PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Visual and Refractive Outcomes of Small-Incision Lenticule Extraction for the Correction of Myopia: One-Year Follow-Up.
AUTHORS	Kamiya, Kazutaka; Shimizu, Kimiya; Igarashi, Akihito; Kobashi, Hidenaga

VERSION 1 - REVIEW

REVIEWER	Alper Ağca Beyoglu Eye Training and Research Hospital
REVIEW RETURNED	14-May-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Iben Bach Pedersen, MD Department of Ophthalmology, Aarhus University Hospital, Denmark
REVIEW RETURNED	30-May-2015

GENERAL COMMENTS	The subject of the article is very interesting, as only a limited number of studies have assessed long-term results after SMILE. Consider following: Abstract: Page 3, l 21. It would be preferable to mention the range of spherical equivalent. Page 3 l 41. Was the change in manifest refraction from 1 week to 1 year significant? Results: In general: Many studies have shown 3 months results of SMILE. It is interesting to see the development from 3 months to 1 year. I would suggest illustrating the 3-month results in Figure 1,2, and 4, in the same graph with 1-year results, to compare difference. Furthermore, there should be a graph showing the development in astigmatism; a graph with the percent of patients reaching specified levels of astigmatism pre and 1 year postoperative. (=<0,25, 0,26-0,50, 0,51-0,75 ect). The efficacy and safety index is commonly used to evaluate

	outcome after refractive surgery. They should be calculated and mentioned under results. Page 13 l 12: As mentioned earlier: was the change in manifest refraction significant from 1 week to 1 year significant? One of the interesting in long term studies after SMILE is to evaluate if there is myopic regression years after operation. Page 13 l 40: It is mentioned that suction loss happened in one case. How was CDVA one year after surgery in this case? Was he/she one of those who lost 2 lines of CDVA? Discussion: For complete overview, it would be preferable to mention the results from Reinstein et al. and Xu et al. in the Table (reference 20 and 21). Page 16, l 15: Check spelling (Hjortdal et al.)

REVIEWER	Dr Sheetal Brar Nethradhama Superspeciality Eye Hospital, Bangalore, India
REVIEW RETURNED	17-Jul-2015

GENERAL COMMENTS	1. Manuscript needs correction for punctuation and grammer by native English speaker 2. Abstract needs to be updated for mean age and mean follow up 3. If 9 eyes lost 1 line and 2 eyes lost 2 lines of CDVA post operatively at 1 year, then how is it possible to have 20/20 vision or more? 4. Was the change in manifest SE from 1 week to 1 year statistically significant? 5. Safety and efficacy indices at 1 year need to be calculated 6. The authors have compared endothelial cell density before and after SMILE and shown that there was no significant change at 1 year. However,they have not clarified the very purpose of studying endothelial cell loss after SMILE. Till date there has not been a single report of corneal decompensation or oedema post SMILE. If the authors have concerns about endothelial cell loss due of lenticule creation with femtolaser , it would be more relevant to analyse the endothelial changes in three categories- low myopia upto 3 D , moderate myopia 3-6 D and high myopia >6D groups and study the change over all post operative visits until 1 year. They should provide data of mean lenticule thickness in each group and then correlate with endothelial cell density changes. They should elaborate this data in a table and find statistical significance of changes compared to preoperative values at all post operative visits. 7. It was also recently shown by Ganesh et al that even combining SMILE with accelerated cross linking for higher degrees of myopia and thinner corneas is safe and do not cause significant changes in endothelial cell density after 1 year. Therefore, significant endothelial changes are not expected in routine cases of SMILE. 8. The authors have stated that this is the first long term study with 1 year follow up on the safety and efficacy of SMILE. However, Sekundo et al have already published 1 year and recently 5 year outcomes of SMILE.

REVIEWER	Rupal Shah New Vision Laser Centers-Centre for Sight, India I am a consultant for the company(Carl Zeiss Meditec), which manufactures the laser used in the procedure highlighted here
REVIEW RETURNED	27-Jul-2015

GENERAL COMMENTS	The paper is well written and complete. While it does not address anything new, and the data merely reiterates the data in many other studies of this nature, including in the time frame, as the authors state, it is important for a new procedure to be studies in different groups in terms of ethnicity, amount of myopia, age etc. In this sense, the authors have answered important questions. My only minor quibble is that the authors reiterate a few times throughout the discussion and introduction is that this is the first time anybody has studied endothelial cell counts for refractive lenticule extraction. However, in reference 5 (published by the same group), they have already studied endothelial cell counts. While that study was for FLEx, and not SMILE, the authors do make any case why FLEx and SMILE should have differing results on endothelial cell counts.

VERSION 1 – AUTHOR RESPONSE

To Reviewer: 1 Reviewer Name Alper Ağca
Institution and Country Beyoglu Eye Training and Research Hospital Accept
Thank you for your consideration in this matter.

To Reviewer: 2 Reviewer Name Iben Bach Pedersen, MD
Institution and Country Department of Ophthalmology, Aarhus University Hospital, Denmark
The subject of the article is very interesting, as only a limited number of studies have assessed long-term results after SMILE.
Thank you for your positive comments for revision.

Consider following: Abstract:
Page 3, l 21. It would be preferable to mention the range of spherical equivalent.
[Page 3, lines 5-8]: One sentence has been modified.
“This prospective study evaluated fifty-two eyes of 39 consecutive patients with spherical equivalents of -4.11 ± 1.73 D [mean ± standard deviation][range, -1.25 to -8.25 D] who underwent SMILE for myopia and myopic astigmatism.”

Page 3 l 41. Was the change in manifest refraction from 1 week to 1 year significant?
[Page 3, lines 14-15]: One sentence has been modified.
“Manifest refraction changes of -0.05 ± 0.32 D occurred from 1 week to 1 year postoperatively (p=0.20, Wilcoxon signed-rank test).”
[Page 13, lines 5-8]: One sentence has been modified.
“Manifest spherical equivalent was not significantly decreased, from 0.00 ± 0.35 D 1 week postoperatively, to -0.05 ± 0.16 D 1 year postoperatively (p=0.20, Wilcoxon signed-rank test).”

Results: In general: Many studies have shown 3 months results of SMILE. It is interesting to see the development from 3 months to 1 year. I would suggest illustrating the 3-month results in Figure 1,2,

and 4, in the same graph with 1-year results, to compare difference. Furthermore, there should be a graph showing the development in astigmatism; a graph with the percent of patients reaching specified levels of astigmatism pre and 1 year postoperative. (=<0,25, 0,26-0,50, 0,51-0,75 ect).
We have added the 3-month results of SMILE in Figures 1, 2, and 4. We have also added a graph showing the development in astigmatism in Figure 5.

The efficacy and safety index is commonly used to evaluate outcome after refractive surgery. They should be calculated and mentioned under results.
We have calculated the safety and efficacy indices at all postoperative visits.
[Page 11, lines 13-15]: One sentence has been added.
"The safety index was 0.86 ± 0.17, 0.95 ± 0.24, 0.97 ± 0.21, 0.97 ± 0.21, and 1.00 ± 0.20, 1 week, 1, 3, and 6 months, and 1 year postoperatively, respectively."
[Page 12, lines 6-8]: One sentence has been added.
"The efficacy index was 0.75 ± 0.21, 0.83 ± 0.24, 0.84 ± 0.25, 0.86 ± 0.25, and 0.91 ± 0.25, 1 week, 1, 3, and 6 months, and 1 year postoperatively, respectively."

Page 13 l 12: As mentioned earlier: was the change in manifest refraction significant from 1 week to 1 year significant? One of the interesting in long term studies after SMILE is to evaluate if there is myopic regression years after operation.
We found no significant change in manifest spherical equivalent from 1 week to 1 year postoperatively.
[Page 13, lines 5-8]: One sentence has been modified.
"Manifest spherical equivalent was not significantly decreased, from 0.00 ± 0.35 D 1 week postoperatively, to -0.05 ± 0.16 D 1 year postoperatively (p=0.20, Wilcoxon signed-rank test)."

Page 13 l 40: It is mentioned that suction loss happened in one case. How was CDVA one year after surgery in this case? Was he/she one of those who lost 2 lines of CDVA?
CDVA as well as UDVA was excellent (20/16)(-0.10 logMAR) 1 year postoperatively in this eye.
[Page 14, lines 5-6]: One sentence has been added.
"This eye had UDVA and CDVA of 20/16 1 year postoperatively."

Discussion: For complete overview, it would be preferable to mention the results from Reinstein et al. and Xu et al. in the Table (reference 20 and 21).
We have added the data by Reinstein et al. and Xu et al. in modified Table 3.
[Page 15, lines 16-18]: One sentence has been modified.
"Reinstein et al20 and Xu et al21 reported that 91% and 99% of eyes had an unchanged CDVA or gained lines, and that 96% and 83% of eyes had a UDVA of 20/20 1 year postoperatively, respectively."
[Page 16, lines 12-13]: One sentence has been modified.
"With regard to predictability, 77 to 100% and 94.2 to 100% of eyes have been reported to be within ± 0.5 and 1.0 D of the targeted correction, respectively.6-8,10,11,15-21"
[Page 17, lines 11-13]: Two sentences have been modified.
"Reinstein et al20 reported that the mean refraction was 0.10 D, -0.05 D, and -0.05 D, 1, 3, and 12 months after surgery, respectively. Xu et al21 showed that the change in manifest refraction from 1 day to 1 year was -0.06 ± 0.37 D."
We have modified Table 3.

Page 16, l 15: Check spelling (Hjortdal et al.)
We have corrected spelling. Thank you for your correction.
[Page 15, lines 12-14]: One sentence has been modified.
"Hjortdal et al11 also demonstrated that the safety and efficacy indices were 1.07 ± 0.22 and 0.90 ± 0.25 3 months postoperatively, respectively."

[Page 16, lines 14-16]: One sentence has been modified.
“Hjortdal et al11 stated that the average difference between achieved correction and attempted correction was 0.25 D of undercorrection, which may be added when planning SMILE.”

To Reviewer: 3 Reviewer Name Dr Sheetal Brar
Institution and Country Nethradhama Superspeciality Eye Hospital, Bangalore, India
Thank you for your insightful comments for revision.
1. Manuscript needs correction for punctuation and grammer by native English speaker
We have corrected punctuation and grammar again by a native English speaker.

2. Abstract needs to be updated for mean age and mean follow up
We have added the data of mean age. No eyes were lost during the 1-year follow-up in this series, and thus mean follow-up is 1 year.
[Page 3, lines 5-8]: One sentence has been modified.
“This prospective study evaluated fifty-two eyes of 39 consecutive patients (31.8 ± 6.9 years, mean age ± standard deviation) with spherical equivalents of -4.11 ± 1.73 D (range, -1.25 to -8.25 D) who underwent SMILE for myopia and myopic astigmatism.”
[Page 11, line 8]: One sentence has been modified.
“No eyes were lost during the 1-year follow-up in this series.”

3. If 9 eyes lost 1 line and 2 eyes lost 2 lines of CDVA post operatively at 1 year, then how is it possible to have 20/20 vision or more?
Two and nine eyes had CDVAs of 20/12.5 and 20/16 preoperatively, respectively.

4. Was the change in manifest SE from 1 week to 1 year statistically significant?
We found no significant change in manifest spherical equivalent from 1 week to 1 year postoperatively.
[Page 13, lines 5-8]: One sentence has been modified.
“Manifest spherical equivalent was not significantly decreased, from 0.00 ± 0.35 D 1 week postoperatively, to -0.05 ± 0.16 D 1 year postoperatively (p=0.20, Wilcoxon signed-rank test).”

5. Safety and efficacy indices at 1 year need to be calculated
We have calculated safety and efficacy indices at all postoperative visits.
[Page 11, lines 13-15]: One sentence has been added.
“The safety index was 0.86 ± 0.17, 0.95 ± 0.24, 0.97 ± 0.21, 0.97 ± 0.21, and 1.00 ± 0.20, 1 week, 1, 3, and 6 months, and 1 year postoperatively, respectively.”
[Page 12, lines 6-8]: One sentence has been added.
“The efficacy index was 0.75 ± 0.21, 0.83 ± 0.24, 0.84 ± 0.25, 0.86 ± 0.25, and 0.91 ± 0.25, 1 week, 1, 3, and 6 months, and 1 year postoperatively, respectively.”

6. The authors have compared endothelial cell densit before and after SMILE and shown that there was no significant change at 1 year. However, they have not clarified the very purpose of studying endothelial cell loss after SMILE. Till date there has not been a single report of corneal decompensation or oedema post SMILE. If the authors have concerns about endothelial cell loss due of lenticule creation with femtolaser , it would be more relevant to analyse the endothelial changes in three categories- low myopia upto 3 D , moderate myopia 3-6 D and high myopia >6D groups and study the change over all post operative visits until 1 year. They should provide data of mean lenticule thickness in each group and then correlate with endothelial cell density changes. They should elaborate this data in a table and find statistical significance of changes compared to preoperative values at all post operative visits.
We have analyzed the endothelial changes in three categories (low myopia, moderate myopia, and high myopia). As mentioned in Methods section, we assessed the endothelial cell density

preoperatively and 1 year postoperatively. We have provided the preoperative and postoperative data of endothelial cell density according to the degree of myopia (low, moderate, high myopia) in Table 2. We have also evaluated the relationship of the endothelial cell loss with the amount of spherical equivalent correction and the lenticule thickness in this series.
[Page 13, lines 15-16]: One sentence has been added.
"The preoperative and postoperative endothelial cell density and the lenticule thickness according to the degree of myopia are shown in Table 2."
[Page 13, lines 18-19, and Page 14, lines 1-2]: One sentence has been modified.
"We found no significant correlation of the endothelial cell loss, with the amount of spherical equivalent correction (Spearman correlation coefficient r=0.14, p=0.34), or with the lenticule thickness (r=0.12, p=0.38)."
We have added Table 2.

7. It was also recently shown by Ganesh et al that even combining SMILE with accelerated cross linking for higher degrees of myopia and thinner corneas is safe and do not cause significant changes in endothelial cell density after 1 year. Therefore, significant endothelial changes are not expected in routine cases of SMILE.
We have cited the reference by Ganesh et al, and have mentioned the change in the endothelial cell density after SMILE with accelerated cross-linking in Discussion.
[Page 18, lines 2-5]: One sentence has been modified.
"Ganesh et al recently reported that the endothelial cell density was not significantly changed, from 2695.13 ± 222.8 cells/mm2 preoperatively, to 2682.5 ± 231.8 cells/mm2 1 year postoperatively, in eyes undergoing SMILE with accelerated cross-linking.25"
[Page 24, lines 13-15]: One reference has been added.
"25. Ganesh S, Brar S. Clinical Outcomes of Small Incision Lenticule Extraction with Accelerated Cross-Linking (ReLEx SMILE Xtra) in Patients with Thin Corneas and Borderline Topography. J Ophthalmol. 2015;2015:263412."

8. The authors have stated that this is the first long term study with 1 year follow up on the safety and efficacy of SMILE. However, Sekundo et al have already published 1 year and recently 5 year outcomes of SMILE.
Thank you for your insightful comments. We have cited the paper regarding the 1-year outcomes by Sekundo et al. Although we did not found any peer-reviewed literature of the 5-year outcomes of SMILE by PubMed search on August 12, 2015, we have deleted the following sentence.
[Page 14, lines 17-18, and Page 15, line 1]: One sentence has been deleted.
"To the best of our knowledge, this is one of the longest-term studies to assess the safety, efficacy, predictability, stability, and adverse events of SMILE.15,20,21"
[Page 23, lines 5-8]: One reference has been added.
"15. Sekundo W, Gertnere J, Bertelmann T, et al. One-year refractive results, contrast sensitivity, high-order aberrations and complications after myopic small-incision lenticule extraction (ReLEx SMILE). Graefes Arch Clin Exp Ophthalmol. 2014;252:837-843."

To Reviewer: 4 Reviewer Name Rupal Shah
Institution and Country New Vision Laser Centers-Centre for Sight, India
The paper is well written and complete. While it does not address anything new, and the data merely reiterates the data in many other studies of this nature, including in the time frame, as the authors state, it is important for a new procedure to be studies in different groups in terms of ethnicity, amount of myopia, age etc. In this sense, the authors have answered important questions.
Thank you for your positive comments for revision.

My only minor quibble is that the authors reiterate a few times throughout the discussion and introduction is that this is the first time anybody has studied endothelial cell counts for refractive

lenticule extraction. However, in reference 5 (published by the same group), they have already studied endothelial cell counts. While that study was for FLEx, and not SMILE, the authors do make any case why FLEx and SMILE should have differing results on endothelial cell counts.
We agree with your opinion that SMILE is essentially equivalent to FLEx in terms of corneal endothelial cell density, since both surgical techniques are similar, except for the presence or absence of corneal flap making, and thus we have deleted the following statements in our manuscript.
[Page 5, lines 4-8]: Two sentences have been modified.
"Moreover, the endothelial cell loss after this surgical procedure, which is a major concern in the prognosis of the patient, has not so far fully elucidated. Although we did not assess the other aspects of this surgical technique on corneal biomechanics and ocular surface in this study, this is one of the long-term studies to assess the safety, efficacy, predictability, stability, and adverse events of SMILE."
[Page 7, lines 2-5]: One sentence has been deleted.
"Moreover, the endothelial cell loss after this surgical procedure, which is a major concern in the prognosis of the patient, since this technique requires photodisruption not only for thinner cap making but also for deeper lenticule manufacture, has not so far been investigated."
[Page 17, lines 17-18]: One sentence has been deleted.
"To our knowledge, this is also the first study to assess the endothelial cell density after SMILE."

VERSION 2 – REVIEW

REVIEWER	Iben Bach Pedersen, MD Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark
REVIEW RETURNED	23-Aug-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Sheetal Brar Nethradhama Superspeciality Eye Hospital, Bangalore
REVIEW RETURNED	12-Sep-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.