NOW WITH THE OPTION TO
TREAT & EXTEND
IN YEAR 1

FOR TREATMENT-NAIVE patients with uAMD

WHAT YOU
START TODAY
MAKES A
DIFFERENCE
TOMORROW

Prescribing Information available overleaf

© Bayer AG, September 2018.
Eylea® 40 mg/ml solution for injection in a vial (aflibercept)

**Prescribing Information**

(Right to full Summary of Product Characteristics [SmPC] before prescribing) **Presentation:** 1 ml solution for injection contains 40 mg aflibercept. Each vial contains 100 microfilters, equivalent to 4 mg aflibercept. **Indication(s):** Treatment of neovascular (wet) age-related macular degeneration (wAMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DMO) in adults and visual impairment due to myopic choroidal neovascularisation (myopic CNV). **Posology & method of administration:** For intravitreal injection only. Must be administered according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. Each vial should only be used for the treatment of a single eye. Extraction of multiple doses from a single vial may increase the risk of contamination and subsequent infection. The vial contains more than the recommended dose of 2 mg. The extractable volume of the vial (100 microfilters) is not to be used in total. The excess volume should be expelled before injecting. Refer to SmPC for full details. **Adults:** The recommended dose is 2 mg aflibercept, equivalent to 50 microfilters. For wAMD treatment is initiated with 1 injection per month for 3 consecutive doses. The treatment interval is then extended to 2 months. Based on the physician’s judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at 2 months or further extended using a treat-and-extend dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly to a minimum of 2 months during the first 12 months of treatment. There is no requirement for monitoring between injections. Based on the physician’s judgement the schedule of monitoring visits may be more frequent than the injection visits. Treatment intervals greater than 4 months between injections have not been studied. For DMO (branch RVO or central RVO), the initial injection, treatment is given monthly at intervals not shorter than 1 month. Discontinue if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment. Treat monthly until maximum visual acuity and/or no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there is insufficient data to conclude on the length of these intervals. Shorten treatment intervals if visual and/or anatomic outcomes deteriorate. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient’s response. For DMO, initiate treatment with 1 injection/month for 5 consecutive doses, followed by 1 injection every 2 months. No requirement for monitoring between injections. After the first 12 months of treatment, and based on visual and/or anatomic outcomes, the treatment interval may be extended such as with a treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes; however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The schedule for monitoring should therefore be determined by the treating physician and may be more frequent than the schedule of injections. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, treatment should be discontinued. For myopic CNV, a single injection is to be administered. Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease. The schedule for monitoring treatment should be determined by the treating physician. The interval between 2 doses should not be shorter than 1 month. Hepatic and/or renal impairment: No specific studies have been conducted. Available data do not suggest a need for a dose adjustment. Elderly population: No special considerations are needed. Limited experience in those with DMO over 75 years old. **Paediatric population:** No suitable data available. **Contraindications:** Hypersensitivity to active substances or any excipient, active or suspected ocular or periocular infection, active severe intraocular inflammation. **Warnings & precautions:** As with all intravitreal injections endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iridogenic traumatic cataract have been reported. Aflibercept injection technique is essential. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients may develop any symptoms of endophthalmitis or any of the above mentioned events without delay. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection; special precaution is needed in patients with poorly controlled glaucoma (do not inject while the intraocular pressure is > 30 mmHg). Immediately after injection, monitor intraocular pressure and perfusion of optic nerve head and manage appropriately. There is a potential for immunogenicity with as with other therapeutic proteins; patients should report any signs or symptoms of intraocular inflammation e.g pain, photophobia or redness, which may be a clinical sign of hypersensitivity. Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors. Safety and efficacy of concurrent use in both eyes have not been systematically studied. No data is available on concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular). Caution in patients with risk factors for development of retinal pigment epithelial tears including large and/or high pigment epithelial retinal detachment. Withhold treatment in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes; with retinal break and do not resume treatment until the break is adequately repaired. Withhold treatment and do not resume before next scheduled treatment if there is: decrease in best-corrected visual acuity of ≥30 letters compared with the last assessment; central foveal subretinal haemorrhage, or haemorrhage ≥50%, of total lesion area. Do not treat in the 26 days prior to or following performed or planned intravitreal surgery. Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection. In patients presenting with clinical signs of irreversible ischaemic visual function loss, aflibercept treatment is not recommended. Populations with limited data: There is limited experience in DMO due to type 1 diabetes or in diabetic patients with HbA1c over 12% or with retinopathy or diabetic retinopathy. Eylea has not been studied in patients with active systemic infections, concurrent eye conditions such as retinal detachment or macular hole, or in diabetic patients with uncontrolled hypertension. This lack of information should be considered when treating such patients. In myopic CNV there is no experience with Eylea in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions. Interactions: No available data. Fertility, pregnancy & lactation: Not recommended during pregnancy unless potential benefit outweighs potential risk to the foetus. No data available in pregnant women. Studies in animals have shown embryo-fetal toxicity. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last injection. Not recommended during breastfeeding. Exciton in human milk: unknown. Male and female fertility impairment seen in animal studies with high systemic exposure not expected after ocular administration with very low systemic exposure. Effects on ability to drive and use machines: Possible temporary visual disturbances. Patients should not drive or use machines if vision inadequate. Undesirable effects: Very common: Visual acuity reduced, conjunctival haemorrhage (wAMD phase III studies: increased incidence in patients receiving anti-thrombotic agents); eye pain. Common: Retinal pigment epithelial tear (known to be associated with wAMD); observed in wAMD studies only); detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract (nuclear or subcapsular), corneal abrasion or erosion, increased intraocular pressure, blurred vision, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, increased lacrimation, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival or ocular hyperaemia. Serious: cf. C/NS/EP - in addition blindness, culture positive and culture negative endophthalmitis, cataract traumatic, transient increased intraocular pressure, vitreous detachment, retinal detachment or tear, hypersensitivity (during the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions), vitreous haemorrhage, cortical cataract, lenticonus opacities, corneal epithelium defect/erosions, vitreitis, iritis, iridocyclitis, anterior chamber flare, arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. As with all therapeutic proteins, there is a potential for immunogenicity. Consult the SmPC in relation to other side effects. **Overdose:** Monitor intraocular pressure and treat if required. **Incompatibilities:** Do not mix with other medicinal products. **Special Precautions for Storage:** Store in a refrigerator (2°C to 8°C). Do not freeze. Unopened vials may be stored at room temperature (below 25°C) for up to 24 hours before use. **Legal Category:** POM. **Packaging Quantities & Basic NHS Costs:** Single vial pack £816.00. Further information available from: Bayer plc, 400 South Oak Way, Reading RG2 6AD, United Kingdom. Telephone: 0118 206 3000; Date of preparation: July 2018. Eylea® is a trademark of the Bayer Group References: 1. EYLEA (aflibercept solution for injection) Summary of Product Characteristics Berlin, Germany: Bayer Pharma AG, July 2018. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/ yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Bayer plc. Tel.: 0118 2063500, Fax.: 0118 2063573, Email: pvuk@bayer.com
Top ophthalmic challenges in 2019
Medical, surgical advances define the year ahead

Reversing gland atrophy
Thermal pulsation benefits meibomian gland

Pinhole IOL + monofocal IOL
Combining technologies for good outcomes

ECP is routinely added to phacoemulsification for the treatment of mild to moderate glaucoma for long-term IOP decrease and reduction or elimination of patient medications.
(Image courtesy of Beaver-Visitec International)
NEXT FRONTIER IN EDOF-IOL DESIGN:

Turn your Automated Capsulotomies into Great Vision!
Issue Feature

6 Top ophthalmic challenges in 2019: What to watch in the year ahead
Members of the OTE Editorial Advisory Board discuss medical, surgical advances

Cataract & Refractive

12 Pinhole IOL + monofocal IOL: Spot-on vision at all distances
Combining pinhole technologies and monofocal lens has good results

16 Large series finds LASIK safe, effective for retreatment after SMILE
Study shows viability of LASIK if retreatment after SMILE is needed

18 High- vs medium-add multifocal IOLS
Medium-add multifocal addresses intermediate vision dissatisfaction

Retina

23 Intestinal microbiome proposed as potential therapeutic target for AMD
A link between the gut microbiome and age-related macular degeneration

25 How converging technologies lead to cost-effective anti-VEGF therapy
Anti-VEGF therapy and OCT imaging in the management of nAMD

27 Treatment of macroaneurisms in macular oedema patients
Navigated laser leads next generation of photocoagulation therapy

27 Targeting angiopoietin-2 + VEGF-A to treat diabetic macular oedema
Effective treatment of DMO in a Phase II multicentre study

Glaucoma

33 Managing ocular surface integral in glaucoma care
Minimising dry eye an important consideration in glaucoma treatment

35 Reversibility of meibomian gland atrophy by thermal pulsation therapy
Thermal pulsation therapy has potential to improve gland structure in most

General

39 Five things to know about modern visual electrophysiology testing
Debunking myths concerning visual electrophysiology

Regulars

42 Product News
Eidon FA merges together **ultra-high resolution** and **wide field** imaging.

A **fully automated** system transforming Fluorescein Angiography as never seen before.
As the year 2018 winds to a close, thoughts begin to turn to the next challenges for ophthalmology in the new year.

Top of mind for many are concerns over the diagnosis and management of refractive disease, cataracts and intraocular lenses, glaucoma, and retinal disease, in addition to the role of imaging in ophthalmology. Five members of the Ophthalmology Times Europe Editorial Advisory Board share their perspectives on the top challenges that ophthalmologists likely will face in 2019.

Dr Alió:
The debate over small-incision lenticule extraction (SMILE) versus LASIK has been around for the last 5 years. Even though the outcomes of both techniques are similar, the potential and logical advantages that SMILE has over LASIK in the preservation of biomechanics and tear film stability should be in favor of SMILE. Improving centration, astigmatism control, and biomechanics are a real challenge for the clinical researchers and the industry. SMILE will open the doors to intralaminar refractive surgery, which, in my opinion, in a given moment will replace LASIK as it is technologically more cost effective (we eliminate the need for flap and other technology associated to it), and it is minimally invasive.

Presbyopia is a long-standing problem that is still unsolved. At this moment, intracorneal inlays have failed to work as many thought they would. Intracorneal inlays are declining because their promising results have not been confirmed in clinical practice by many surgeons. Unrealistic expectations and overly positive reported outcomes from the industry have led to their discredit. Some of them have even disappeared from the market following years of theoretically proven benefits. These technologies, such as the Kamra inlay, will have a better future once a more systematic approach to their implantation, centration, and long-term outcomes are available. Pharmacology treatment of presbyopia is an open issue still unsolved. Intraocular phakic...
presbyopic lenses are a new upcoming issue that should provide a stimulating option for the patients. PresbyLasik is successful today as long as adequate patient selection is performed with the adequate technology. PresbyMax from Schwind, LVV from Zeiss, and PresbyOn from Bausch & Lomb are finding their role in the treatment of presbyopia.

Intraocular lenses are the state-of-the-art over the age of 55 as they provide a permanent solution but a higher risk, as intraocular surgery is always more invasive.

**Dr Alió:** Multifocal lenses are reaching maturity because the latest improvements in multifocality have demonstrated safety and tolerance by many patients. However, the greater the near vision add, the greater the challenge for neuroadaptation, distortion, halos, and glare. Extended depth-of-focus (EDOF) lenses have tried to reduce these problems with so-called extended depth of field, which provide small changes in the optical behavior of the IOL, which adds some value for near. The problem is that these changes, such as asphericity changes, are not customised and work unevenly in different patients. Changes like achromatisation do not really extend the depth of field but, rather, increase other functions. Overall, EDOF lenses cannot be based only on aberrations because when aberration changes are high, they decrease the optical quality of the retina to unacceptable levels. The amount of customisation that multifocal with EDOF changes is still to be defined. Pure EDOF lenses are, in my opinion, failing because they induce unacceptably bad quality of vision and are insufficiently strong for near vision to be spectacle independent. Finally, accommodative lenses show evidence that sulcus implantation is ideal. We should continue to see promising results about this in peer-review journals.

**Dr Augustin:** Cataract surgery is increasingly characterised by patient expectations to live without glasses and the relative attempt to make a surgical correction of presbyopia. The introduction of multifocal IOLs has allowed a response to this request. Since their introduction, multifocal IOLs have the ability to promote near and distant vision simultaneously. Nevertheless, some subjective complaints, such as glare, halos, starbursts and unsatisfactory distance vision have been reported by the patients. Moreover, there is the increased demand of intermediate vision among the population using tablets and smartphones. These patients request “something more” than a normal multifocal IOL. The goals of reducing spectacle dependency and optimising postoperative visual quality after cataract surgery have driven the development of EDOF IOLs. The main advantage of EDOF lenses compared to multifocals includes a reduced incidence of photic phenomena, improved uncorrected
Which multifocal Interventional Research in the 8 DECEMBER 2018 ophthalmic challenges in 2019 ISSUE FEATURE

Dr Augustin: Research in the field of antiglaucomatous medications has recently led to the introduction of a new class of drugs into the pharmaceutical market in Japan and the U.S.: the Rho kinase (ROCK) inhibitors. These new drugs represent members of the first new class of clinically useful ocular hypotensive agents since the U.S. Food and Drug Administration approval of latanoprost in 1996. The ROCK inhibitors act by modulating the cytoskeleton at the level of trabecular meshwork and Schlemm’s canal, thereby reducing the outflow pathway resistance and—by doing so—reducing the intraocular pressure. I believe it is fundamental to have another treatment option in the management of glaucoma. Moreover, the ROCK inhibitors also have showed two other considerable effects. First, they have been demonstrated to be effective in combination with other ocular hypotensive medications, such as the prostaglandin analogues. In addition, they also appear to have a neuroprotective activity, a favorable impact on ocular blood flow, and even an antifibrotic effect that may prove to be useful in conventional glaucoma surgery. The combinations of all these properties offer a great chance for specialists to battle an arduous disease such as glaucoma.

Dr Holló: To prove the advantage of the various microinvasive glaucoma surgery (MIGS) devices over classic mitomycin C (MMC) trabeculectomy based on their cost/benefit ratio remains a challenge. In countries where a general health insurance system is used (e.g., in many countries in Europe) a trabeculectomy with an adjunctive antimetabolite is much cheaper than a MIGS device alone. Thus, the price of the various MIGS devices on the top of the cost of surgery cannot be justified for reimbursement. In particular, the IOP-lowering efficacy does not exceed that of MMC trabeculectomy, even when the best studied MIGS devices are considered. Therefore, I think that in countries with a general health insurance system, the use of MIGS will remain minimal in 2019.

In 2018, two separate prospective multinational European studies on the referral of glaucoma patients for diagnosis of glaucoma and for first-time glaucoma surgery were published. In the article that addressed the appropriateness of referral for glaucoma diagnostics by general practitioners, optometrists, and ophthalmologists, the figures were generally poor for all categories. In the second article, it was found that patients with open-angle glaucoma are referred for their very first glaucoma surgery later and in a more severe stage of the disease in the old European Union countries than in the new European Union countries and in the new European Union countries than in the non-European Union European countries. This clearly shows that the more options ophthalmologists have to avoid surgery, the longer time that is necessary for the decision on surgery. However, the price paid for this is disease worsening. This attitude should be changed, and surgery should be promptly recommended to patients. This will be a major task for the upcoming years.

Dr Kermani: Interventional glaucoma surgery is gaining ground, and I believe in 2019 we will triple our numbers. The question our CFO is bringing up first is about the cost of the MIGS devices. It’s nice and elegant surgery, but it’s expensive. In our clinic, we have two schools—one favors simple goniotomy, and the other prefers the iStent as an adjunctive antimetabolite. In night vision, glare and halos.

The main task is to identify a “good” patient. There is no 100% prediction that your pick and recommendation is correct, even if you are an experienced surgeon. I also do not believe in pre-op behavior evaluations. After all, what counts is when the IOL is in the eye and you take the bandage off the day after surgery. Everything can be different from what you expected. My solution? I am shifting to multifocal AddOn systems, the Cristalens from France, 1st Q from Germany, and Rayner from Great Britain have excellent sulcus AddOn trifocal IOLs. The winning point is the reversibility. If the IOL does not perform and the patient is unhappy, it is so easy to take it out again. So what? Nothing has happened.
Dr Holló: The understanding of the time-dependent changes in OCT angiography (OCT-A) remains a major challenge in glaucoma research. Recently it has been shown in prospective longitudinal studies that peripapillary OCT angiography results are more variable than the corresponding retinal nerve fiber layer thickness (RNFLT) results; removal of the effect of the large retinal vessels improves the detection of glaucomatous progression with peripapillary OCT angiography; posterior subcapsular cataract influences the peripapillary OCT-A measurements more that the RNFLT measurements; and smoking and breath holding have no influence on the measured peripapillary OCT-A results. Thus, to better use peripapillary OCT-A for the detection and measurement of glaucomatous progression, further studies are necessary.

Dr Stefánsson: Retinal imaging should be recognised as surrogate endpoints for treatment intervention. For example, in diabetic macular oedema (DMO), it should be recognised that reducing retinal oedema as seen on OCT images is a relevant treatment endpoint. Because diabetic retinopathy grades on fundus photographs are already recognised as a surrogate endpoint, the OCT also should be acceptable. This is also in agreement with many other surrogate endpoints, such as intraocular pressure in glaucoma, arterial blood pressure in stroke, and tumour size in cancer.

Dr Augustin: The most recent progress in the field of retinal imaging has been focused on the ultra wide-field (UWF) approach, which has allowed visualisation to reach the retinal periphery up to 200°, having the capability to cover approximately 82% of the retina in a single image. This new method offers the possibility to have a fast, detailed and unique comprehensive overview of the whole retina without the need of a post-processing reconstruction of more images. I think it’s a considerable development, mostly for the achievable application of UWF imaging to fluorescein angiography (FA) and indocyanine green angiography (ICGA). The introduction of UWF-FA may lead to a great improvement in the diagnosis and management of diabetic retinopathy through the identification of novel angiographic features, including the exact quantification of the extent of ischemia and other pathologies in peripheral retina. UWF-ICGA may be useful to better analyse peripheral abnormalities in age-related macular degeneration (AMD) and alterations of the vascular permeability in the central serous chorioretinopathy that otherwise would not have been imaged. Moreover, UWF-ICGA plays a relevant role in the analysis of some uveitic conditions, including birdshot chorioretinopathy, the presence of Type 1 choroidal neovascularisations associated with signs of increased choroidal thickening and hyperpermeability. The latter features are distinctive of pachychoroid spectrum disease, which also includes pachychoroid pigment epitheliopathy, central serous chorioretinopathy, and polypoidal choroidal vasculopathy. It has been demonstrated that these pathologies share common features, such as choroidal vascular dysfunction, abnormalities of the retinal pigment epithelium without showing typical characteristics of AMD, and, occasionally, choroidal new vessels. As a way to approach this new disorder, I would suggest using a multimodal imaging modality, improved by the use of OCT-A. The development of the most recent OCT-A software offers valuable help, mostly to distinguish choroidal neovascularisation in the spectrum of pachychoroid disease from typical neovessels appearing in AMD, leading to a more specific and individualised management.

‘The introduction of UWF-FA may lead to a great improvement in the diagnosis and management of diabetic retinopathy through the identification of novel angiographic features.’ - Dr Augustin
**THOUGHTS ON Retinal disease, diabetic eye disease**

**Dr Stefánsson:** The global epidemic of diabetes continues. Over 400 million persons have diabetes now and this is projected to exceed 600 million by 2030. This is one of the biggest epidemics in the history of mankind.

We know that two-thirds of diabetic patients develop diabetic retinopathy within 20 years, and one-third develop sight-threatening retinopathy. The global epidemic of diabetes will become a global epidemic of blindness if preventive measures are not instituted.

Diabetic eye screening and appropriate preventive treatment are proven ways to reduce the risk of blindness from diabetes. However, only a small minority of diabetic people, perhaps 10% or less, have access to regular screening. The participation of patients with diabetes in eye screening programs must be increased around the world to prevent a wave of diabetic blindness in the future.

Diabetic eye screening can be made more efficient and economically feasible. With annual eye screening for diabetic patients, only 2–3% are referred for treatment. Individualised risk assessment can improve this ratio. If screening frequency is based on the individual risk profile (i.e., each person’s risk of developing sight-threatening retinopathy) the overall number of screening visits can be cut in half while catching all diabetic patients who need treatment.

Risk profiling increases the screening frequency of high-risk patients, while low-risk patients are spared from unnecessary clinic visits. The cost to individuals and society can be cut in half while maintaining medical effectiveness. This makes systematic diabetic eye screening more economically feasible, also for poorer nations.

Retina clinics are being overwhelmed with the number of intravitreal injections needed for our patients. In my small clinic in Iceland (population 350,000) we have gone from no injections to 8000 per year in a decade, and this is by far the busiest activity in clinic. It is also the most common “operation” in the hospital. While relatively rich developed countries are able to sustain this effort, it is clearly beyond the capacity of many countries around the world.

While wet AMD is responsible for the majority of intravitreal injections, diabetic eye disease is an important and rising cause. Diabetes is increasing rapidly in most populations and is still the most common cause of visual impairment in working-age people in many counties. Diabetic macular oedema (DMO) and recently some cases of proliferative diabetic retinopathy are treated with intravitreal injections. DMO is the most common cause of visual impairment in diabetes. There are currently 25- to 30-million people with DMO in the world, but only about 2 million are receiving intravitreal injections or implants.

Monthly intravitreal injections are not a sustainable treatment option for large populations on a global basis. Drug delivery options that are less demanding on health care resources must be developed. Several options are being studied. These include intravitreal injectables and implants that have longer duration of treatment as well as noninvasive treatment options, including eye drops. Eye drops have the obvious advantage of being self-administered, making them more accessible to large populations.

While anti-vascular endothelial growth factor (VEGF) drugs have been a godsend for patients with wet AMD and DMO, and several other sight-threatening diseases, this treatment is not perfect. Our AMD patients no longer face the threat of losing 6 lines of vision, and DMO patients can expect some improvement in vision rather than the stability offered by laser treatment before. However, only about one-third of patients with wet AMD and DMO can expect optimal outcomes from anti-VEGF treatment with substantial improvement of vision and a similar ratio of patients see virtually no improvement in visual acuity following intravitreal injections.

We need to do better and offer these patient groups a higher probability of visual improvement.

New treatment pathways are being explored, and an emphasis needs to be placed on the inflammatory and ischemic origins of these diseases. Combination treatments have done wonders in many fields of medicine, such as with AIDS and high blood pressure. Combination treatments should be explored in AMD and diabetic eye disease, and regulatory agencies need to support this approach.
Dr Alió: Cost effectiveness is becoming an issue. The ophthalmologist and, generally speaking, the economy of an ophthalmic office cannot afford techniques that are not cost effective because the investment is never recovered, and neither is there a benefit for the patient. Studies that demonstrate that a new technology is capable of bringing advantages to patients and guarantees a return that is payble or recovered in some way are those that will be chosen by doctors in the future. This information is necessary because costs are becoming a long-standing problem in health care, both in private practices and in public health care systems.

‘Costs are becoming a long-standing problem in health care.’ - Dr Alió
The pinhole intraocular lens (IOL) design in the AcuFocus IC-8 IOL (AcuFocus Inc.) provides good visual outcomes over the range of vision from near to distance. This extended depth of focus is achieved by a combination of technologies, i.e., the small aperture combined with a monofocal lens. This IOL uses the same principle as that used in the Kamra inlay, also from AcuFocus, Inc. According to Matteo Piovella, MD, a non-diffractive 3.23-mm diameter opaque mask is the innovation that creates the pinhole effect. It has a 1.36-mm central aperture that is embedded in a 6.0-mm one-piece hydrophobic acrylic lens. He explained that the mask provides almost 3.0 diopters (D) of extended depth of focus by its ability to block the unfocused peripheral light rays and concentrate the rays that are more focused centrally and the paracentral rays through the central aperture.

The IC-8 is implanted in the patient’s non-dominant eye, with a refractive target of –0.75 D, and an aspheric IOL is implanted in the dominant eye, with a refractive target of plano.

Clinical study
A study began in May 2015 that included patients 45 years of age and older who had clear intraocular media other than a cataract, and a best-corrected distance visual acuity (BCDVA) of 20/30 or worse due to the cataract. The fellow eye could have the natural crystalline lens or had undergone previous implantation of an aspheric IOL.

Twenty one patients were included in this 3-year study. Dr Piovella reported that, at all distances, the mean monocular postoperative uncorrected spherical equivalent with the IC-8 was 0.83 ± 0.71 D, and the BCDVA with the monofocal IOL was 0.14 ± 0.26 D. The binocular results combined the best of both technologies. The mean binocular uncorrected VAs were 20/18 at far, 20/18 at intermediate and 20/20.5 at near.

Dr Piovella, who is the medical director of Centro Microchirurgia Ambulatoriale, Milan, Italy, commented, “By achieving the refractive targets of –0.75 D in the eye implanted with the IC-8 IOL and plano in the monofocal eye, the visual outcomes were further optimised”.

Today’s market
Patients have a number of options for achieving a wide range of vision after cataract surgery, all of which have their associated advantages and disadvantages. Dr Piovella pointed out the different IOL model-specific technical characteristics:

- A) Trifocal IOLs are approved for distance, intermediate and near vision. This design is less sensitive to small postoperative refractive errors than bifocal IOLs, and the trifocal design may be the best technology for clear near vision.
- B) Extended depth of focus models have received approval only for addressing distance and intermediate vision. These IOLs are less sensitive to small postoperative refractive errors as a result of the far extended depth of focus.

IN SHORT
A small-aperture intraocular lens (AcuFocus IC-8) provides good visual outcomes over the range of vision with extended depth of focus achieved by combining the effects of the pinhole technologies and a monofocal lens.
Seeing to succeed in cataract surgery.

ZEISS OPMI LUMERA 700

»We are able to give our patients a much more predictable outcome. That I think is key for today’s cataract surgeons, the ability to predict and deliver what we tell them we’re going to do.«

Ronald Yeoh, MD
Eye and Retina Surgeons
Camden Medical Centre, Singapore

Passionate about his profession, Dr. Yeoh is committed to providing cataract patients with the best possible outcome. The superb imaging and markerless toric IOL alignment capabilities of the OPMI LUMERA® 700 and CALLISTO® eye from ZEISS enable him to deliver on patient expectations. We share his commitment to his calling. What’s your calling?

www.zeiss.com/mycalling
The pinhole IOLs eliminate the need for toric correction of up to 2 D, Dr Piovella noted. The distance quality of vision is based on the dominant eye and the best monofocal IOL. There is no far monovision; the distance VA is at least 20/25 with the IC-8 implant. “This is the best IOL technology for use in patients who have undergone RK or in those with aberrating corneas,” he said.

These advanced-technologies IOLs have replaced bifocal multifocal technologies in countries where they are commercially available.

Another advantage of the IC-8 is that it is easier to centre in the eye compared with the Kamra inlay.

With the IC-8, the binocular contrast sensitivity is equal to that in the eye with the aspheric IOL. “Neuroadaptation and the retinal response to illumination will further boost the contrast performance in the eye implanted with the IC-8 IOL,” Dr Piovella said.

He concluded, “The clinical study showed that the IC-8 IOL provided visual outcomes with continuous and uninterrupted range of vision, excellent image quality across the entire range of vision, good-quality night vision with less nighttime glare or halos. Importantly, this design provides good near and intermediate vision without negatively affecting the distance vision”.

MATTEO PIOVELLA, MD
E: piovella@piovella.com
Dr Piovella is a consultant to Acufocus.

1. Perfectly centred IC-8 IOL 1 month postoperatively (mydriasis).
2 and 3. Perfectly centred IC-8 IOL 1 month postoperatively.
4. IC-8 IOL design.
(Images courtesy of Matteo Piovella, MD)
Seeing to succeed in cataract surgery.

ZEISS OPMI LUMERA 700

»The key moment in my research was when I could see the space of Berger for the first time using intraoperative OCT from ZEISS.«

Marie-José Tassignon, MD, PhD, FEBO
University Hospital of Antwerp, Belgium

When performing the unique cataract surgery technique she is known for, Dr. Tassignon benefits from the integrated intraoperative OCT in the OPMI LUMERA® 700 from ZEISS. The clear, sharp OCT images provide her with insights that enable her to continue her exploration of new approaches — and to share her experience with her peers and students. We share her commitment to her calling. What’s your calling?

www.zeiss.com/mycalling
The rate of refractive enhancement after SMILE is low. If retreatment is needed and there is sufficient tissue to safely create a flap, thin-flap LASIK is a viable option that provides excellent visual and refractive outcomes, according to Dan Z. Reinstein, MD, MA (Cantab).

Dr Reinstein presented data from a retrospective study [Reinstein DZ, et al. J. Refract. Surg. 2018; 34,578-588] that reviewed 2643 consecutive SMILE procedures performed between September 2013 and January 2016. A total of 116 (4.4%) eyes underwent retreatment, of which 100 were with LASIK. Flaps, created using the VisuMax femtosecond laser (Carl Zeiss Meditec), were ≤110 microns in all but three eyes.

The attempted SEQ for the eyes retreated with LASIK ranged from –1.88 to +1.50 D (mean –0.05 ± 0.99 D) and mean cylinder was –0.70 ± 0.55 D. Postoperatively, mean SEQ relative to the target was +0.19 ± 0.49 D, the refractive outcome was within ±0.5 D of target in three-fourths of eyes, and mean cylinder was –0.29 ± 0.24 D.

Eighty-one percent of eyes achieved uncorrected distance visual acuity of 20/20 or better, up from 11% before the retreatment and relative to 95% of eyes with corrected distance visual acuity of 20/20 or better. No eyes lost ≥2 lines of corrected distance visual acuity, and only one eye lost 1 line.

“Initially it was thought that only surface ablation could be done for eyes needing retreatment after SMILE, and then techniques were developed to convert the SMILE cap interface into a LASIK flap by performing a side cut or Circle procedure. Although some of the software is not available yet for our US counterparts, there are workarounds to provide patients with a better retreatment option,” said Dr Reinstein, medical director, London Vision Clinic, London, and professor of ophthalmology, Columbia University Medical Center, New York.

“The advantages of doing thin-flap LASIK are that it has less chance of causing inflammation and haze compared with surface ablation, and compared with converting the SMILE cap interface into a LASIK flap, it leaves a greater amount of uncut stromal fibres and therefore causes less biomechanical weakening if the original SMILE cap was relatively thick,” Dr Reinstein said.

**Treatment planning and technique**

In order to perform thin-flap LASIK, there must be sufficient space in between the epithelium and the SMILE cap to safely create the flap. Making that determination requires the ability to visualise the full cap and epithelial thickness and obtain accurate measurements of the distance between the maximum epithelium thickness and the minimum cap thickness. Either very-high-frequency digital ultrasound (Artemis Insight 100, ArcScan) or anterior segment optical coherence tomography (e.g., RTVue, Optovue) can be used for the anatomical evaluation.

Providing some general rules, Dr Reinstein said, “A thin LASIK flap can be created if there is at least 40 microns between the maximum epithelium thickness and the minimum cap thickness. Either very-high-frequency digital ultrasound (Artemis Insight 100, ArcScan) or anterior segment optical coherence tomography (e.g., RTVue, Optovue) can be used for the anatomical evaluation.

The approach for lifting the flap has also evolved over time. The majority of cases were done using what Dr Reinstein terms the bimanual inferior pseudo-hinge fulcrum technique, which was designed to reduce the risk of entering the small incision and creating a tear or accessing the original SMILE interface.

He reported that SMILE interface access or an incision tear occurred in 10 (7.2%) of the 139 procedures. There were no intraoperative complications in the 84 consecutive cases that were done using the most recent iteration of the flap lift technique.

The technique involves inserting the flap lifter and
McPherson’s forceps in the inferior third of the flap. Upward pressure is applied while pushing the instrument across the interface to prevent the instrument tip breaking through to the original SMILE interface. C. The McPherson’s forceps is inserted to the mid-point of the flap and swept superiorly, thereby separating the region of the small incision with the arm of the instrument and not the tip. The flap lifter is held in place using the inferior unseparated portion of the flap to provide counter-traction for the McPherson’s forceps. A second sweep is made to separate the other half of the flap. D. The McPherson’s forceps is then placed against the superior hinge to provide counter-traction for the flap lifter to be used to separate the inferior portion of the flap in the usual manner. Reprinted with permission from Reinstein DZ, Archer TJ, Carp GI. The Surgeon’s Guide to SMILE: Small Incision Lenticule Extraction. Thorofare, NJ: SLACK Incorporated; 2018.

McPherson’s forceps in the inferior third of the flap. Upward pressure is applied to avoid the instrument tip breaking through to the original SMILE interface. While holding one instrument at the hinge to provide counterforce, the second instrument is used to separate the inferior third of the interface towards the hinge. The rest of the separation and flap lift can be completed using a standard technique. US surgeons will have to make a few small changes to this technique to account for the current software restrictions on incision size and location, Dr. Reinstein said.

He also reported that there were no cases of epithelial ingrowth requiring flap lift or Nd:YAG laser treatment in the thin-flap LASIK series.

“In contrast, in a study where we reviewed 3470 eyes that underwent flap lift retreatment after LASIK, flap lift and/or Nd:YAG treatment for epithelial ingrowth was required in 151 (4.4%) eyes.”

Additional refinements

The 100 eyes that underwent retreatment with LASIK included 58 with hyperopia/mixed cylinder and 42 with myopia.

Subgroup analyses of treatment predictability showed that the refractive outcome was on target in the hyperopes, but there was a tendency for overcorrection for cases of consecutive myopia retreatment.

“It appears there is a different nomogram required for doing LASIK as a retreatment after SMILE than after LASIK, and it probably has to do with differences in epithelial remodeling after the two procedures,” Dr. Reinstein said.

Using their outcomes data, Dr. Reinstein and colleagues have adjusted the nomogram for LASIK correction of myopia after SMILE.

DAN Z. REINSTEIN, MD, MA (CANTAB)
E: dzr@londonvisionclinic.com
Dr. Reinstein is a consultant to Carl Zeiss Meditec and has a financial interest in the Artemis Insight 100 VHF digital ultrasound.
The goal with presbyopic implant surgery is to achieve high levels of patient satisfaction and spectacle independence. In general, this means providing excellent distance, intermediate and near vision (in both dim and bright light), with an acceptable level of light phenomenon while driving at night. The challenge for cataract surgeons is that, in addition to surgical skills, we must also have the communication skills to determine patients’ visual needs and enough knowledge about IOL technology to understand the strengths and weaknesses of each lens.

Over the years I have implanted nearly 6,000 presbyopia-correcting IOLs. We have developed a multivariate regression analysis model to evaluate how presbyopic lenses fare when implanted bilaterally or in various combinations. The model now includes more than 40 independent variables, including a wide range of objective clinical metrics and subjective patient responses related to performance of common visual tasks (see sidebar).

**Tecnis Multifocal +4.00 vs. Tecnis Multifocal +3.25**

Most recently, I used this model to determine predictors of overall patient satisfaction in cohorts of patients implanted bilaterally with either ZMB00 (Tecnis Multifocal +4.00, Johnson & Johnson Vision) or ZLB00 (Tecnis Multifocal +3.25, Johnson & Johnson Vision) IOLs. Both cohorts were comprised of ‘best case’ patients: they were all at least 6 months postoperative so that any neuroadaptation had already occurred; all necessary Nd:YAG procedures had been completed; residual refractive error, if any, had been treated; and the ocular surface was well managed. The same regression analysis methodology was applied to both cohorts.

In both cohorts, satisfaction levels were high: 100% of subjects rated themselves either ‘satisfied’ or ‘very satisfied’ overall. If one were to evaluate a cohort that included patients with dry eye or uncorrected astigmatism, the spread of results would be greater (i.e., greater variance), but it would also be impossible to know whether their responses were related to the IOL.

There was a statistically significant increase in the rate of ‘very satisfied’ patients in the bilateral +3.25 cohort (82%) vs. the bilateral +4.00 (64%) cohort (Fig. 1).

Satisfaction with intermediate vision improved significantly in the +3.25 cohort compared to the +4.00 cohort, while satisfaction scores for distance and near vision were equivalent between the two (Table 1).

<table>
<thead>
<tr>
<th>Table 1: Mean satisfaction (scale of 0.0–4.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZMB00</strong> (TMF +4.00, <strong>N=55</strong>)</td>
</tr>
<tr>
<td>Distance</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>Near</td>
</tr>
</tbody>
</table>

**IN SHORT**

> Intermediate vision is the most likely source of dissatisfaction with contemporary multifocal IOLs, but a medium-add multifocal IOL addresses this issue.
**Table 2: Characteristics of Tecnis Multifocal IOLs of varying add powers**

<table>
<thead>
<tr>
<th>TMF MODEL</th>
<th>NOMINAL ADD POWER (IOL PLANE)</th>
<th>ADD POWER (SPECTACLE PLANE)</th>
<th>CENTRAL BUTTON ADD POWER (SPEC PLANE)</th>
<th>NEAR FOCAL POINT (APPROX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZMB00</td>
<td>+4.00</td>
<td>+3.00</td>
<td>+1.50</td>
<td>14 in</td>
</tr>
<tr>
<td>ZLB00</td>
<td>+3.25</td>
<td>+2.37</td>
<td>+1.20</td>
<td>17 in</td>
</tr>
<tr>
<td>ZKB00</td>
<td>+2.75</td>
<td>+2.00</td>
<td>+1.00</td>
<td>20 in</td>
</tr>
</tbody>
</table>

**Predictors of success**

Regression analysis revealed that three variables related to intermediate vision were statistically significant predictors of overall patient satisfaction in the ZMB00/+4.00 cohort: ability to ‘read a newspaper’ without glasses ($p<0.005$); ability to ‘work at a computer’ without glasses ($p<0.005$); and ‘intermediate visual acuity at the patient’s preferred focal distance’ ($p=0.05$). Next, I made ‘intermediate visual acuity at the preferred focal distance’ an independent variable to see if any of the regression factors would predict who would achieve better intermediate vision. Smaller ‘mesopic pupils’ ($p<0.005$) and better ‘IOL centration’ ($p=0.02$) were statistically significant predictors of superior intermediate vision. This observation was beyond the pinhole effect because better distance and near vision were not correlated with decreasing mesopic pupils.

A unique design feature of the Tecnis family of multifocal IOLs helps to explain the regression findings related to smaller mesopic pupils. These lenses have a central 1.0-mm button with half the add power of the total near add (Table 2). As the mesopic pupil decreases, the percentage of light being processed through the central intermediate button increases, thereby enhancing intermediate vision. Results from the FDA clinical trial for the ZMB00 model demonstrate this same effect:

Subjects with smaller pupils also achieved better intermediate vision in that study (Fig. 2).

In the +3.25 cohort, the data strongly suggests that the improved intermediate vision is responsible for the increased percentage of patients responding at the ‘very satisfied’ level (82%+/3.25 vs. 64%+/4.00). Table 1 shows that the raw scores for ranking intermediate vision were significantly higher without any difference in the raw scores for distance or near vision. The increased focal length of the +3.25 IOL (17 inches vs. 14 inches for the +4.00) is likely responsible for the improved intermediate vision.

**Impact on clinical decision making**

Regression revealed that pre-op mesopic pupil size is a reliable predictor of post-op intermediate vision. This information is powerful for pre-op planning. For example, if you were initially planning to implant two +3.25 IOLs, but pre-op testing revealed large mesopic pupils, which may result in less than optimal intermediate vision, you should consider changing your surgical plan. This patient would likely achieve greater overall patient satisfaction if one of the +3.25 lenses was replaced with a Symfony or Symfony Toric IOL.
CASE OF THE MONTH

Presbyopic Commercial Airline Pilot Finds a Class One Medical Approved Corneal Refractive Surgery Solution for Presbyopia

By Dan Z Reinstein, MD MA(Cantab) FRCSC DABO FRCOphth FEBO
Medical Director of the London Vision Clinic

CASE HISTORY

A 58-year-old woman presented with a request to explore options for vision correction that would meet the vision needs in her occupation as a commercial airline pilot. The patient, who is also a medical doctor, has a dual career as an Aeromedical Examiner. She had moderate myopia with low astigmatism in both eyes. Her uncorrected distance visual acuity (UDVA) was 20/160 in the right eye and 20/125 in the left eye. Her manifest refraction was 3.50 -0.50 x 146 (20/20) in the right eye and -2.25 -0.75 x 10 (20/20) in the left eye. Near vision was N10/J4 binocularly. She was using varifocal glasses for distance and near vision and single vision glasses for intermediate vision.

As a pilot, she works in a complex visual environment that necessitates clear vision at a variety of distances. Near and various intermediate visual distances are important for the controls and displays within the cockpit (Figure). When wearing varifocal glasses, viewing the controls above the head was particularly challenging as it is difficult to look through the near vision portion of the lens. Viewing an iPad for navigation to the side and buttons above, below, and in front prove challenging for any presbyopic pilot. Clear vision at very far distance is also needed for safe operation while taxiing, landing, and parking the plane, including in low visibility conditions (Figure).

Figure. Pilots work in a complex visual environment requiring clear vision at a variety of distances inside and outside of the cockpit. Arrows indicate controls and displays located at near and various intermediate visual distances.

The findings from her examination showed the patient was suitable for PRESBYOND and all diagnostics were normal in both eyes. She was right eye dominant and able to tolerate -1.50 D of anisometropia with minimal cross-blur symptoms. Surgery was planned with a refractive target of plano in the right eye and -1.50 D in the left eye. Total treatment was -3.50 -0.50 x 146 in the right eye and -0.75 -0.75 x 10 in the left eye.

OUTCOME

By 1 month after surgery, the patient’s binocular vision was 20/16 at distance, J3 at intermediate and J1 at near. The manifest refraction was +0.75 DS (20/16) in the right eye and -1.50 DS (20/20) in the left eye. The UDVA in the right eye was 20/50, which was better than expected for the nominal -1.50 DS refraction. Contrast sensitivity was unchanged or slightly increased for 3, 6, 12, and 18 epd. Stray light scatter by C-Quant had returned to the preoperative level. Subjectively, the patient reported night vision to be unchanged from before surgery.

Two months after surgery, the patient passed the United Kingdom Civil Aviation Authority vision standards for a Class 1 medical certificate without spectacle restrictions, with UDVA in the left eye improving another line to 20/40. The result has been stable in the longer term with the same binocular vision at the most recent follow-up, 3.5 years after surgery. The manifest refraction was +0.50 -0.50 x 7 (20/162) in the right eye and -1.75...
DS (20/16)\(^2\) in the left eye. UDVA in the left eye had even improved slightly further to 20/32\(^2\). Contrast sensitivity was also stable in the high normal range, equal to or above the preoperative level. The objective scatter index (OSI) (HD Analyzer, Visiometrics Costa Mesa, CA/USA) was 0.6 in both eyes, demonstrating excellent optical quality.

**DISCUSSION**

An ideal surgical treatment for presbyopia in patients with a clear lens would simultaneously correct refractive error to provide clear vision at distance, allow continuous vision to intermediate and near, maintain binocularity and optical quality, and have a short adaptation time with a good safety profile. Such a treatment should also be correctable in the event the patient is not happy with the outcome and adjustable to compensate for progressive presbyopia or future changes in refraction. PRESBYOND successfully met the complex visual needs of the patient in this case.

PRESBYOND is a laser procedure that combines a small functional anisometropia (≤1.5 D) with a non-linear aspheric ablation profile that induces a controlled amount of spherical aberration to increase depth of field. The anisometropia is small enough that patients maintain functional stereo-acuity uncorrected and do not lose best spectacle corrected stereo-acuity. Compared with refractive lens exchange, PRESBYOND does not expose patients to the low but potential risks for vision-threatening complications that can occur with intracocular surgery. If a patient experiences halo or glare from the small anisometropia in PRESBYOND, this is almost always reversed by a pair of spectacles that reduce the anisometropia given that spherical aberration is controlled within neural filtration limits; but this in contradistinction to the commonly reported side effects of glare and halo after multifocal IOLs which if not neuro-adapted to, cannot be reversed without further surgery.\(^2,3\)

Unlike other corneal refractive laser approaches that create a multifocal cornea, PRESBYOND provides a continuous range of vision from near to far along with the refractive accuracy and safety of a standard LASIK procedure. The outcomes and advantages are highlighted by this case where the very demanding visual needs of a presbyopic commercial airline pilot were achieved. By contrast, use of multifocal and diffractive IOLs are currently not compatible with pilot certification in the United Kingdom.\(^1\)

The outcome for this patient is also echoed by my own personal experience and that of 17 other ophthalmic surgeons who underwent PRESBYOND at London Vision Clinic, representing another category of patients with very demanding visual needs!

PRESBYOND offers the advantage of being a routine bilateral laser procedure performed in 10 minutes, with patients being able to read and watch TV within a few hours and return to most activities the next day as is the case in general for LASIK the world over. The ablation is performed using the MEL 80 or MEL 90 excimer laser (Carl Zeiss Meditec AG, Jena/Germany) based on a profile created using proprietary software for the CRS-Master workstation (Carl Zeiss Meditec AG, Jena/Germany).

The treatment plan for each patient is customized for preoperative ametropia (including plano presbyopia) and pupil size and takes into account preoperative spherical aberration and functional age of the eye. The ablation creates a continuous refractive power gradient for the entire optical zone.

**CONCLUSION**

PRESBYOND using a nonlinear aspheric ablation profile with a well-tolerated modified binocular vision approach delivers continuous quality vision from near to far along with the refractive accuracy and safety of a standard LASIK procedure. The outcomes and advantages are highlighted by this case where the very demanding visual needs of a presbyopic commercial airline pilot were achieved. By contrast, use of multifocal and diffractive IOLs are currently not compatible with pilot certification in the United Kingdom.\(^1\)

The outcome for this patient is also echoed by my own personal experience and that of 17 other ophthalmic surgeons who underwent PRESBYOND at London Vision Clinic, representing another category of patients with very demanding visual needs!

---

**References**

1. Guidance following eye surgery.

---

**Case Study**

**Dan Z Reinstein, MD** is a consultant to and receives travel expenses from Carl Zeiss Meditec AG and has a financial interest in ArcScan Inc.
Conclusions

In summary, this study revealed:

1. A significantly greater level of ‘very satisfied’ patients in the bilateral +3.25 cohort versus the bilateral +4.00 cohort.
2. Improved intermediate vision was responsible for the higher levels of satisfaction.
3. The intermediate vision was improved without sacrificing the quality of either near or distance vision.

which would enhance the overall bilateral intermediate function. If the patient had small mesopic pupils you should stick with the bilateral +3.25 lenses which would maximise the near vision while achieving excellent intermediate vision in both eyes because of the small pupils.

We are currently applying the regression evaluation method to our +3.25/Symfony cohort, which appears to be achieving very high levels of patient satisfaction.

4. The increased focal length of 17 inches in the +3.25 group versus 14 inches in the +4.00 group and subsequent improved intermediate vision did not ‘wash out’ the mesopic pupil effect in the +3.25 patients. Smaller mesopic pupils still strongly correlated with enhanced intermediate vision in the +3.25 patients as observed in the +4.00 cohort.

5. Our findings of increased satisfaction in the +3.25 cohort with improved intermediate vision without sacrificing near vision, along with the mesopic pupillary effect strongly support further efforts at customization of the pre-op surgical plan like the combination of a +3.25 with the Symfony or Symfony toric.

Finally, high levels of success with presbyopia-correcting IOLs are dependent on (1) choosing the IOLs that will maximise the patient’s bilateral visual performance at distance, intermediate and near; (2) aggressively treating residual refractive error (≤0.50 D of residual sphere and astigmatism); and (3) aggressively managing the ocular surface.

REFERENCE

Intestinal microbiome proposed as potential therapeutic target for AMD

A link between the gut microbiome and age-related macular degeneration

By Cheryl Guttman Krader
Reviewed by Sebastian Wolf, MD, PhD

Associations between the gut microbiome and disease is a hot topic in medical research. Sebastian Wolf, MD, PhD, described accumulating evidence pointing to a role of the gut microbiome in the development of age-related macular degeneration (AMD).

“We have shown that the gut microbiome is altered in patients with AMD compared to healthy controls, and our research supports the idea that the gut microbiome may constitute a link between nutrition, the complement system and the development of AMD,” said Dr Wolf, professor of ophthalmology and director and chairman, University Eye Hospital Bern, Bern, Switzerland. “Perhaps, in the future, the composition of the gut microbiome will be a target for the treatment or prevention of AMD.”

Dr Wolf explained that people have up to 100 trillion bacteria residing in the gastrointestinal tract. These microorganisms, which represent more than 10,000 different species, play a major role in the digestion of food and thereby influence the global metabolism of the host.

Composition of the gut microbiome has been shown to influence the immune and complement system, and to be associated with the development of neurodegenerative and metabolic diseases.

Knowing that nutrition and genetics play a role in the development of AMD, Dr Wolf and colleagues undertook a series of animal and human studies to investigate whether those associations might be mediated by the gut microbiome.

Research done in a mouse model showed that the gut microbiome was significantly altered in animals that were deficient in complement 3 (C3). In another preclinical study, mice fed a high-fat diet were found to have an altered gut microbiome and increased choroidal neovascularisation compared with controls.

“Relative to control mice, the mice in the high-fat diet group had an increased abundance of the phylum Firmicutes, which includes various gram-positive bacteria, while the control mice had more anaerobic Bacteroides spp. in their guts,” Dr Wolf reported.

Next, a pilot study was performed in humans that evaluated whether the compositional and functional diversity of the intestinal microbiome was associated with AMD. It enrolled 12 patients with AMD and 11 age-matched controls without AMD, and used next-generation sequencing to characterise levels of different microbiome species and metagenomic features.

The study found significant differences between the patients with AMD and controls.

“Consistent with our animal experiment, we found more Bacteroides spp. in the control group and more Firmicutes in the patients with AMD,” Dr Wolf reported. Specifically, the genera Anaerotruncus, Oscillibacter, Ruminococcus torques and Eubacterium ventriosum were relatively enriched in the patients with AMD compared with the controls.

Looking at the functional diversity of the microbiome showed that bacteria related to fatty acid digestion were present in higher levels in the controls compared with the AMD patients.

Patients with AMD, however, had greater levels of bacteria affecting glutamate and arginine biosynthesis pathways.

The findings give a basis for suggesting that the gut microbiome links nutrition with AMD risk.

IN SHORT

- Study findings suggest that the gut microbiome is linked to age-related macular degeneration (AMD) development due to its effect on nutrient uptake.
“We have shown that the gut microbiome affects bioavailability of long-chain polyunsaturated fatty acids and it is known that increased levels of arginine are associated with progressive chorioretinal atrophy,” Dr Wolf explained.

Next, a larger study was undertaken to validate the findings of the pilot trial. The follow-up study included 57 patients with AMD and 58 controls. This study analysed the gut microbiome and included sequencing of single-nucleotide polymorphisms in complement genes. Comparisons between the two groups showed, not unexpectedly, that there were differences in the complement system genes that have been associated with AMD. Otherwise, the patients and controls were similar in their demographic characteristics and smoking history, Dr Wolf said.

Analyses of the gut microbiome reproduced the findings from the pilot clinical trial and of the study of mice fed a high-fat diet. The healthy controls had significantly more *Oscillo bacter* spp. compared with the AMD patients and the AMD patients had significantly more *Firmicutes* spp.

Based on the collective findings of their research, Dr Wolf and colleagues speculate that the composition of the gut microbiome influences the risk of developing AMD through its effects on nutrient levels.

They have also expanded their research to look for associations between the gut flora and other retinal diseases.

‘Perhaps, in the future, the composition of the gut microbiome will be a target for the treatment or prevention of AMD.’ – Dr Sebastian Wolf

SEBASTIAN WOLF, MD, PHD
E: Sebastian.Wolf@insel.ch
Dr Wolf did not indicate any proprietary interest in the subject matter.

What’s Trending

See what the ophthalmic community is reading on Europe.OphthalmologyTimes.com

1. **3 pearls for uveitis diagnosis**
   http://bit.ly/2RX2oXy

2. **DME: What it is and how to treat it**

3. **Zeroing in on the presence of dry eye**

4. **IPL + thermal pulsation: A thorough dry eye approach**

Video

See how iStent implantation affects cataract surgery, go to https://bit.ly/2FgjOx3
(Video courtesy of Doug Katsev, MD)

Twitter

Follow Ophthalmology Times Europe at @OTEurope

Digital App

Check out the Ophthalmology Times Europe app. Download it for free today at OphthalmologyTimes.com/OTEapp
How converging technologies lead to cost-effective anti-VEGF therapy

Anti-VEGF therapy and OCT imaging in the management of nAMD

By Cheryl Guttman Krader

Reviewed by Philip J. Rosenfeld, MD

Anti-VEGF therapy guided by optical coherence tomography (OCT) has clearly revolutionised the management of neovascular age-related macular degeneration (nAMD), and Philip J. Rosenfeld, MD played an integral part in its development.

At AAO 2018, Dr Rosenfeld received the Jackson Memorial Lecture Award in recognition of his role in advancing treatment for nAMD and for his many other contributions. Delivering his lecture titled “Lessons learned from Avastin (bevacizumab, Genentech) and OCT: The great, the good, the bad, and the ugly,” Dr Rosenfeld traced the history of anti-VEGF therapy and OCT imaging in the management of nAMD, including all of the bumps and detours encountered along the way, and he gave credit to all of the “heroes” whose support and efforts were vital in his story’s positive ending.

Dr Rosenfeld said, “The history of Avastin and OCT is a great story of two technologies converging and the many great researchers, ophthalmologists and government officials who came together to preserve access to bevacizumab and save vision for millions worldwide, while saving tens of billions of healthcare dollars”.

How it began

Dr Rosenfeld is professor of ophthalmology, Bascom Palmer Eye Institute, University of Miami, Miami, Florida, USA. His personal story with OCT and anti-VEGF therapy began in 1992 as a resident at the Massachusetts Eye and Ear Infirmary in Boston. At that time, Boston was the epicentre for the development of both OCT and anti-VEGF therapy with numerous researchers working in these areas across multiple institutions.

Moving to the University of Miami’s Bascom Palmer Eye Institute (BPEI) as a vitreoretinal fellow in 1995, he stayed on as faculty and was fortunate to have the freedom to pursue his clinical and research agendas while collaborating with so many outstanding colleagues. It was in his early years at BPEI that he began to appreciate how OCT enabled an understanding of how VEGF and anti-VEGF therapy affects the eye.

In 2001, as lead investigator for the Phase 1 clinical trial of ranibizumab (then known as rhuFab V2; Lucentis, Genentech), he described the rationale for using the 0.5 mg dose to treat nAMD in subsequent clinical trials. “We found in the Phase 1 study that higher doses caused severe inflammation, although it was later determined that the reactions were a property of the lyophilised preparation being used at the time,” Dr Rosenfeld said. A subsequent Phase 2 dose-escalation study found that a 2 mg dose of ranibizumab could be tolerated if the ranibizumab dose was slowly escalated every 2 weeks or every month. The dose-escalation study was also noteworthy as it was the setting for the first time use of OCT to evaluate the response to anti-VEGF therapy, said Dr Rosenfeld. “We could follow patients after the formal dosing was completed and retreat at our own discretion. That’s when the benefits of OCT imaging became obvious. I remember presenting the data from the Phase 2 study in 2004 at the Retina Subspecialty Day meeting. At the time, retina specialists were wedded to fluorescein angiography and were skeptical that the simple non-invasive imaging technique could provide more useful information,” Dr Rosenfeld said, adding that he showed how OCT detected the recurrence of fluid and the need for retreatment. Based on these initial observations, the PrONTO study, which was Genentech’s first investigator sponsored trial (IST) in ophthalmology, investigated a variable-dosing OCT-guided regimen using ranibizumab, and this study set the stage for widespread acceptance of OCT-guided anti-VEGF therapy.

IN SHORT

› The journey of Dr Rosenfeld, who received the Jackson Memorial Lecture Award at AAO 2018 in recognition of his role in advancing treatment for nAMD and for his many other contributions, is summarised.
Around the same time, Dr Rosenfeld began to turn his attention to bevacizumab. Researching the literature, he found that the antigen binding fragment (Fab) from bevacizumab was derived from the same plasmid that encoded the anti-VEGF Fab for ranibizumab. Thinking that patients would rather receive systemic intravenous bevacizumab treatment rather than monthly intravitreal injections of ranibizumab, he became interested in designing a trial using systemic bevacizumab, but Genentech wasn’t interested in supporting this trial, so he funded it himself using donations raised from grateful patients.

Results of this small trial using systemic bevacizumab were very promising. However, a new black box warning in the product’s prescribing information announcing a 1% increased risk of thromboembolic events raised concerns among retina specialists at a meeting to design a clinical trial, and he was directed by his colleagues to find the lowest effective dose of bevacizumab.

While calculating the dilutions needed to test lower doses of bevacizumab, Dr Rosenfeld found that the packaged molar concentrations of ranibizumab and bevacizumab were nearly identical. As a result, Dr Rosenfeld realised that the same volumes of bevacizumab and ranibizumab would provide the same amount of VEGF binding activity. Encouraged by research showing that full-length antibodies did penetrate the retina after an intravitreal injection despite their larger size compared with ranibizumab and the reassurance from the director of his pharmacy at the BPEI about the legality of compounding bevacizumab into syringes for intravitreal delivery, Dr Rosenfeld performed his first case of an intravitreal bevacizumab injection in a patient with nAMD who had failed all other therapies.

He said the use of intravitreal bevacizumab to treat nAMD took off after the 2005 meeting of the American Society of Retina Specialists in Montreal, Canada, fueled by Dr Rosenfeld’s presentations on his experience with systemic bevacizumab and the first case of intravitreal bevacizumab, anecdotal reports from colleagues, and the positive results of the ranibizumab MARINA study.

“All was going extremely smoothly, but then came the bad and the ugly,” Dr Rosenfeld said.

His plan to move forward with a prospective clinical trial of intravitreal bevacizumab was put on hold by the FDA, but then Dr Rosenfeld came under scrutiny by the Office of Human Research Protection (OHRP) after they received a complaint letter accusing Dr Rosenfeld of heinous human experimentation relating to the dangerous, clandestine, and unauthorised use of intravitreal bevacizumab. After 16 months of intensive investigation, he was completely exonerated. Next, prompted by referral of the case by OHRP to the FDA, Dr Rosenfeld’s records became the subject of a surprise FDA audit that also resulted in his being vindicated from any wrongdoing.

Overcoming another obstacle

Although ranibizumab received FDA approval for treatment of nAMD in 2006, bevacizumab continued to dominate the market as a cost-effective alternative. Soon thereafter, however, access to the sight- and cost-saving treatment was threatened by an effort to block the sale of bevacizumab to compounding pharmacies by Genentech based on the claim that the product was just unsafe for intraocular use and a lot of bevacizumab, which was found to contain glass particles, had to be destroyed because it was unsafe for intraocular use, and this cost Genentech many millions of dollars. This obstacle was overcome thanks to outrage and skepticism from the ophthalmologic community, their specialty societies, and the investigative work of Jack Mitchell of the Special Committee on Aging who discovered that the problem was a manufacturing issue that prevented the use of bevacizumab for all indications, and the FDA never required Genentech to restrict the sale of bevacizumab to compounding pharmacies. “That was the last major battle in the bevacizumab wars, and while there have been many skirmishes since, the ophthalmologic community has succeeded in running prospective clinical trials to show the benefits and safety of bevacizumab,” he said.

Dr Rosenfeld went on to highlight two recent papers describing the financial benefits of OCT-guided therapy compared with monthly or bimonthly labeled dosing of anti-VEGF drugs. In a study sponsored by ARVO, Dr Rosenfeld and colleagues showed a 21-fold return on investment from 2008 to 2015 when they compared the $400 million in grants awarded for the development of OCT with the $9 billion in savings to Medicare.

He then used the same Medicare databases to show a savings of over $17 billion from the use of bevacizumab compared with ranibizumab or aflibercept.

Dr Rosenfeld went on to say, “Thanks to bevacizumab, OCT and the hard work of many great ophthalmologists, we have prevented blindness in millions of patients with exudative eye diseases, and bevacizumab continues to dominate the markets worldwide as a low-cost, effective and safe alternative to expensive anti-VEGF drugs”. 

PHILIP J. ROSENFELD, MD
E: prosenfeld@med.miami.edu
Dr Rosenfeld received the Jackson Memorial Lecture Award—in recognition of his role in advancing treatment for nAMD and for his many other contributions—at the 2018 meeting of the American Academy of Ophthalmology. This article was adapted from his lecture. Dr Rosenfeld did not indicate any financial interest.
Macular oedema is the pathological accumulation of exudate or transudate within or beneath the layers of the macula and, because the retina is without lymphatic drainage, this fluid has limited recourse for reabsorption.

Macular oedema is associated with several conditions such as systemic hypertension leading to vein occlusions, natural aging processes and, most commonly, diabetes. These conditions promote disordered vascularisation, changes in the permeability of vessels that promote leakiness, and failure of the normal function of the retinal pigment epithelium (RPE), leading to the formation of microaneurysms and macroaneurysms that cause oedema.

These pathological changes in turn can result in distorted vision and even blindness.

Traditional treatment options for macular oedema involve the use of lasers to induce photocoagulation. Briefly, laser light pulsed for 10–200 ms on micro/macroaneurysms and regions of oedema generates coagulation through a thermal effect that causes vaporisation of liquids and denaturation of proteins, controlled tissue necrosis, scar formation, and relief of autoregulatory vasoconstriction.

This process has been shown effective for the closure of microaneurysms as well as macroaneurysms.

However, all structures to be treated should be located far enough from the fovea as coagulation leads to significant vision reduction.

Administering the laser traditionally involves the use of a slit lamp and a foot-pedal-controlled laser. A contact lens placed on the eye allows the visualisation of the retina and the cone-shaped laser beam to be focused and deployed on the retina in the region with oedema.

**Focusing slit lamp for photocoagulation**

First, the retina is brought into focus with the slit lamp to identify areas to be treated.

If the targeted structure is a macroaneurism, the slit lamp is slightly re-positioned to only get the top part of the Macroaneurism in visualisation focus. This is done in order to protect the RPE.

However, as laser is – due to its characteristics of a collimated beam – a displacement of the beam primarily results into an increased area over which the laser is applied and decreases the intensity and fluence of the beam on the level of the RPE.

To protect other layers of the retina from unintended damage by the laser, the wavelength of the beam needs to be selected based on the absorption characteristics of different retinal layers. Yellow wavelengths (570–590 nm) are ideal because they are absorbed primarily by oxyhemoglobin and reduced hemoglobin.

Macroaneurisms are usually located ‘above’ the RPE and photoreceptor layers.

Due to the absorption profile, the majority of laser energy will be absorbed by the blood instead of the structures beneath this blood contained in macro-...
With the Navilas, the laser is well stabilised, and its positioning is controlled by eye-tracking software. Empirical evidence from clinicians suggests that if they are exclusively focused on a microaneurysm, the power from the laser beam will stop at the aneurysm and will not reach the RPE. Thus, focalisation is not a problem, and the risk of unintentional injury to other structures is diminished. This is highlighted in the cases below.

Additionally, among the many possible applications of this new laser, the treatment of macroaneurysms with the non-contact objective is one of the most attractive, both in terms of implementation and anatomical/functional results.

The use of overlays to visualise what has been treated previously is clinically valuable for long-term management, as is the detailed post-treatment report generated by the software.

For these reasons, Navilas has accumulated a substantial track record in significantly improving the precision of treatment and comfort for clinicians and patients alike.

Looking to the next generation
The Navilas 577’s is a yellow laser equipped with a camera coupled to an eye tracker that allows previously unachievable precision of treatment with a conventional laser. The pre-planning capabilities combined with the eye-tracking features significantly improve the lateral positioning of the laser to micro- or macroaneurysms. While the slit lamp as a traditional laser delivery device provides a stereoscopic view of the retina, the Navilas is based on a computer screen. This enables a slightly different use principle.

While on the slit lamp depth perception is needed to localise oedema, this is readily mapped by importing either optical coherence tomography (OCT) thickness mapping or an ICG/FA (indocyanine green chorioangiography/fluorescein angiography) image.

For the treatment of large microaneurysms as well as macroaneurysms, lateral precision is more important than depth focusing.

With the Navilas, the laser is well stabilised, and its positioning is controlled by eye-tracking software. Empirical evidence from clinicians suggests that if they are exclusively focused on a microaneurysm, the power from the laser beam will stop at the aneurysm and will not reach the RPE.

Thus, focalisation is not a problem, and the risk of unintentional injury to other structures is diminished. This is highlighted in the cases below.

Additionally, among the many possible applications of this new laser, the treatment of macroaneurysms with the non-contact objective is one of the most attractive, both in terms of implementation and anatomical/functional results.

The use of overlays to visualise what has been treated previously is clinically valuable for long-term management, as is the detailed post-treatment report generated by the software.

For these reasons, Navilas has accumulated a substantial track record in significantly improving the precision of treatment and comfort for clinicians and patients alike.

Looking to the next generation
The Navilas 577’s is a yellow laser equipped with a camera coupled to an eye tracker that allows previously unachievable precision of treatment with a conventional laser. The pre-planning capabilities combined with the eye-tracking features significantly improve the lateral positioning of the laser to micro- or macroaneurysms. While the slit lamp as a traditional laser delivery device provides a stereoscopic view of the retina, the Navilas is based on a computer screen. This enables a slightly different use principle.

While on the slit lamp depth perception is needed to localise oedema, this is readily mapped by importing either optical coherence tomography (OCT) thickness mapping or an ICG/FA (indocyanine green chorioangiography/fluorescein angiography) image.

For the treatment of large microaneurysms as well as macroaneurysms, lateral precision is more important than depth focusing.

With the Navilas, the laser is well stabilised, and its positioning is controlled by eye-tracking software. Empirical evidence from clinicians suggests that if they are exclusively focused on a microaneurysm, the power from the laser beam will stop at the aneurysm and will not reach the RPE.

Thus, focalisation is not a problem, and the risk of unintentional injury to other structures is diminished. This is highlighted in the cases below.

Additionally, among the many possible applications of this new laser, the treatment of macroaneurysms with the non-contact objective is one of the most attractive, both in terms of implementation and anatomical/functional results.

The use of overlays to visualise what has been treated previously is clinically valuable for long-term management, as is the detailed post-treatment report generated by the software.

For these reasons, Navilas has accumulated a substantial track record in significantly improving the precision of treatment and comfort for clinicians and patients alike.

Looking to the next generation
The Navilas 577’s is a yellow laser equipped with a camera coupled to an eye tracker that allows previously unachievable precision of treatment with a conventional laser. The pre-planning capabilities combined with the eye-tracking features significantly improve the lateral positioning of the laser to micro- or macroaneurysms. While the slit lamp as a traditional laser delivery device provides a stereoscopic view of the retina, the Navilas is based on a computer screen. This enables a slightly different use principle.

While on the slit lamp depth perception is needed to localise oedema, this is readily mapped by importing either optical coherence tomography (OCT) thickness mapping or an ICG/FA (indocyanine green chorioangiography/fluorescein angiography) image.

For the treatment of large microaneurysms as well as macroaneurysms, lateral precision is more important than depth focusing.
**Case presentations**

**CASE 1:**  
A 79-year-old male with 1yr h/o macular oedema secondary to a superior retinal vein occlusion OD, visual acuity 20/30. He had benefited from multiple injections of anti-VEGF and corticosteroids, but perifoveolar oedema persisted.  
On ICG, we found a venous macroaneurysm close to the fovea that would not have been accessible to treatment by standard slit-lamp procedures due to foveal proximity. Instead, we were able to occlude the lesion using Navilas.  
His results at 3 months post-treatment show retreat of macular oedema on OCT and a visual acuity of 20/20 (Figure 1).

---

*The use of overlays to visualise what has been treated previously is clinically valuable for long-term management.*

---

*Images courtesy of Dr Jean-Christophe Ramel*
CASE 2:
An 82-year-old female with a h/o diabetes and macular oedema refractory to multiple intravitreal injections, 20/400.
There was a visible parafoveal macroaneurysm in the fundus and on angiography.
She was treated with Navilas and at 5 months showed diminished oedema on OCT, visual acuity 20/50 (Figure 2).

CASE 3:
An 84-year-old female with an arterial macroaneurysm, chronic oedema and dry exudates, 20/1000.
She was treated using the Navilas non-contact lens protocol.
Her results at 1 month post-treatment showed decreased retinal thickness, 20/200 (Figure 3).

Concluding thoughts
Macular oedema is a disabling pathological accumulation of fluid in the macula and is common in developed countries among diabetic and aging patients.
Current treatments with photocoagulation using the slit lamp are efficacious, but the Navilas endorses automated focusing and eye-tracking software that greatly enhance the precision and ease of treatment.
In short, Navilas augments clinicians’ competence in treating patients by improving the safety, speed and precision of photocoagulation treatment.

REFERENCES
Intravitreal faricimab (previously known as RG7716, Genentech/Roche) shows promise for improving outcomes and reducing the treatment burden for diabetic macular oedema (DMO), according to results of a Phase II study.

Faricimab is a first-in-kind bispecific antibody that simultaneously binds and neutralises VEGF-A and angiopoietin-2. It is also optimised for fast systemic clearance and to avoid effector function.

Known as BOULEVARD, the Phase II study compared faricimab at doses of 1.5 mg and 6.0 mg against ranibizumab 0.3 mg (Lucentis, Genentech). Patients received six monthly injections (up to week 20), after which they were followed monthly (off treatment) up to week 36 to evaluate the durability potential of the drug. The primary endpoint analysed adjusted mean change in BCVA letter score from baseline to week 24 in treatment-naïve patients, which showed a statistically significant difference favouring faricimab 6.0 mg against ranibizumab (13.9 vs. 10.3 letters; P=0.03).

Analyses looking at percentages of patients achieving ≥2-line or ≥3-line improvements in BCVA and improvements in Diabetic Retinopathy Severity Score (DRSS)* also favored faricimab over ranibizumab. In addition, the investigational agent showed a benefit for better control of disease activity during the 16-week observation period, following the last study injection, reported Arshad M. Khanani, MD.

“Angiopoietin-2 levels are elevated in the vitreous of patients with diabetic retinopathy (DR) and DMO. The results from this Phase II study confirm the role of blocking angiopoietin-2 to stabilise the vasculature and decrease leakage and inflammation in these patients,” said Dr Khanani, BOULEVARD Investigator, managing partner and director of clinical research at Sierra Eye Associates and clinical associate professor, University of Nevada, Reno, NV.

“Two large global Phase III pivotal studies, YOSEMITE and RHINE, have been initiated and are currently enrolling patients (clinicaltrials.gov id: NCT03622580).”

BOULEVARD is a U.S. multicentre, randomised, double-masked study that enrolled 229 patients (168 treatment-naïve and 61 previously treated) with diabetic macular oedema (DMO) according to results of a Phase II study.

IN SHORT
- The Phase II BOULEVARD study comparing intravitreal treatment with faricimab (previously known as RG7716, Genentech/Roche) to intravitreal ranibizumab (Lucentis, Genentech) met its primary endpoint with a statistically significant difference favouring the first-in-kind bispecific VEGF-A/angiopoietin-2 antibody. The primary endpoint results were supported by several secondary outcomes.
Patients treated with faricimab 6.0 mg showed potential for extended durability, with a higher proportion of patients maintaining disease stability over time after the last dose.

BCVA from baseline to week 24 was achieved by 57.0% of patients in the ranibizumab group, 61.2% of patients treated with faricimab 1.5 mg, and 70.5% of those receiving faricimab 6.0 mg. Rates of patients with a ≥3-line improvement in BCVA in the three treatment groups were 32.7%, 36.7% and 43.2%, respectively.

“These data show that, compared with ranibizumab, faricimab 6.0 mg was associated with impressive relative increases of 24% in the percentage of 2-line gainers and 32% in the percentage of 3-line gainers in treatment-naïve patients,” Dr Khanani said.

Data on central subfield thickness changes from baseline to week 24 supported the primary efficacy outcome, showing a dose-dependent effect with faricimab and more improvement with the investigational agent compared with ranibizumab.

**Effect on diabetic retinopathy**

In the treatment-naïve study population, 39% of patients treated with faricimab 6.0 mg and 12% of ranibizumab-treated patients had a ≥2-step improvement in DRSS at week 24. Among the high-risk population with a baseline DRSS ≥53 (i.e., ≥ severe nonproliferative diabetic retinopathy), 25% of ranibizumab-treated patients versus 88% of those treated with faricimab 6.0 mg showed an improvement of at least 2 steps in their diabetic retinopathy severity.

In the off-treatment observation period, patients treated with faricimab 6.0 mg showed potential for extended durability, with a higher proportion of patients maintaining disease stability over time after the last dose.

Fenicimab was well-tolerated and showed no new or unexpected safety signals.

*DRSS simplified conversion table (http://www.icoph.org/dynamic/attachments/resources/diabetic-retinopathy-detail.pdf)
Managing ocular surface integral in glaucoma care

Minimising dry eyes is an important consideration in glaucoma treatment

By Dharmendra (Dave) Patel, MD

Whether from lifestyle changes or just paying more attention, we know that the incidence of ocular surface disease is increasing. Current estimates are more than 16 million US adults diagnosed with dry eye disease (DED) and, although age is a risk factor, incidence is still notable among those aged 18–34 years.¹

However, a prospective evaluation of cataract surgery patients found that more than 75% of them had symptoms of dry eye when evaluated, although only 13% had complained about symptoms ahead of time.²

In glaucoma patients, a major German population study found the incidence of dry eye to be over 50%.³ This is attributed in large part to the preservatives used in anti-hypotensive medications.

Benzalkonium chloride (BAK), the most common preservative in topical glaucoma drops, decreases the density of goblet cells in the conjunctival epithelium, destabilising the tear film and compromising its ability to provide protection and trophic factors to the cornea.⁴ It then increases concentrations of inflammatory markers, alters tear film quality and tear breakup time in a dose-dependent manner. It has been suggested that each additional eyedrop containing BAK is associated with a 2 times greater chance of showing abnormal results on a lissamine green staining test.⁵

While it may be tempting to dismiss the ‘discomfort’ of dry eye disease as of lesser significance than loss of sight from glaucoma, ignoring it may be of great detriment to our patients. First, dry eye disorders have been significantly correlated with decreased compliance to medical treatment of glaucoma.⁶ Second, long-term use of topical glaucoma drops increases the risk of failure of later incisional glaucoma surgery.⁷

Getting rid of the BAK

Considering that glaucoma is a chronic disease that will have to be treated for the duration of the patient’s life, it is essential to think ahead when prescribing drops. For me, the long view of drops always means decreasing the preservative load on the eye. Fortunately, we have both BAK-free options and fixed combination drops that allow a patient to get the needed active agent without the negative side-effects of the preservative. SofZia-preserved drops show less keratopathy and conjunctival hyperemia compared to drops with BAK, but still have negative effects on the cornea and demonstrate little improvement in patient comfort.⁸,⁹

Studies show that patients who are switched to BAK-free preparations show improvements in tear break-up time (TBUT) and decreased use of lubricants, suggesting an improvement in symptoms of DED as well.¹⁰

Current non-preserved options include Timpotin in Ocudose (Bausch + Lomb), Zioptan (Akorn Pharmaceuticals), Cosopt PF (Akorn Pharmaceuticals) and Simple Drops combinations formulations (Imprimis Pharmaceuticals). The Simple Drops compounded formulations not only have the benefit of being preservative free, they also improve compliance by providing multiple IOP-lowering agents in a single drop. Given that at least 40% of patients in the Ocular Hypertension Treatment Study needed two or more medications to reach target IOP, a fixed combination drop presents significant advantages.

Another means of reducing medications is to perform a minimally invasive surgical procedure. Selective laser trabeculoplasty (SLT) is a familiar tool in our armamentarium, and we now have many other options, including iStent (Glaukos Corporation), iStent inject (Glaukos Corporation), Kahook Dual Blade (New World Medical), and others.

Endoscopic cyclophotocoagulation (ECP) with the EndoOptiks E2 laser and endoscope system (Beaver-Visitec International) is another minimally invasive option that I have used with great success. ECP is one of the few procedures that addresses aqueous production

IN SHORT

The detrimental effects of dry eye disease can be overcome, and Dr Patel urges consideration of the ocular surface in glaucoma treatment.
and secretion, can be performed either as a stand-alone procedure or in conjunction with cataract surgery, and generally produces a decrease in IOP between 20 and 40%.11

Caring for the ocular surface
While we currently have many tools to reduce the medication burden and preservative load on the eye, this may not be enough. DED risk factors tell us that, even without BAK, ocular surface disease is common in the same population as glaucoma.1 It’s essential to actively diagnose and treat DED in our glaucoma patients. Diagnosis includes the SPEED questionnaire for every patient, and tear osmolarity testing (Tear Lab) and lipid layer and blink pattern analysis (TearScience) in those patients that merit further investigation.

The inflammatory cycle has been well documented in DED, and we now have the immunomodulators Restasis (cyclosporine; Allergan), Xiidra (lifitigrast; Shire), and Klarity-C (cyclosporine; Imprimis Pharmaceuticals) to arrest the inflammatory pathway. Managing DED is based on the DEWS recommendations and is targeted to the level of disease. For patients with mild DED, therapy usually involves preservative free lubricants and lid hygiene. In moderate stages of disease, adding cyclosporine or lifitigrast is necessary. Any DED treatment has to be balanced with reduction of BAK burden from glaucoma medications. Fixed combinations and preservative-free glaucoma medications are essential for this group of DED sufferers. In severe DED patients, surgical treatment for glaucoma is necessary to eliminate the toxicity from topical medications.

Given the detrimental effects of DED, and the many tools we currently have to address it, it is simply becoming inexcusable not to consider the ocular surface of our glaucoma patients.
Reversibility of meibomian gland atrophy by thermal pulsation therapy

Thermal pulsation therapy has the potential to improve gland structure in most patients with dry eye disease have meibomian gland dysfunction (MGD) as a primary or contributory cause of their ocular surface problems. We know that MGD is a progressive disease that gets worse the longer it goes untreated. Over time, the glands become obstructed, which then leads to meibomian gland atrophy.

Established treatments for MGD include re-esterified omega-3 fatty acid supplementation, lid hygiene measures (lid scrubs and warm compresses), blepharoexfoliation, and thermal pulsation therapy. Thermal pulsation therapy has been widely viewed as most effective when performed earlier in the disease process, before a patient reaches end-stage MGD with significant gland atrophy and dropout. Although it was previously unknown whether thermal pulsation therapy could reverse gland atrophy, the general consensus is that atrophy is permanent.

In order to evaluate this assumption more closely, we conducted a retrospective, observational study to determine whether there were changes in the visible gland structure (VGS) of the lower lids of patients who had undergone thermal pulsation therapy.

**Study design**
We identified 102 patients who had undergone LipiFlow thermal pulsation therapy (Johnson & Johnson Vision) 1–2 years prior and for whom high-quality, pre-treatment dynamic meibomian imaging (DMI, LipiView II, Johnson & Johnson Vision) was available. Patients were brought back for follow-up as part of the current study.

In addition to repeating the DMI, a battery of dry eye testing was re-evaluated, including a SPEED questionnaire, tear break-up time (TBUT), corneal staining, osmolarity, MMP-9, and meibomian gland evaluation. All parameters were compared pre- and post-treatment. Data were also compared to those of a control group of patients (n=32) who received DMI and a recommendation for thermal pulsation therapy in the past but who did not undergo treatment.

We used Adobe Photoshop to look at the DMI at a pixel-by-pixel level. Using manual tracing, we were able to precisely evaluate sectors of the lower eye lid for the amount of VGS and amount of atrophy and dropout over time.

This is in contrast to other studies that have utilised estimation, grouping into broad categories, or mathematical algorithms to simplify the quantification of visible meibomian gland structure. Our method allowed for a precise quantification and comparison of the degree of atrophy in the glands in specific regions in pre- vs. post-treatment imaging and compared results to the control group.

**IN SHORT**

- Meibomian gland atrophy can be reversed by thermal pulsation therapy, as discussed by Drs Alice Epitropoulos and Arjan Hura.

**Figure 1**
Dry eye disease markers pre- and post-therapy

![Graph showing improvements in SPEED score, TBUT, and MGE Score pre- and post-therapy](https://example.com/final-graph.png)

(Figure 1) Treatment with thermal pulsation therapy resulted in improvements in several different markers of dry eye disease.
Consistent with those reports, we saw a significant improvement in tear osmolarity, TBUT, corneal staining and MGE slit lamp evaluation in the treatment group compared to the control group even in cases that were 2 years post-treatment.

Beyond the durability of the treatment effect, the potential for the meibomian glands to reactivate once they have atrophied was also quite interesting. In the past, researchers and clinicians have typically estimated gland atrophy using a morphometric analysis. In more than half the subjects evaluated so far, there were visible improvements in gland structure from pre-treatment to post-treatment as shown.

Results

Data collection is complete for 56 eyes (39 treatment and 17 control). In comparison with the control group, for the eyes receiving treatment (Figure 1), TBUT increased by 4.2 seconds (p=0.0001), slit lamp meibomian gland evaluation improved by 7.9 points (p=0.001), and there was an improvement in corneal staining (p=0.004).

Of the 39 treated eyes, 69% showed an improvement in VGS, with most showing a modest (≤10%) improvement. In the untreated control eyes, only 29% had some improvement in VGS, while 71% had a decline in VGS. Figure 2 shows the change in gland structure in several eyes before and after treatment.

To our knowledge, this is the first time that reversibility of gland atrophy has been shown.

Post-treatment evaluation of the remaining subjects is ongoing. Completion of this study, as well as further research, is needed to definitively determine whether LipiFlow therapy can reverse gland atrophy and potentially restore meibomian gland function in previously atrophied glands.

Discussion

There have been several published reports of long-term results after treatment with LipiFlow. Comparing our findings, we saw a significant improvement in tear osmolarity, TBUT, corneal staining and MGE slit lamp evaluation in the treatment group compared to the control group even in cases that were 2 years post-treatment.

Beyond the durability of the treatment effect, the potential for the meibomian glands to reactivate once they have atrophied was also quite interesting. In the past, researchers and clinicians have typically estimated gland atrophy using a morphometric analysis. In more than half the subjects evaluated so far, there were visible improvements in gland structure from pre-treatment to post-treatment as shown.

(FIGURE 2) In subjects with meibomian gland atrophy, the same areas of the visible gland structure were analysed and quantified using morphometric analysis. In more than half the subjects evaluated so far, there were visible improvements in gland structure from pre-treatment to post-treatment as shown. (Images courtesy of Dr Alice Epitropoulos and Dr Arjan Hura)
Updated

Eye-to-Eye

Innovation Video Series

Brought to you by Ophthalmology Times Europe, in conjunction with our industry partners, to provide the latest information & insights into cutting-edge developments within ophthalmology.

For further details & to watch our latest videos, please go to www.OphthalmologyTimes.com/eye-to-eye
grading system with large gradations. There are two commonly used scales with a grading of 0 to 3 or 0 to 4, where 0 represents no disease and grade 3 or grade 4 represent end-stage disease with loss of more than 67% (grade 3 max scale) or more than 75% (grade 4 max scale) of the gland structure.

Better understanding of when meibomian gland atrophy begins, how it progresses, and whether it can be reversed is likely to be important in the future.

These grading systems are useful to group patients by disease severity (none, mild, moderate, severe) but they are not sensitive enough to register more subtle changes over time. In this study, the improvements in VGS were typically 10% or less, which would not register as a change on the gross scales but nevertheless represents a significant clinical improvement, especially if one compares that to the expected progression of gland loss in untreated eyes. To our knowledge, this is the first time that reversibility of gland atrophy has been shown.

Better understanding of when meibomian gland atrophy begins, how it progresses, and whether it can be reversed is likely to be important in the future. Not only is MGD highly prevalent in the population, but recent research suggests that the proliferation of smart phones and other digital devices is affecting meibomian gland health very early in life. More than 40% of children and teens evaluated in a recent study had evidence of meibomian gland atrophy. It is very encouraging that a single thermal pulsation treatment can have long-lasting results and, in some patients, improve the VGS. It is also important to recognise that patients may have multifactorial disease. If they also have aqueous deficiency and associated inflammation, for example, we would start them on immunomodulatory therapy and a high-quality nutritional supplement, and then proceed with thermal pulsation treatment. Additionally, if the patient is considering ocular surgery, it is critical to treat the ocular surface disease before proceeding with surgery, as MGD and dry eye can lead to inaccurate measurements and patient dissatisfaction.

**REFERENCES**


**ALICE EPITROPOULOS, MD**
**E:** eyesmd33@gmail.com
Dr Epitropoulos is in private practice at Ophthalmic Surgeons and Consultants of Ohio and is a Clinical Assistant Professor at The Ohio State University. She is a consultant for Allergan, BlyheVx, Johnson & Johnson Vision, PRN Nutriceuticals, Shire and TearLab.

**ARJAN HURA, MD**
**E:** huraas@mail.uc.edu
Dr Hura is an ophthalmology resident at the University of Cincinnati. Investigator-initiated financial support for this study was provided by Johnson & Johnson Vision.

---

**in case you missed it**

**PAGE 6**
Top ophthalmic challenges in 2019

**PAGE 18**
High- vs medium-add multifocal IOLs

**PAGE 23**
Intestinal microbiome for AMD

**PAGE 39**
Five things to know about visual electrophysiology
Forget about the visual electrophysiology devices you may have used back in school. The advances that have been made over the last two decades have been so significant that ophthalmologists all over the world are now using these tests every day in their practice to help with early detection and managing disease.

In the following, we offer five crucial facts to know about visual electrophysiology testing performed on Diopsys platforms from the perspective of an anterior segment surgeon and a retina specialist.

While we each manage different kinds of eye diseases, the fact that two ophthalmologists practicing in different subspecialties find great utility for electrophysiology speaks to the broad applicability of such testing in working with patients on a routine basis.

1. **Visual electrophysiology is practical**

   **Myth:** Electrophysiology is only really relevant for rare eye diseases and is only available in institutional settings.

   **Reality:** The objective functional data that is gathered with the various types of modern electrophysiology testing used in the clinical setting is highly relevant for managing patients with common eye diseases.

   In Dr Williamson’s practice, electrophysiology testing is most frequently used to help confirm a diagnosis of glaucoma. In patients with ocular hypertension or signs of glaucoma, pattern electroretinography (ERG) can be used to monitor the health of the retinal ganglion cells.

   Any derivation from the initial result is an indication that the viability of the ganglion cells is being threatened. The test is sensitive to subtle changes in signal, and loss of function can be identified up to 8 years earlier with pattern ERG compared with OCT.1

   In this regard, pattern ERG is most often a tie breaker when other testing methods and the clinical evaluation are inconclusive in making a diagnosis. Because of recent changes in reimbursement, pattern ERG is no longer a covered test once the patient receives an official diagnosis of glaucoma.

   That is an unfortunate decision, as serial pattern ERG in a patient with confirmed glaucoma is useful for a number of reasons, including to gauge the effectiveness of treatment and to gain a better understanding of the disease’s progression.

   **IN SHORT**

   - Drs Williamson and Tewari discuss the myths and reality of using visual electrophysiology, highlighting five crucial facts.
understanding of patients’ optimal target IOP.

In the anterior segment, flicker ERG is often used with patients with dense cataracts to ascertain whether the retina is viable—situations where obscured media limits the ability to use OCT and perform a fundus exam. The information from a flicker ERG test might show if cataract surgery is even warranted.

Another way flicker ERG results are useful is in deciding if a patient with astigmatism and a dense cataract might be a candidate for a toric IOL.

2. Visual electrophysiology is easy to use

**Myth:** Electrophysiology testing requires special knowledge and it is also difficult to perform in a busy office setting.

**Reality:** Modern electrophysiology testing is not at all difficult to assimilate into the practice and understanding the reports is well within the scope of any ophthalmologist.

The Diopsys platform is set up with streamlined protocols for performing a test. Nevertheless, having a dedicated technician for electrophysiology testing ensures quality, reproducible results. At the same time, Diopsys sponsors regular webinars, trainings and educational opportunities so technicians can stay current on best practices. To make sure testing does not interrupt regular clinic activity, scheduling patients indicated for testing prior to their exam may be a good idea.

For any ophthalmologist, using a new device or technology in practice will naturally take some getting use to. Fortunately, Diopsys has shortened the learning curve with Electrophysiology testing: reports use color coding to note reference values. Beyond that, clinicians will also want to note whether the signal quality was sufficient to run the test, which is the case in the vast majority of testing scenarios.

3. Visual electrophysiology is patient friendly

**Myth:** Electrophysiology testing is uncomfortable for the patient and it is often difficult to educate about testing procedures and protocols.

**Reality:** Modern electrophysiology testing on the Diopsys platform is noninvasive, as sensors are attached to the patient’s skin; there is no contact lens used. In our view, educating patients is not difficult. It is often sufficient to educate patients about why the test is being performed without getting into great detail regarding how the test is used or interpreted. Letting patients know that electrophysiology testing will help us make a diagnosis is usually enough to get them on board.

Most patients indicated for the test are already aware that there is a disease process underway, and they are often willing to undergo testing that helps better understand whether progression is occurring and if there...
is need to start an intervention. In other cases, educating patients can include a simplified message: we have an advanced test that will let us know about the health of the back of the eye.

4. Visual electrophysiology impacts patient management

Myth: Electrophysiology testing may help with prognosis and diagnosis, but it has limited value with respect to making critical decisions in regular clinical settings.

Reality: This is probably the biggest myth that needs to be dispelled. In fact, both of the authors routinely use modern electrophysiology testing to help make diagnosis, follow patients over time, and to help guide treatment decisions.

In Dr Williamson’s practice, using pattern ERG for evaluating glaucoma suspects is an excellent example of the utility of electrophysiology testing and its impact on decision making. Loss of signal on a pattern ERG test indicates stress to the ganglion cells, and has been shown to predate structural changes on OCT; 1 which, in turn, may precede any loss of function discernable on visual field. With that information, the clinician can make a decision to intervene earlier to avoid vision-compromising structural damage long before it occurs.

The advent of the minimally invasive glaucoma surgery (MIGS) category of devices has heralded in an era in which glaucoma is increasingly treated with surgery as opposed to medication. The lower risk of side effects associated with MIGS relative to medical management justifies even earlier initiation of treatment—and especially so in patients with cataracts. Using pattern ERG in this manner, then, arms the clinician with the information needed to make an informed decision regarding the risks and benefits of early intervention, perhaps at a stage when signs and symptoms are just beginning to manifest.

In Dr Tewari’s practice, there are numerous examples of how the various types of electrophysiology testing may help with earlier diagnosis, following patients, and making informed treatment decisions.

One example is in patients with diabetic retinopathy (DR) without macular edema being treated using anti-VEGF injections. Serial testing can be used to gauge the effectiveness of treatment, which becomes crucial when thinking about the timing of treatment intervals and deciding if and when to stop therapy after stabilising the disease.2 Another example is patients being monitored with ERG testing for hydroxychloroquine-induced retinal toxicity. In these patients, timely testing and follow-up can help minimise or eliminate the risk of permanent vision loss.

5. Visual electrophysiology is scientifically validated

Myth: Much of the research performed on the role of electrophysiology testing in eye care is old, outdated, or otherwise irrelevant today.

Reality: There is, in fact, a vast library of published studies dating over the past decade-plus supporting the role of electrophysiology testing for management of both common and rare eye diseases. Diopsys continues to support new research with its devices that demonstrate the many clinical benefits that electrophysiology testing can provide.

Many independent studies and sponsored clinical trials confirm that Diopsys-based electrophysiology testing is additive in making a diagnosis, facilitates patient stratification, is useful for tracking disease progression over time, and helps guide treatment decisions. The examples provided herein by the authors support that notion.

Indeed, electrophysiology tests performed on Diopsys platforms are virtually the same as those performed in traditional settings,3 with some notable exceptions: Diopsys platforms have a much smaller footprint, meaning electrophysiology testing is readily accessible to busy clinicians, the system is noncontact, integration is simple, and because of all of the aforementioned attributes, electrophysiology testing is highly relevant for everyday clinical use.

REFERENCES

3. Dan Lam, BS, Andrew Kryder, BS and Jeff Rabin, OD, MS, PhD, FAAO. Evaluation of a Disposable Skin Electrode for Flash Electoretinograms. ARVO Abstract, 2015.
Haag-Streit releases EyeSuite i9.1 software

HS-UK announces the release of EyeSuite i9.1 software from Haag-Streit Diagnostics.

The new software is available to all Haag-Streit slit lamp imaging and Lenstar customers. It features all the functionality of previous versions of EyeSuite but it has been dramatically improved, and enhancements have been made to the stability of the software for imaging, IOL and biometry.

EyeSuite IOL now includes an extended V2 Hill-RBF method, which is based on more than four times as much data as the previous version. The system now incorporates 12,419 patterns, leading to highly accurate IOL predictions. These improvements will facilitate improved calculations in long and short eyes and expand the boundary model, leading to better patient outcomes. The Barrett formulas have also been updated to the latest status, providing customers with outstanding IOL calculations for standard, toric and post-refractive cases.

With the release of EyeSuite i9.1 Imaging, Haag-Streit has also introduced a portable version of the Fundus Module 300 (FM 300), offering automatic image editing and allowing improved USB connection stability for cameras. The FM 300 can now also be mounted on many non-Haag-Streit slit lamps.

A new registration wizard, which simplifies the registration of an EyeSuite database, is also included in the EyeSuite i9.1 release. This will allow pre-installation of systems and will permit example files to be loaded. The new software also supports the user to respond to the latest GDPR legislation by offering a comprehensive user management process, as well as an audit trail.

Sam Laidlaw, HS-UK Product Manager, said, “The latest release of EyeSuite incorporates some fantastic new features. I am delighted that the FM 300 can now be added to third-party slit lamps, this has been developed in response to customer demand. The extended V2 Hill-RBF method will contribute to improved surgical outcomes and all of the new features in EyeSuite i9.1 will enhance the workflow in a busy practice.”

For further information, go to www.haag-streit.com

Advanced Barrett, Olsen formulas now included in Pentacam AXL

OCULUS introduces the new, advanced Barrett Toric calculator, including the posterior cornea and the Olsen ray-tracing formula, within the IOL Calculator of the Pentacam AXL. Both formulas are available to all Pentacam AXL users in a free software update.

The new Barrett Toric calculator takes now measurements of the posterior cornea surface into account, making it an advancement of the known and proven Barrett Toric calculator. The Olsen formula is based on a ray-tracing approach. It uses the anterior and posterior corneal data, corneal thickness, ACD and axial length to calculate a unique model of the patient’s eye.

For more information, go to www.oculus.de

Santen announces drug discovery, development agreement with PeptiDream

Santen Pharmaceutical Co. Ltd. announced it has entered into a broad-based, multitarget discovery and development agreement with PeptiDream Inc.

Under the agreement, PeptiDream will use its proprietary Peptide Discovery Platform System (PDPS) technology to identify macrocyclic/constrained peptides against multiple ophthalmic disease targets of interest selected by Santen, and to optimise hit peptides into therapeutic peptides products for such indications. PeptiDream will be responsible for drug discovery and part of preclinical development aspects, while Santen will be responsible for preclinical and clinical development of identified candidates.

“With this partnership, Santen intends to strengthen and broaden its ability to address unmet needs. In addition to biologics and small molecules, we will now have access to promising new constrained peptides to manage ocular pathologies,” said Naveed Shams, MD, PhD, chief scientific officer and head of global R&D at Santen.

Under the terms of the agreement, Santen would pay an undisclosed upfront payment and research funding to PeptiDream. For the future, Santen would pay preclinical, clinical and commercialisation milestone payments and royalties on sales of any products that arise from the collaboration to PeptiDream.

For more information, go to www.santen.com
Experience the power of swept-source OCT technology at its best. Perform the most relevant anterior segment exams in one modular, upgradeable platform.

**Introducing ANTERION®.**

Take the lead with a dynamic, workflow-efficient imaging platform that delivers powerful results.

www.anterion.com
Contraindications:
Hypersensitivity to any component of this medicine, reactive airways disease, including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, sick sinus syndrome, sino-atrial block, second- or third-degree atrioventricular block not controlled with pacemaker, overt cardiac failure, cardiogenic shock, severe renal impairment (CrCl <30 ml/min) or hyperchloraemic acidosis.

Patients with severe peripheral circulatory disturbances (disorders) (i.e., severe forms of Raynaud’s disease or Raynaud’s syndrome), should be treated with caution. Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. Use with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk. Use with caution in patients with hepatic impairment. Concomitant use of dorzolamide with oral carbonic anhydrase inhibitors is not recommended. Use of two topical beta-adrenergic blocking agents is not recommended. Contraindicated in patients subject to spontaneous hypoglycaemia or with diabetes. These signs and symptoms of acute hypoglycaemia and hypothyroidism may be masked. Caution in patients with renal diseases. The ophthalmologist should be informed when a patient is receiving timolol as beta-blocking opthalmological preparations may block systemic beta-agent effects e.g. of adrenaline. Though no acid-base disturbances have been observed with COSOPT (preserved formulation), patients with a prior history of renal calcius may be at increased risk of uraemia. Patients with acute angle-closure glaucoma require therapeutic interventions in addition to ocular hypotensive agents. This medicinal product has not been studied with acute angle-closure glaucoma. Corneal edema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery while using dorzolamide. Precautions should be used when prescribing in these groups of patients. Patients with a history of contact hypersensitivity to silver should not use COSOPT Multi as dispersed drops may contain traces of silver from the container. This medicinal product has not been studied in patients wearing contact lenses. There is limited experience with COSOPT® in infants and children. Please refer to the SmPC.

Interactions with Other Medicinal Products: There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, calcium antagonists, betablockers, or beta-adrenergic blocking agents, antihypertensives (including amiodarone), digitals, glycosides, parasympathomimetics, quinidine, narcotics and monamine oxidase (MAO) inhibitors. Indentified systems beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with VP-2060 inhibition (e.g. quinidine, fluoxetine, paroxetine) and timolol. Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenergic (sympathomimetics) has been reported occasionally.

Pregnancy and Breast Feeding: Do not use in pregnancy or during breast-feeding.

Driving and using machines: Possible side effects such as blurred vision may affect some patients’ ability to drive and/or operate machinery.

Undesirable Effects: (Refer to SmPC for complete information on side effects). The side effects observed with COSOPT or one of its components include: headache, depression, burning and stinging, conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing, eyelid inflammation, eyelid irritation, lid oedema, signs and symptoms of ocular irritation including blepharitis, keratitis, decreased corneal sensitivity and dry eyes and visual disturbances including refractive changes (due to withdrawal of systemic therapy in some cases), phos, bradycardia, syncope, sinusitis, dyspepsia, dysgeusia, nausea and dysgeusia, urticaria, signs and symptoms of systemic allergic reactions, including angioneuritis, urticaria, pruritus, rash, anaphylaxis, anaphylactic shock, hypoglycaemia, cardiac arrest, heart block, AV block, cardiac failure, chest pain, palpitation, oedema.

Overdoses: Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Special Precautions for storage: Do not store above 25°C.

Price: COSOPT® Preservative-Free 20 mg/ml (0.2mL single-dose container) £28.19; COSOPT® Multi 1 x 10mL bottle (60 days treatment) £28.00.

MA Holder: Santen Oy, Niittyhaankatu 20, 33720 Tampere, Finland.

MA Numbers: COSOPT® Preservative-Free PL 16058/0015 COSOPT® Multi PL 16058/0023

Legal Category: POM

Date of Prescribing Information: September 2018.

Job Code: NP-CSPTPF-UK-0005

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Santen UK Limited (Email: medinfo@santen.co.uk or telephone: 0345 076 4963).