

Input from external experts and manufacturer on the **2nd draft assessment**
“Femtosecond laser-assisted cataract surgery (FLACS) for the treatment of
age-related cataract”
(Project ID:OTCA07)



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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT



The 2nd version of the Rapid Assessment on **Femtosecond laser-assisted cataract surgery (FLACS) for the treatment of age-related cataract** was open to review between 17/07/2018 and 14/08/2018.

EXTERNAL EXPERTS

Comments were received from:

Name	Affiliation
Professor Gianmaria Cavallini	Azienda Ospedalerio Universitaria di Modena, Italy
Dr Tommaso Verdina	Azienda Ospedalerio Universitaria di Modena, Italy
Dr Marco Vecchi	AUSL-IRCCS di Reggio Emilia

Comment from	Page number	Line or section number	Comment and suggestion for rewording <i>Please insert each new comment in a new row.</i>	Character of comment • 'major' ^a =1 • 'minor' ^b = 2 • 'linguistic' ^c =3	Author's reply
Gianmaria Cavallini Tommaso Verdina	General		We carefully revised the second draft of the assessment on FLACS for the treatment of cataract. It is very interesting and well done, everything seems to be correct to us and we don't have any other comment to address.		Thank you
Marco Vecchi	General		I do not have any comment or suggestion to append to your file. Everything seems to be fine by my personal point of view.		Thank you

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Manufacturers

Comments were received from:

Name

Alcon (Novartis)	Factual accuracy check
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Description and technical characteristics of the technology					
Alcon	51	1060	<p>[B0002] – What is the claimed benefit of FLACS in relation to standard cataract surgery?</p> <p>We are of the considered view that there are a number of potential benefits associated with FLACS that have not been outlined in this section of the Draft Assessment, we have detailed these below and request that these be included in the final assessment:</p> <ol style="list-style-type: none"> 1. FLACS may allow less experienced surgeons to obtain better results 2. FLACS may be beneficial for complex cases 3. FLACS contributes to refractive potential of IOLs through effective lens positioning: 4. FLACS may help reduce the risk of posterior capsular opacification requiring YAG capsulotomy: <ol style="list-style-type: none"> 1. FLACS may allow less experienced surgeons to obtain better results 	1	<p>The additional proposed claimed benefits have not been considered relevant during Scoping, nor suggested or recognized as such by external experts, nor are they acknowledged in the biomedical literature that met inclusion criteria of this REA.</p> <p>This extensive comment is not a “factual accuracy check” and no reply can be provided as per EUnetHTA procedures.</p> <p>Manufacturer should note that:</p> <p>Comments and suggestions provided do not comply with the Eunetha code of conduct of manufacturers' participation.</p> <p>Most issues have already been raised and addressed during the review of the Project Plan</p> <p>The references and the methods of</p>

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			<p>A well-centered, sized, shaped, intact (anterior tear), capsulotomy is critical to the safety and efficacy of cataract surgery and is recognised as the most difficult step of manual phacoemulsification by trainee surgeons (Dooley et al., 2006). As detailed in the points above, consistently sized and shaped capsulotomy with greater precision appears to be a significant advantage of FLACS; thus, it is the case that FLACS (including LenSx® Laser) may allow less experienced surgeons to obtain better results (Triakha et al., 2013).</p> <p>In Brunin et al. (2017), Cohen et al. (2015) & Hou et al. (2015), the authors conclude that FLACS can be safely incorporated into surgical training programmes and that the technology is safe and effective compared to manual cataract surgery when performed by less experienced surgeons. It is also the case that in Brunin et al (2017), a higher rate of posterior capsule tear was apparent in the manual phaco group, while in Hou et al (2015), fewer complications were also noted in the FLACS group (In total, four posterior capsular tears and one burn wound occurred in the manual group, and in both instances the figure for FLACS was zero). In both studies, FLACS cases were performed using the LenSx® Laser platform.</p> <p>With respect to anterior (AC) and posterior capsule (PC) tears – Roberts et al. (2013) in a prospective study of 1500 patients, reported rates of 0.32 and 0.08%, respectively for patients receiving FLACS</p> <ul style="list-style-type: none"> • This is significantly less than the 0.79% to 5.6% for AC and 0.24% to 4.05% for PC tears reported in the medical literature with manual capsulotomy creation (Roberts et al., 2013) <p>2. FLACS may be beneficial for complex cases:</p>		<p>presenting data proposed by the manufacturer do not meet the necessary scientific requirements to be taken into consideration in a EUnetHTA relative effectiveness assessment.</p> <p>Please review EUnethta guidances, Core Model Handbook and methods section of this REA for a comprehension of high quality assessment.</p> <p>Should manufacturers disagree with EUnethta methodology, they are advised to publish an health technology assessment in a peer reviewed journal, comprehensively reporting on their chosen methodology .</p>

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			<p>Complex cataracts remain a challenge to the cataract surgeon. The incidence of posterior capsule tear in routine phacoemulsification has been reported to be between 0% and 4% (Ionides et al., 2001). White cataracts are associated with an increased risk for incomplete anterior capsulotomy and a posterior capsule tear rate up to 11% (Vasavada et al., 1998). In Taravella et al. (2016), the authors conclude that their study results suggest that femtosecond lasers (LenSx® Laser) can be used successfully in cases of white cataracts, dense brunescant lenses, and cataracts in which zonulopathy is encountered. The main utility of FLACS in these cases appears to be in the creation of the capsulotomy. This step can be especially difficult in patients with white cataracts and zonulopathy. Novice surgeons in particular might benefit from a reliable method of capsulotomy formation and lens fragmentation in complex cataracts cases (Taravella et al, 2016).</p> <p>This technology can also be successfully used in certain cases of phacomorphic glaucoma, even if mechanical pupil dilatation is needed (Kranitz et al., 2013). Laser capsulotomies are approaching the smoothness of manual capsulorhexis. The LenSx® post-soffit platform showed the least anomalies and the smallest difference for the coefficient of variation CoV and homogeneity metrics compared with the manual method (Bala et al., 2013).</p> <p>Furthermore, Femtosecond laser-assisted cataract surgery is an effective approach for cataract surgery in patients with Marfan syndrome with mild, moderate, and even severe lens subluxation, due to the benefits of causing minimal further zonular damage (Crema et al., 2015).</p> <p>Research has demonstrated that FLACS reduces the rate of corneal endothelial cell loss and uses lower CDE with a shorter EPT than conventional phacoemulsification surgery (Mayer., 2014, Mastropasqua., 2014, Nagai., 2009, Takács., 2012). It has been shown that these factors are</p>		

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			<p>especially important for patients with pre-existing corneal endothelial cell dysfunction such as Fuchs endothelial dystrophy (Mayer., 2014)</p> <p>Indeed, in Fan et al., 2018, the authors concluded that for eyes with Fuchs endothelial corneal dystrophy and cataract, the Central Corneal Thickness (CCT) 12 months after surgery remained thicker than the preoperative thickness. The FLACS group, with a lower CDE, tended to have a thinner CCT and less endothelial cell loss than the phacoemulsification group. The authors also posit that FLACS surgery in these patients might reduce the rate of ECD loss and central cornea thickening and thus postpone the need for corneal transplantation</p> <p>3. FLACS contributes to refractive potential of IOLs through effective lens positioning:</p> <p>The evidence suggests that LenSx® contributes to refractive potential of IOLs through effective lens positioning. In Stephen et al. (2013), the authors report that the variation in the effective lens positioning is significantly less with LenSx® compared with manual phaco. While in He et al. (2012), a significant reduction in intraocular vertical tilt was demonstrated in procedures using LenSx® compared with manual phacoemulsification.</p> <p>FLACS may help reduce the risk of posterior capsular opacification requiring YAG capsulotomy:</p> <p>The evidence also suggests that FLACS may help reduce the risk of posterior capsular opacification (33% lower risk) (Kovacs et al., 2014) and in requiring subsequent ND:YAG capsulotomy: in a comparison between LenSx® with</p>		

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			<p>manual phacoemulsification, 11.5% patients in the LenSx® group vs. 15.2% patients in the manual phaco group required YAG capsulotomy due to posterior capsular opacification. Therefore, patients undergoing manual phacoemulsification were 1.24 times more likely to require YAG capsulotomy compared with patients undergoing LenSx® over the period of three years (RR: 1.24 (0.95-1.62) P=0.04) (Dan et al., 2016).</p> <p>A similar result was demonstrated in Bouchet et al. (2017) whereby a lower PCO rate at 2 years was demonstrated for FLACS (LenSx) compared to standard cataract surgery. In the same study, the following was also demonstrated in favour of FLACS (LenSx): favorable post-op emmetropia <0.5D, faster visual recovery (better BCDVA at 1 week), and lower post-op complications of CME vs. PCS</p>		
Alcon	52	1068	<p>We agree with the authors with respect to FLACS being expected to reduce phaco energy, which may in turn reduce the heat damage to ocular tissues by ultrasound and this may translate into reducing endothelial cell loss (ECL), and consequently, better outcomes in terms of visual acuity and safety.</p> <p>Although we are cognizant of the rationale provided in the Draft Assessment (the absence of SDs), we would like to inquire to why the data for ECL was not pooled for meta-analysis, as has been done in previous work in the area? In Chen et al (2016), the authors detail a methodology which they use to pool the data, was this tried for the purposes of this assessment?</p> <p>Indeed, this meta-analysis concluded that the mean ECL was significantly lower for patients undergoing FLACS versus standard cataract surgery at 1 week, 1 month and 3 months after surgery. (Chen et al., 2016)</p>	1	<p>This comment is not a “factual accuracy check” and no reply can be provided as per EUnetHTA procedures. Please see above comment and be advised to review Eunetha guidances, Core Model Handbook and methods section of this REA for a comprehension of high quality assessment</p>

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Alcon	General		<p>We wish to inquire why the below was outlined in the author's reply to the manufacturers' comments on the project plan and yet these outcomes were not considered in the Draft Assessment?</p> <p><i>"CDE, phaco energy and circularity of capsulotomy will be addressed in the TECH domain, but not in EFF and SAF domains"</i></p> <p>https://www.eunetha.eu/wp-content/uploads/2018/03/Project-Plan-Draft_comments-form-manufacturers_fact-check.pdf</p> <p>We are surprised that the clinically relevant outcome of 'circularity of capsulorrhexis' was not considered and evaluated in the Draft Assessment. The evidence suggests that improving the quality of the capsulorrhexis enables improved capsule overlap, better intraocular lens (IOL) placement and centration of the IOL. These advantages improve post-operative visual and refractive outcomes (Nagy et. al, 2014).</p> <p>An independently conducted meta-analysis (Chen 2016) demonstrates that the FLACS group had a significantly higher quality of circularity compared with the standard cataract group (WMD: 0.06, 95% CI: 0.03 to 0.09, P <.001, I² > 50%).</p> <p>Furthermore, phaco power and time required for manual lens fragmentation may cause complications. With evidence suggesting the potential of slow visual recovery (Conrad-Hengerer et al., 2015) significant endothelial cell loss (Takács et al., 2012; Reuschel et al., 2010) and in some cases post-surgical macular oedema (Escedy et al., 2011; Nagy et al., 2010). It has been shown that these factors are especially important for patients with pre-existing corneal endothelial cell dysfunction such as</p>	1	<p>TECH domain provides descriptive information and does not provide assessment. Answer on choice of outcomes can be found in the detailed description of methodology and process for selection of outcomes and rating of their importance as well as in the description of criteria for studies' inclusion</p> <p>The remaining extensive comment is not a "factual accuracy check" and, as per EUnetHTA procedures, no comments related to EFF and SAF can be taken into consideration.</p> <p>Please see previous comment and be advised to review Eunetha guidances, Core Model Handbook and methods section of this REA for a comprehension of high quality assessment</p>

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			<p>Fuchs endothelial dystrophy (Mayer., 2014)</p> <p>In Chen et al. (2016) the authors synthesized evidence from 5 studies reporting mean phacoemulsification energy and cumulative dissipated energy (CDE). Findings show that FLACS required significantly less phacoemulsification power than manual phacoemulsification – with the overall effect in phacoemulsification power favored FLACS (WMD: -6.57, 95% CI: -7.08 to -6.05, P < .001, I2 > 50%).</p> <p>Furthermore, Kohnen et al. (2017) conducted a systematic review and meta-analysis comparing FLACS with conventional cataract surgery which included prospective and retrospective clinical trials (34 studies included) and found the following:</p> <p>In eyes treated with FLACS uncorrected distance visual acuity (UDVA) (2215eyes, P<0.01) was better, endothelial cell loss was less (1,335eyes; P<0.01), circularity was better (330eyes; P<0.01; risk for anterior capsule rupture higher (4,731eyes; P<0.01), and effective phacoemulsification time less (1,382eyes; P<0.01).</p> <p>So too in a meta-analysis conducted by Bouchet et al. which indicates that LenSx is significantly better than standard cataract surgery in terms of lower EPT, lower phaco energy, and lower CCT at 1 week</p> <p>We are of the view that these are important outcomes and should be considered in this assessment, in-line with the author's previous reply.</p>		
Alcon	52	1066-1067	We agree with the comment that: "Given that for toric and multifocal intraocular lenses, centration of the capsulorhexis is especially important, the precision of FLACS could have relevant impact in case of implantation of	2	

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			Intraocular lens premium"		
Alcon	93	2159-2167	<p>We would like to point out that only one Femtosecond Laser Platform (Catalys Precision Laser System; Abbott Medical Optics) is evaluated in the <i>“two large publicly funded adequately powered ongoing RCTs”</i> (FEMCAT & FACT) that the authors posit are: <i>“expected to add relevant evidence which may more adequately answer public health questions on cataract surgery and may help to establish whether FLACS provides any advantage over conventional phacoemulsification”</i>,</p> <p>Given that there are currently five available platforms for femtosecond laser cataract surgery, which differ in image capture, adaptability, docking methods, lens fragmentation patterns in addition to speed of action (Nagy 2015, Alio 2014) – we are of the considered view that the results from these trials could not possibly represent FLACS technology as a whole but may only offer to help establish whether the Catalys Precision Laser System provides any advantage over conventional phacoemulsification.</p>	1	It is not within the scope of this assessment to carry out comparisons between platforms.
Alcon	70	1501	<p>We would like to bring to the authors attention that a cost-effectiveness study comparing FLACS vs. manual phacoemulsification has not been included in the review of evidence (Lee et. al., 2016). This study was conducted to assess the cost-effectiveness of FLACS compared to manual phacoemulsification for medically necessary cataract removal in a publicly funded hospital in Canada. Incremental QALY gain was observed in FLACS group over time and over lifetime FLACS resulted in incremental cost-effectiveness ratio (ICER) of Canadian \$18,099 over manual phacoemulsification. A figure which is well within what is typically viewed as cost-effective by HTA bodies.</p>	1	<p>This extensive comment is not a “factual accuracy check”.</p> <p>Please see previous comment and be advised to review Eunethta guidances, Core Model Handbook and methods section of this REA for clarification and comprehension of high quality assessment</p>
Alcon	General		Inclusion criteria	1	This comment is not a “factual accuracy check” and reply to this issue has already been provided

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			<p>It is our view that a more holistic approach should be taken when considering the evidence on FLACS, as in the case of medical devices, traditional clinical trials may be challenging or impractical to conduct. This is true due to the realities of medical device innovation and development cycles, ethical issues that may arise with treatment assignment, and other similar challenges in executing traditional trials (Food and Administration, 2017).</p> <p>Analyses of RWD, using appropriate methods, may in some cases provide similar information with comparable or even superior characteristics to information collected through a traditional clinical trial (Food and Administration, 2017)</p> <p>It is our view that, excluding all non-RCTs from all but one of the review questions, narrows the evidence base considerably and acts to undervalue observational data, which as outlined above (and in particular in the case of medical devices) may provide comparable or superior information compared with RCTs.</p> <p>A balanced approached is required in light of the challenges with MedTech and the technologies being fast paced. This would mean that a criteria which goes beyond looking at RCTs should be considered and discussed with the decision making panel.</p>		<p>during Project Plan review process.</p> <p>Please see previous comment and be advised to review Eunethta guidances, Core Model Handbook and methods section of this REA for clarificationa and comprehension of high quality assessment</p>
Alcon	201	Table A 27 Regulatory status	<p>The below information to be added to table A 27 specific to the European Union</p> <ol style="list-style-type: none"> 1. The following information should be inserted in the table under "Verbatim wording of the (anticipated) indication" <ul style="list-style-type: none"> ➤ Design and manufacture of ophthalmic surgical lasers and patient interfaces for cataract surgery and creation of flaps, corneal pockets and corneal tunnels 	1	Thank you for providing the missing information that has been added.

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			<p>2. The following information should be inserted in the table under "Specified contra-indications"</p> <ul style="list-style-type: none"> ➤ See Owners manual sections 1.4,1.5,1.6,1.7 <p>3. The following information should be inserted in the table under "Approval number (if available)"</p> <ul style="list-style-type: none"> ➤ EC Cert CE 568180 		

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