EMERGING MONOFOCAL INTRAOCULAR LENSES IN EUROPE: POTENTIAL ROLE FOR AVANSEE™ PRESET

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Abstract

Intraocular lens (IOL) technology has evolved dramatically during recent years due to the development of injectors that insert a folded IOL into the eye through a small incision. This allows fast, reliable, reproducible and controlled insertion that avoids the need for stitches and reduces the risk of postoperative complications. A number of injectable hydrophobic monofocal IOLs are currently available in Europe. This review compares the characteristics of these IOLs with Avansee – one of the most widely used IOLs in Japan that is due to be launched in Europe in 2014. Studies show that Avansee IOLs inserted using the fully preloaded AvanseePreset injector system are relatively quick and easy to insert with one hand. Once inserted in this way, Avansee IOLs provide high levels of corrected visual acuity, assume a stable position in the eye without exerting zonal stress or transformation of the capsular bag, and fully regain their optical properties after injection. Moreover, Avansee IOLs are associated with a low risk of infection and postoperative complications such as posterior capsule opacification (PCO) and endophthalmitis, and have a low propensity for glistenings over time.

Introduction

Cataracts account for approximately five per cent of blindness in Western Europe and almost 50 per cent of blindness, worldwide.[1] Currently, the only treatment for cataract is surgery. The clouded lens is removed (usually by phacoemulsification) and an IOL is inserted through a small incision into one of three positions; the capsular bag, the sulcus ciliaris, or (less frequently) the anterior chamber in front of the iris. In each case, the IOL replaces the natural lens and acts as a refractive medium for the visual correction of aphakia. IOL implantation is the most frequently performed surgical procedure worldwide. According to industry estimates, nearly 3.6 million IOL implants were performed in Western Europe in 2012, 78 per cent of which were carried out in Germany, France, Italy, Spain and the UK. This number is predicted to rapidly increase as the population continues to age.

IOL technology has evolved dramatically during recent years. The development of foldable IOLs enables the lens to be injected into the eye through a small incision (<2.8mm), thus avoiding the need for stitches and reducing the risk of postoperative complications.[2] After insertion, the optic gently unfolds and the haptic (the flexible support) holds the lens in position, absorbing the omnidirectional shrinking power of the capsular bag. Originally, IOLs were spherical with only one optical function – compensating aphakia. More recent designs include 'premium' or 'enhanced' IOLs that can improve the quality of vision without the need for glasses and can allow the surgeon to select a lens that suits the individual patient's lifestyle. For example, aspheric monofocal IOLs can provide a high-quality image for distant vision and enhance contrast perception; toric lenses can correct astigmatism, and multifocal lenses can compensate for presbyopia.[3] However, according to the European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO), monofocal IOLs are still used in more than 95 per cent of cases.[4;5]

The quality of the IOL largely depends on the IOL design, material and manufacturing process.[3;6-9] Optics made from hydrophobic acrylic are most popular, accounting for 80.8 per cent of implants, followed by hydrophilic acrylic (14.0 per cent) and silicone (3.5 per cent).[4] Ideally, IOLs should have the characteristics outlined in **Table 1**.

Characteristics of an ideal IOL	Characteristics of an ideal IOL injector system
• Provide high levels of corrected visual acuity (CVA) • Be fully preloaded into an advanced injection system, allowing fast, reliable, reproducible and controlled insertion through a micro-incision • Quickly and fully regain their mechanical and optical properties after injection (even when misaligned) • Assume a stable position after insertion without exerting zonal stress or causing transformation of the capsular bag • Be associated with a relatively low risk of postoperative complications, such as posterior capsule opacification and endophthalmitis • Have a low propensity for glistening, whitenings and general deterioration over time	• Fully preloaded • Single-use to avoid the need for cleaning and sterilisation prior to use • IOL delivery through the smallest possible incision (generally 2.4 to 2.8mm) • Smooth and controlled IOL delivery • Lightweight with a plunger-type injector, allowing one-handed IOL delivery • Excellent IOL centring within the capsular bag • Contamination-free implantation • Reduced haptic damage/breakage • Reduced optic marking or crimping

Table 1: *Characteristics of an ideal IOL/IOL injector system*

1. Avansee/AvanseePreset

A wide range of aspheric monofocal IOLs are available in Europe, including CT Asphina (Carl Zeiss Meditec), AcrySof IQ (Alcon Laboratories, Inc), KS-3Ai (Staar Surgical), Sensar AR40e (Abbott Medical Optics, Inc), AF-1 YA-60BB (Hoya Surgical Optics GmbH) and Envista MX60 (Bausch & Lomb, Inc). In Japan, the most popular monofocal IOLs include AcrySof IQ, followed by NX-60 (Eternity; Santen), Sensar AR40e, and Avansee (Kowa Co, Ltd).

Avansee is a posterior chamber monofocal IOL with modified 3-piece (3P) C-loop haptics made from soft, flexible polyvinylidene fluoride (PVDF) to reduce the risk of breakage during insertion. It is manufactured using a stringently-controlled cast-molding method and carved after polymerisation to provide a square edge. The optic is made from a UV-absorbing, hydrophobic, highly cross-linked, soft acrylic material in yellow (PN6, PN6A, PN6AS, AN6K, AN6MK and AN6KA) or clear (PU6, PU6A, AU6K and AU6KA). After phacoemulsification, the AvanseePreset injector system (PN6, PN6A, PU6 or PU6A) can be used to inject Avansee into the capsular bag through a 2.8 or 3.0mm incision (for sclera-corneal and corneal insertion, respectively) or, if using the small incision AvanseePreset injector system (PN6AS), through a 2.4 to 2.6mm incision. A one-piece (1P) version of Avansee that can be inserted through a smaller 2.2mm incision is currently in development by Kowa Co, Ltd.

Avansee was launched in Japan in 2007.[10] The initial 3P spherical models (AN6K, AU6K and AN6MK) were followed by a fully pre-loaded, single-use spherical AvanseePreset injector system (PN6 and PU6) in 2010 and then by aspheric counterparts (AN6KA, AU6KA, AN6MA, PN6A, PU6A and PN6AS) in 2013/2014.[11] AvanseePreset is due to be launched in Europe in 2014. The aim of this review is to compare the characteristics of Avansee/AvanseePreset with other commonly-used aspheric monofocal IOLs in order to understand the potential role for AvanseePreset in Europe.

2. Avansee is safe and effective for the correction of visual acuity in the majority of aphakic eyes

According to ISO 11979-7:2006(E) Annex B regulations, IOLs must provide a CVA of 0.5 (20/40 vision) or better in at least 88.0 per cent of cases. However, the 1998 EUREQUO survey, which analysed preoperative and intraoperative data from 31 surgical units across 13 European countries (n=2,950), showed a large variation in visual outcome between participating centres, with many units reporting results considerably above and below the averages.[12] In this study, a corrected distance visual acuity (CDVA) of 0.5+ in the operated eye was achieved by approximately 84 per cent of patients after six months. The more recent 2013 EUREQUO survey, which analysed data from 368,256 cataract extractions in 15 European countries, suggests that results have improved over recent years.[13] Here, 94.4 per cent of all patients achieved a CDVA of 0.5+ after seven to 60 days and 61.3 per cent achieved a CDVA of 1.0+ (20/20 vision). The best results were achieved in age groups 40 to 74 years, with men being more likely to achieve 20/20 vision than women. The strongest predictors for poor visual outcome were ocular comorbidity and postoperative complications, although surgical complications and ocular changes requiring complex surgery also had an effect.

CVA rates for Avansee were assessed in 71 eyes in patients aged 40+ years (62 per cent female) undergoing surgery for uncomplicated senile cataract at one of two medical institutes specialising in ophthalmology in Japan.[14] Overall, 65/70 eyes (92.9 per cent) and 51/53 eyes (96.2 per cent) achieved a CVA of 0.5+ after six and 12 months, respectively (150-210 days and 330-390 days after implantation), including 52 (73.2 per cent) and 37 (69.8 per cent) achieving a CVA of 1.0+. No complications related to the use of Avansee were observed and the implanted lenses were deemed to be 'safe' in 100 per cent of eyes. A similar study carried out in 70 patients (100 eyes) aged 42+ years attending one of four ophthalmic hospitals in Japan showed that 98 per cent of eyes achieved a CVA of 0.5+ after one year, with 85 per cent of eyes achieving a CVA of 1.0+ (data provided by K Miyake, Y Tanifuji, O Nishi, and K Inoue). Posterior capsule opacification (PCO) occurred in two patients six months to one year after surgery. However, corrective surgery was not required because CVAs remained high (1.0 and 0.6). Moreover, data collected between 2007 and March 2014 show that more than half a million units of Avansee/AvanseePreset were supplied to surgeons in Japan, with 22 adverse events (0.0032 per cent) and two serious adverse events (0.0003 per cent) reported (data provided by Kowa Co, Ltd).

3. Preloaded advanced-design injection systems, such as AvanseePreset, can improve the reliability, reproducibility and speed of IOL surgery

Prior to the development of IOL injectors, problems during IOL implantation were relatively common. Placement of rigid or manually-folded lenses into the eye using forceps often led to damaged IOLs, infection, surgically-induced astigmatism and large incisions that often required suturing.[15] The development of IOL injectors has enabled a faster, more controlled, consistent IOL insertion that reduces the risk of error, wastage, infection and postoperative complications (**Table 1**). In fact, a retrospective 10-year study of all cataract surgeries carried out at an ophthalmology department in the UK showed that, compared with manually-folded lenses (n=412) the relative risk of endophthalmitis was significantly lower (43.8 per cent) with injected lenses (n=10,815; P<0.001).[16] Authors suggest this is primarily due to differences in incision size and lack of contact between the IOL and the ocular surface.

Three major types of injector system are currently available. The first type is the non-preloaded injector (eg, Viscojet [Medicel]) that requires expert skills in lens-loading and cartridge insertion prior to surgery. The second type of device (eg, Skyjet, Blu Mix 2.2 and AcriTec [Zeiss]) is the partially-preloaded system that comes in two sections – the insertion device and an IOL that is already loaded into the cartridge. This type is easier to use than the non-preloaded injector and reduces the risk of IOL misloading, damage and contamination/infection. The third type of device is the single-use, fully preloaded injector system, such as AvanseePreset, Monarch (AcrySert C; Alcon) and Unfolder Emerald (Tecnis; Abbot Medical Optics). **Whereas the first two types of injector system are sometimes reusable, the fully preloaded injectors are disposable, which means they do not require cleaning or sterilisation. Injector systems such as AvanseePreset and AcrySert C also have the benefit of being light and having a syringe-type injector, rather than a screw-type injector, which allows the surgeon to operate with one hand. Moreover, IOL insertion using AvanseePreset can be performed in only three simple steps: one to inject the ophthalmic viscosurgical device (OVD), one to remove the stage and the third to push the plunger. Together, these features eliminate the risk of IOL misloading, reduce the risk of IOL damage, minimise the volume of wastage, increase the reproducibility and speed of the injection process, reduce the risk of contamination/infection, and facilitate IOL manipulation inside the eye. These characteristics are expected to translate into lower failure rates, more operations per hour and improved cost-effectiveness.**

A major challenge for injectors is the gliding ability of the cartridge. Friction between the polypropylene cartridge and the IOL can increase the thrust force required to expel the lens from the injector. Excessive pressure may cause the IOL to stick to the cartridge wall resulting in lens damage or crimping and/or haptic breakage. In addition, cartridge damage or rupture can put unwanted stress on the incision, thereby increasing the risk of postoperative complications. To avoid this, the inside of some injectors (including AvanseePreset) are lubricated to facilitate gliding and reduce thrust force. However, thrust force also depends on the flexibility of the lens and the ratio between the diameter of the injector tip and the folded haptic. Data collected between 2010 (when AvanseePreset was first launched) and March 2014 show that approximately 0.2 million units of AvanseePreset were supplied to surgeons in Japan, with only 122 complaints (0.0624 per cent) about movement abnormalities, including trauma to the optic or haptic, incorrect optic or haptic movement, trapped lens in the nozzle, abnormal resistance force during injection and failure of lens implantation. The reasons underlying these problems are unknown but could relate to user error. To date, no reports of manufacturing errors have been received for AvanseePreset (data provided by Kowa Co, Ltd).

In general, hydrophilic acrylic lenses require a lower injection force than hydrophobic acrylic lenses but forces vary within each IOL class according to the IOL and injector characteristics.[9] In one study, a force of 14 to 19N was required for injection of hydrophilic IOLs (Finevision [Physiol. S.A.], Ioflex [Mediphacos Ltd.], and AcriTec 366D IOL [Carl Zeiss Meditec AG]) compared with 23 to 29N for most hydrophobic IOLs (Sensar AR40e, iSert 251 [Hoya], Envista MX60) and up to 71N with resultant cartridge damage for the hydrophobic AF-1 YA-60BB.[9] In this study, all IOLs were preloaded into the same type of injector (Accuject 2.2-1P [Medicel AG]), which suggests the differences in injection force were due to IOL characteristics, rather than injector design.

Results from a prospective observational study in which routine phacoemulsification was followed by AcrySof SN6CWS implantation using the supplied preloaded injector (n=85) showed that correct IOL delivery was achieved in only 45 per cent of eyes, whereas 55 per cent of eyes required additional rotational manipulation of the IOL.[17] Other problems included trapped trailing haptics, haptic-optic adhesion, overriding of the plunger over the optic and trauma to the optic edge. In this study, risks were similar irrespective of IOL power and the experience of the operating surgeon. These results can be explained by a further study in which the maximum forces required to expel AcrySof SN6CWS from the supplied preloaded injector and NX-60 from the non-preloaded MXJ-60 injector into phacoemulsified porcine eyes (n=5 to 6 per IOL) were significantly higher than those required by KS-Xs (Staar Japan) and AvanseePreset (**Figure 1**).[18] Authors suggest that the low IOL delivery force required by the KS-Xs and AvanseePreset injectors have the potential to lessen hand stress, facilitate injector manoeuvring and improve IOL insertion accuracy, thereby reducing the risk of surgical complications such as those experienced with AcrySof SN6CWS.

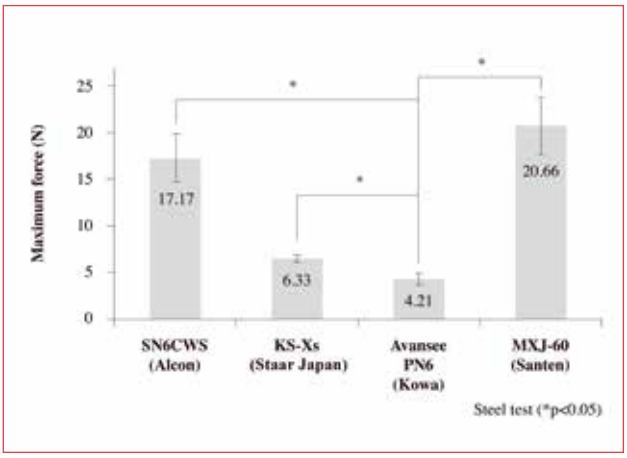


Figure 1: *The thrust force required to expel an IOL from its supplied preloaded injector into phacoemulsified porcine eyes varies between IOLs[18]*

4. Avansee regains its biomechanical and optical properties after injection

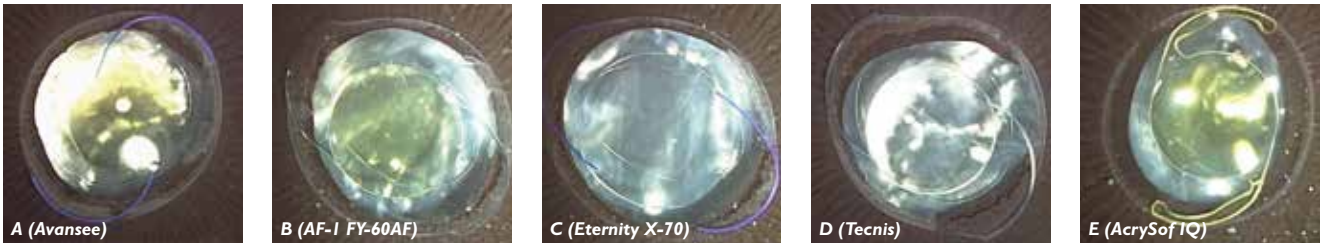


Figure 2: *Miyake apple views showing the stability of five different IOLs in the capsular bag. A) Avansee does not cause zonal stress or transformation of the capsular bag and the soft haptics are unlikely to damage the eye; B) With AF-1 FY-60AF, the hard haptics have grown into the capsular bag; C) With Eternity X-70, the IOL has caused transformation of the capsular bag; D) With Tecnis, the hard haptics have grown into the capsular bag; E) With AcrySof IQ, the shape of the capsular bag is good but the contact area between the IOL and the capsular bag is small. This can lead to IOL misalignment (data provided by I Ota)*

4.1 Biomechanical properties: shape recovery after injection

The compressive forces applied to the IOL during injection can potentially lead to IOL damage and loss of optical performance after implantation due to lens deformation.[2] Whereas hydrophilic IOLs have a relatively high degree of elasticity and good shape memory, some (but not all) hydrophobic IOLs fail to fully regain their initial shape after injection.[9] This can lead to impaired visual performance and postoperative complications such as PCO.

IOLs with higher water content often have lower glass transition temperature (Tg; the temperature at which a material passes from its rigid glassy state into its soft, flexible state). This means they are less likely to be damaged during folding and injection, and are more likely to quickly and fully regain their shape after implantation. A study comparing the biomechanical properties of 11 benchmark IOLs showed that pre-equilibrated IOLs (eg, iPure, Podeye, Finevision, AcriTec 366D and Ioflex) had a higher water content, lower Tg, and less residual deformation after compression than the dry-packaged IOLs (AcrySof SN60WF, Tecnis ZCB00, Sensar AR40e, AF-1 YA-60BB, and iSert 251).[9] Another study showed that, among the six dry-packaged hydrophobic IOLs examined, water content was highest for Avansee AU6 (≤2.0 per cent), followed by Sensar AR40e (≤0.7 per cent), AcrySof MA60BM and SA60AT (≤0.3 per cent), AF-1 VA-60BB [Hoya] (≤0.16 per cent) and Nex-Acri N4-18B (≤0.1 per cent).[19] Corresponding Tgs were 15.0, 13.0, 18.5, 12.0 and 3.6°C. Although biomechanical studies are required to compare the time and extent of shape regain after compression for Avansee versus other IOLs, Avansee's high water content and relatively low Tg suggests that its flexibility will be at least as good as that observed for other dry-packaged IOLs.

4.2 Optical properties: axial displacement and tilt

The alignment of an IOL within the eye largely depends on the pressure applied to the capsular bag by the IOL haptic. Too much pressure can change the shape of the capsular bag from a circle to an ellipse, leading to misalignment (decentring and tilt) of the IOL along the optic axis. For some IOLs, this can lead to reduced vision quality.[8] Data from the Miyake Eye Hospital in Japan show that, once inserted, Avansee does not cause zonal stress or transformation of the capsular bag and that the soft haptics are unlikely to damage the eye (**Figure 2**; data provided by I Ota). Moreover, IOL stability was shown to increase as the angle of contact between the loop and the lens capsule gets larger and,

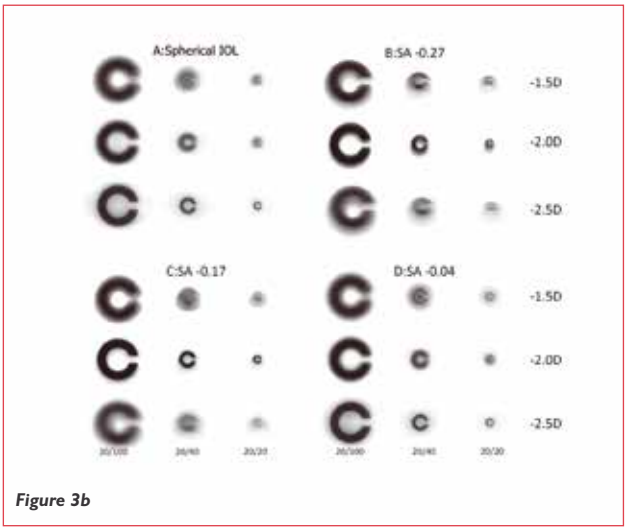


Figure 3b

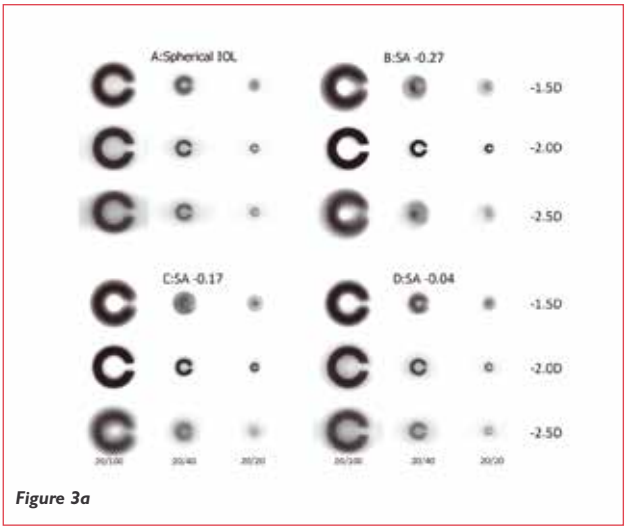


Figure 3a

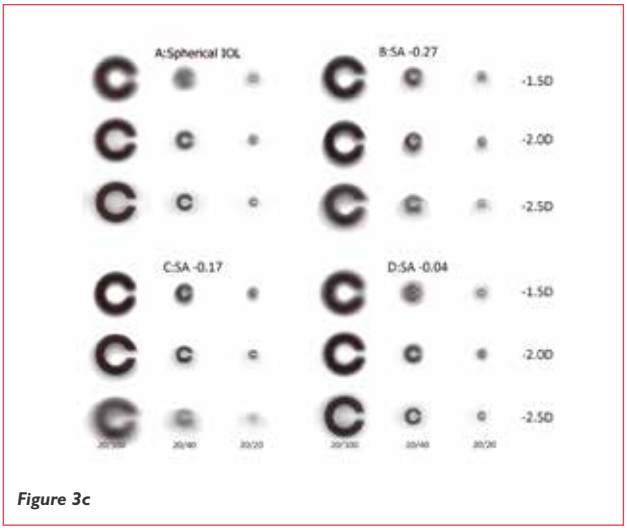


Figure 3c

Figure 3: *Landolt ring simulation for model eyes (pupil diameter 6mm) with IOLs that correct spherical aberration to different degrees and are, a) Not misaligned; b) Decentred by 0.5mm and c) Tilted by 5.0 degrees. The position of the best image surface where the Strehl ratio was highest was set at -2.0 D. The defocused image was calculated by inserting the Zernike defocus term (Z20) corresponding to ±0.5 D from the best-image position[23]*

compared with other lenses, the angle of contact for Avansee is relatively large (75.8° vs 59.6° for AcrySof IQ, 64.6° for Tecnis, 81.1° for AF-1 FY-60AD and 97.47° for Eternity X-70). Together, these results suggest that Avansee may be more stable than other IOLs and less prone to misalignment.

The effect of IOL misalignment on vision quality varies between IOLs.[8] Most aspheric IOLs, including Tecnis and AcrySof SN60WF, are designed to induce negative spherical aberration (SA) in order to fully or partially compensate for the positive SA present in the aging cornea.[20;21] Although this can improve contrast sensitivity, common levels of IOL decentration can reduce the overall visual performance of these lenses. In contrast, the misalignment of IOLs that retain the SA of the eye, such as Avansee and Akreos (Bausch & Lomb, Inc.), has little effect on visual performance.[22-25] In fact, a study carried out in a model eye with an average centring error for IOLs in normal human eyes showed that coma aberration (determined by wavefront aberration analysis) was approximately proportional to the degree of centring error or tilt and that retinal images (determined by Landolt ring simulation) deteriorated accordingly (**Figure 3**).[23] In this study, four 3P acrylic IOLs (one spheric and three aspheric IOLs with SA -0.27µm, -0.17µm and -0.04µm were inserted into IOL holders without misalignment, with a shift of 0.5mm, or with a tilt of 5.0 degrees. Compared to IOLs without misalignment, defocused modulation transfer function (MTF) and defocused point spread function (PSF) significantly deteriorated for IOLs with a decentring error or tilt and a greater degree of SA corrective power, whereas the IOL with same asphericity as Avansee (SA -0.04µm) was largely unaffected. These data suggest that the depth of focus was large and the influence of IOL shift or tilt on the retinal image was slight in IOLs that retain, or minimally correct, the SA of the eye.

5. The rate of postoperative complications varies between IOLs

According to the EUREQUO study (n=523,921), the most common complications within 60 days of IOL implantation in Europe are postoperative PCO that disturbs vision (mean incidence 0.21 per cent), endophthalmitis (0.036 per cent), persistent corneal oedema (0.15 per cent), uveitis requiring medication (0.35 per cent) and uncontrolled elevated intraocular pressure (0.06 per cent).[4]

5A. Avansee is associated with a low rate of PCO

PCO is caused by hyperplasia and cellular migration of lens epithelial cells (LECs) from the anterior capsule to the posterior capsule following IOL implantation, leading to a thickening (Soemmerring's ring formation), opacification and clouding of the posterior lens capsule (often called a secondary cataract).[26] Although treatment with neodymium-yttrium-aluminium-garnet (Nd:YAG) laser capsulotomy is effective, treatment is expensive and carries a risk of retinal detachment, macular oedema and intraocular pressure elevation. PCO should therefore be avoided whenever possible.

The risk of PCO varies according to IOL material, manufacturing process and design.[26-30] A recent meta-analysis of data from nine randomised clinical trials in 861 eyes showed that hydrophobic IOLs were associated with significantly lower PCO rates than hydrophilic IOLs with a similar platform (P=0.0002 and P=0.0001 after one and two years, respectively).[29] Authors suggest this is because hydrophilic surfaces promote proliferation and migration of LECs from the equatorial area to the visual region,[31] whereas hydrophobic IOLs block the migration of LECs via tight adherence to the collagen membrane,[32] tight apposition of the IOL in the posterior lens capsule, and strong adhesiveness through fibronectin.[33]

A three-year retrospective comparative study including 1,265 uncomplicated cataract operations showed that the rates of Nd:YAG surgery due to PCO were significantly lower with AcrySof SN60WF (1.4 per cent) than with Hoya PY60AD (4.3 per cent; P<0.05) or Hoya FY60AD (8.9 per cent; P<0.01).[34] All three of these lenses are hydrophobic but, whereas the first two have a square-edged platform, the third lens is round-edged. A similar difference in PCO rate between Hoya AF-1 YA-60BB and AcrySof SN60AT was observed in a prospective, single surgeon, fellow-eye comparison study.[35] These results can be explained by the fact that IOLs with a square edge to their posterior surface are more likely to induce a sharp bend in the capsular bag than round-edged IOLs, thereby preventing LEC migration.[34;36-38] However, scanning electron microscopy and computer-aided imaging have shown that not all square-edged IOLs have the same degree of squareness.[39] Indeed, AcrySof SN60AT has a much squarer posterior edge than Hoya YA60BB (the areas deviating from a perfect square are 97.2µ^2 and 329.7µ^2, respectively).

In general, hydrophobic IOLs have squarer edges than hydrophilic lenses of the same design,[40] possibly due to differences in manufacturing technique.[35] Moreover, cast-molded hydrophobic IOLs, such as AcrySof and Avansee, that are carved without grinding after polymerisation tend to have squarer edges than IOLs that are manufactured using other techniques (**Figure 4**). Interestingly, the degree of squareness for Avansee (3P) AN6K and AcrySof SN60WF appear to be the same (information provided by Kowa Co, Ltd). Furthermore, a retrospective study in 4,862 eyes attending Miyake Eye Hospital in Japan showed that the proportion of

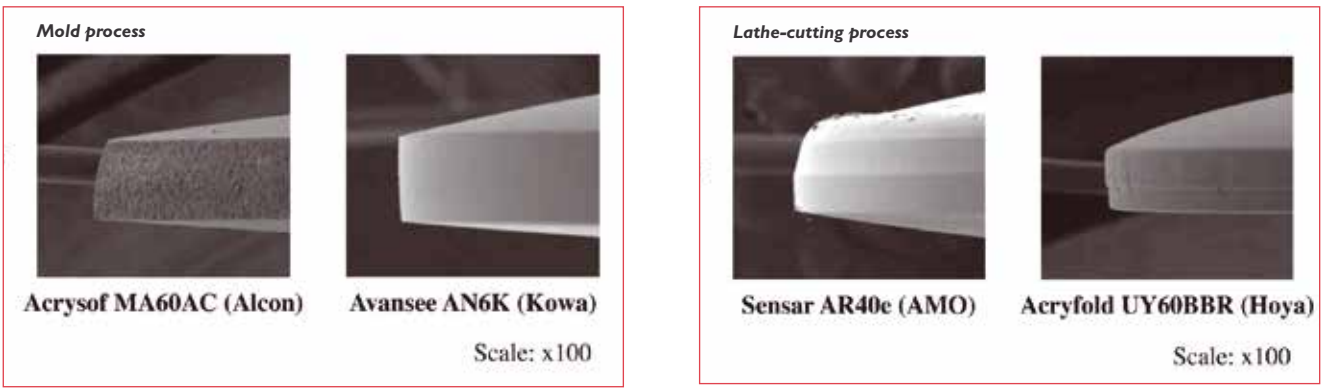


Figure 4: *Electron microscopy shows that molded lenses, such as AcrySof (Alcon) and Avansee AN6K (Kowa Co, Ltd), tend to have a squarer edge than lathe-cut lenses (data provided by Kowa Co, Ltd)*

Company	Model	Number of cases	Number of cases requiring Nd:YAG
Kowa	AvanseePreset AN6K, AN6K, AN6M, and AN6MK	2,206	38 (1.7%)*
Alcon	AcrySof SA60AT, SN60AT, SN60WF	1,604	39 (2.4%)*
Hoya	YA-60BBR	1,052	76 (7.2%)

**P<0.0001 versus Hoya*
Table 2: *The proportion of PCO cases requiring Nd:YAG treatment after two years for benchmark IOLs (data provided by K Miyake)*

PCO cases requiring Nd:YAG treatment after two years was significantly lower in patients receiving Avansee or AcrySof than in those receiving the rounder-edged Hoya YA-60BBR IOL (P<0.0001 for both comparisons) (**Table 2**) (data provided by K Miyake). Together, these results suggest that a hydrophobic, square-edged IOL, such as Avansee and AcrySof SN60WF should be used whenever possible to reduce the risk of PCO.

5B. Endophthalmitis

Acute endophthalmitis is one of the most serious complications of cataract surgery and often results in severe visual impairment, blindness and even death.[16] In most cases, postoperative endophthalmitis is caused by pathogens that are transferred into the eye from the ocular surface during surgery.[41] Compared to manually-folded IOLs, IOL insertion using injectors significantly decreases the incidence of endophthalmitis by limiting the contact between the IOL and the conjunctival flora.[16] However, differences in endophthalmitis rates appear to exist between IOL injection systems.[42] Of the 22 adverse events reported for Avansee between its launch in 2007 and March 2014, two were due to endophthalmitis (data provided by Kowa Co, Ltd). However, both cases were observed with IOLs that were inserted without the AvanseePreset system and neither case was due to a manufacturing error.

6. Glistenings have not been observed with Avansee

The transparency of IOL optics can deteriorate after implantation due to glistenings (small bright spots) and/or whitenings (scattering, sub-surface nano glistening [SSNG]).[43-47] Both events are due to the formation of small, fluid-filled vacuoles in the optic material. Glistenings are caused by vacuoles 1 to 20µm in diameter across the entire IOL optic, whereas whitenings are due to ~100nm vacuoles that scatter light at the sub-surface of the optic.[48] In general, IOLs such as Sensar AR40 (AMO) and Acryfold UY60BBR (Hoya) that have lathe-cut optics made from a stable, uniform and highly cross-linked polymer are less likely to allow water to gather in the micro void of the material and are therefore less susceptible to glistenings and whitenings than IOLs with cast-molded optics, such as AcrySof MA60AC (Alcon) and Avansee.[49] However, incubation of five dry-packaged hydrophobic IOLs and two wet-packaged IOLs with hydrophilic properties (X-60 [Santen] and H60M [Storz]) over a range of temperatures showed that the change in water saturation was

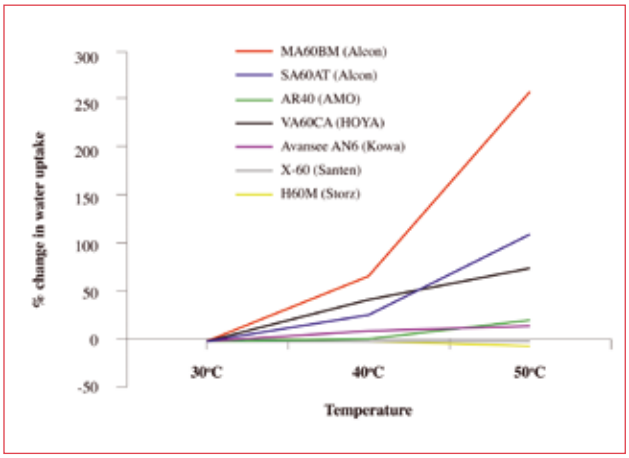
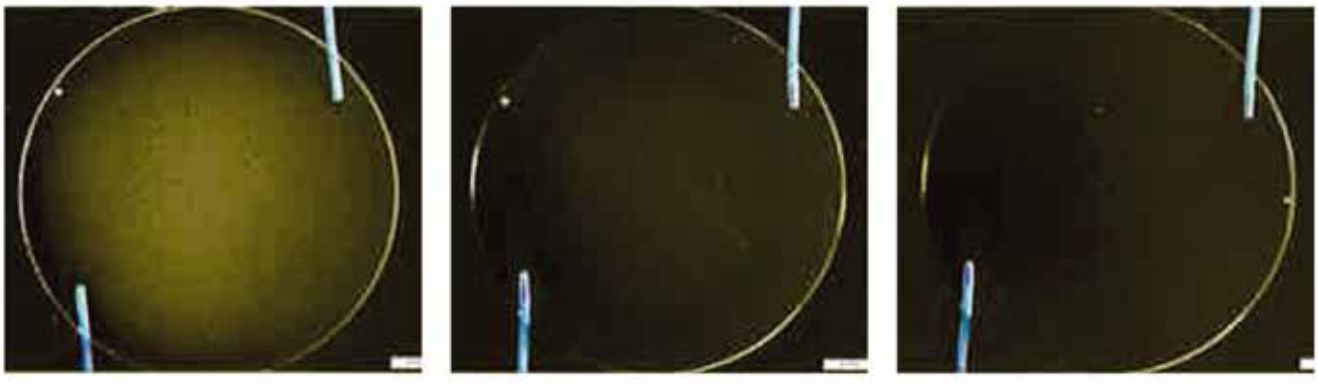


Figure 5: *The change in water uptake over a range of temperatures varies between IOLs (data provided by A Miyata)*



Crosslink density 1/4 ***1/2*** ***1 (Avansee)***

Figure 6: *In IOLs with the same degree of water uptake, the likelihood of glistenings is inversely proportional to the density of cross-linkages in the optic polymer (data provided by H Matsushima)*

considerably lower for Avansee and AR40 than for MA60BM (Alcon), SA60AT (Alcon) and VA60CA (Hoya), and that the change for Avansee was similar to that observed for the wet-packaged IOLs (**Figure 5**).[50] In addition, a series of experiments performed using IOL models with the same rate of water uptake as Avansee showed that glistenings were inversely proportional to the density of cross linkages and that the model with the highest density of cross linkages (similar to the density used for Avansee) remained glistening-free (**Figure 6**) (data provided by H Matsushima).

The rates and severity of glistenings vary between materials and IOLs.[19;43-47;51;52] In one study, severe accelerated deterioration tests were performed on one hydrophilic IOL (HP60M; Bausch & Lomb, Inc.) and six types of hydrophobic acrylic IOLs simulating 20 years of IOL wearing.[19] Glistening-like opacity was detected in five of the hydrophobic IOLs (AcrySof MA60BM and SA60AT, AR40e, VA-60BB and Nex-Acri N4-18B). In contrast, no opacity was detected in the hydrophilic lens or in Avansee. Similar results were obtained from a study in which AcrySof, AF-1 or Avansee were implanted into phacoemulsified rabbits for six months.[47] The removed IOLs (stored in 33°C saline to prevent post-surgical separation of the water phase) were examined under a microscope at constant temperature. The AcrySof lenses showed significant glistenings and whitenings, whereas the AF-1 lenses showed only glistenings and the Avansee lenses showed neither. Although this study was relatively short in duration, results were corroborated by a one-year study in which CVA for Avansee was assessed in 71 eyes (aged 40+ years) undergoing surgery for uncomplicated senile cataract in Japan,[14] and by a four-year observational study carried out in 78 patients (130 eyes) attending the Miyake Eye Hospital in Japan (data provided by I Ota). In the latter study, both AcrySof and AF-1 were associated with some degree of glistenings in the majority of patients, whereas no glistenings were reported with Avansee (**Figure 7**). Furthermore, a study of 12 IOLs extracted from patients three to13 years after implantation showed that H60M

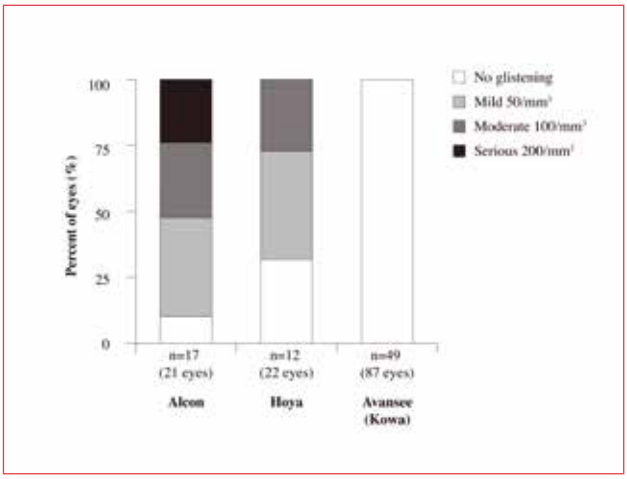


***Figure 7:** Unlike other benchmark IOLs, glistenings have not been reported with Avansee (data provided by I Ota)*

(Bauch & Lomb, Inc.) had a deposition of calcium and MA60BM (Alcon) was associated with whitening, whereas Avansee did not demonstrate whitenings, glistenings or deposition of calcium.[53] Since its launch in 2007, no glistenings have been reported for Avansee.

Some surgeons believe that glistenings and whitenings have a significant impact on vision function (in particular contrast sensitivity[54-59]), whereas others believe they have little or no effect.[45;60] However, a recent case of progressive visual deterioration was reported with an AcrySof IOL due to light-dependent starbursts, disability glare/flare, and/or backlight glare.[59] In cases where visual function is affected by glistenings/whitenings, the lens may need to be removed and replaced with a new one. The use of IOLs that comprise optics with a low propensity for glistening, such as Avansee and Envista, should therefore be given serious consideration.

Conclusions

The development of preloaded injectors that insert a folded IOL into the eye through a small incision has led to significant improvements in the speed, reliability, reproducibility, safety and cost-effectiveness of cataract operations. Ideally, IOLs should provide high levels of CVA. They should also be fully preloaded into a single-use advanced injection system, assume a stable position after injection without exerting zonal stress or causing transformation of the capsular bag, and quickly and fully regain their optical properties after injection. Moreover, they should be associated with a relatively low risk of infection and postoperative complications, and have a low propensity for glistenings and general deterioration over time.

Studies to date show that Avansee – currently one of the most widely used IOLs in Japan and soon to be launched in Europe – fulfills each of these requirements. Moreover, Avansee has demonstrated a low incidence of adverse events since its launch in Japan (the second largest IOL market in the world) in 2007. Together, these data suggest that AvanseePreset will be useful for the treatment of aphakia during cataract surgery in Europe.

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