA, but I suggest rephrasing this part of the abstract to avoid this confusion.

Response: We have modified the Results subsection of the Abstract to include the patient data set that the proportions were derived from. The changes have been made in lines 48-50 and 53-55.

line 52: No diabetic patient (singular)

Response:

Lines 51-52 in the Results subsection of the Abstract has been changed to “...no diabetic patient...”

Results: you are explaining the different patient sets (ITT, mITT, mITT-An), but from the results you mention in the text, it is not always clear which of the different sets you refer to, unless the reader recalculates the percentage values. As an example, line 216 states that 19\%(82.6\%) of the ICMA group had no sign. change in pupil size. 82.6\% means that you refer to 19/23 patients, which is the mITT-An subset. In this example it is also not clear why the reference is not the mITT set with 24 patients. I suggest reporting the results in a different format, for example 82.6\% (19/23, mITT-An group).

Response:

As suggested by the Reviewer, we have modified the Results section of the Manuscript to include the patient data set that the proportions were derived from. The changes are in pages 10-15, lines 230-243, 261-264,280-28,295,321,388,399-400.
Discussion: I would suggest shortening of the discussion somewhat. Just giving one example, the first sentence in line 313 could be omitted. Furthermore, I advise caution in the way you present the advantages of ICMA in the discussion. From a more neutral perspective, this subgroup analysis shows that ICMA works as well for diabetes patients as for the original study group and does not seem inferior to a topical protocol. Limiting the discussion to a few explanations and careful conclusions is especially advisable in a setting where the study is exclusively focused on a single commercial product.

Response: We have shortened the Discussion and modified sentences that presented advantages of ICMA.

The following changes have been made:

Original lines 302-309, 330-338, 359-362 have been deleted.

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