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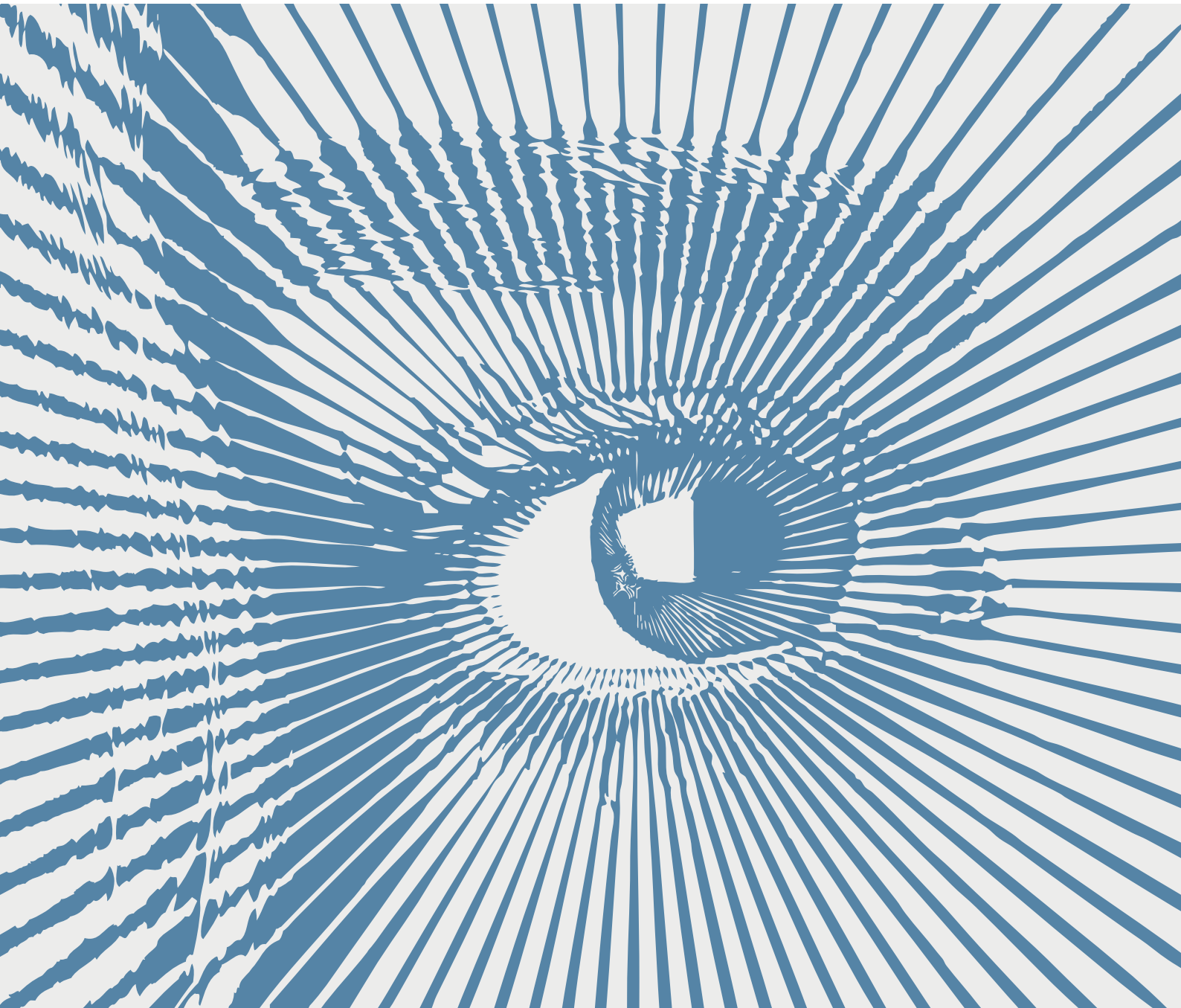
169

DrugDelivery

MARCH 19TH 2025

OPHTHALMIC DRUG DELIVERY



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OPHTHALMIC DRUG DELIVERY

ONdrugDelivery Issue N° 169, March 19th, 2025

This edition is one in the ONdrugDelivery series of publications. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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Gene Therapy, Injections & More: Meeting Rising Demand

In this issue of ONdrugDelivery, we cover the topic of ophthalmic drug delivery, discussing a range of delivery methods and conditions within the subject of eye care, an increasingly important topic as ageing populations around the world are leading to an ever larger demographic suffering from ocular disorders. The issue begins with a look into the growing area of ophthalmic injections and devices that can aid physicians in accurately and consistently delivering these difficult treatments. Following that, the issue features a pair of Expert Views considering the potential for gene and cell therapies to broaden the possibilities of treating challenging ocular conditions (note that, this December, we will be publishing our first issue dedicated fully to the topic "Delivering Gene & Cell Therapeutics"). Lastly, to round out the issue, we have an article on topical treatments for glaucoma – a staple of ophthalmic delivery.

Gerresheimer opens the issue with an article on intravitreal injection (Page 6). The article features an in-depth consideration of the role that intravitreal injections play in treating retinal diseases and the challenges associated with current delivery methods. In particular, Gerresheimer tackles the critical need for silicone-oil-free syringes in this space and discusses the findings of the company's research into this topic.

Next, **West Pharmaceutical Services** discuss injection into the suprachoroidal space, an alternative minimally invasive but challenging route for delivery of ocular treatments (Page 14). West's article introduces the company's Suprachoroidal Advanceable Microneedle Device, aimed at facilitating this delivery method and mitigating some of the difficulties associated with administration to the suprachoroidal space. The article includes discussion of a directional study West conducted in late 2024 on the effectiveness of the device to these ends.

Following these articles, **WuXi AppTec** and **Springboard** each share an Expert View on the progress of gene and cell therapies in the ophthalmic sector. WuXi AppTec focuses on the potential of antisense oligonucleotides for treating genetic and multifactorial ocular diseases, discussing both the benefits and challenges these therapies could bring (Page 20). Springboard, meanwhile, offers a broader perspective on cell and gene therapies in ophthalmology, considering the emerging clinical pipeline and how various drug developers will deliver these novel drugs, before looking to the future of these therapies in the sector (Page 24).

To conclude the issue, **Nemera** features an article on ongoing efforts to optimise the treatment of glaucoma (Page 30). Nemera's article covers the need for safe, preservative-free eye drops to meet the self-administration needs of patients, and how the company's Novelia eyedropper is a well-established solution to meet this need. The article explores how Novelia supports patient needs while also meeting sustainability demands in the eyedropper market.

James Arnold
Production Editor

SILICONE OIL-FREE

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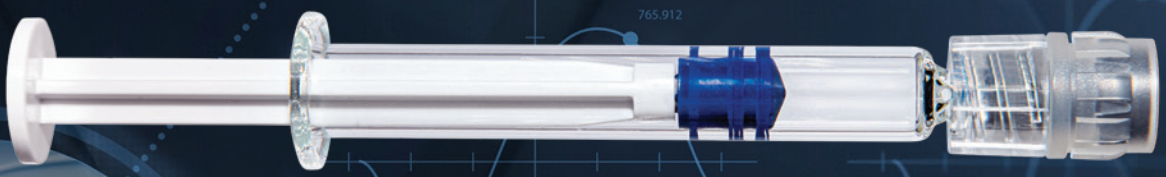

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A COMPREHENSIVE APPROACH TO ADDRESSING UNMET NEEDS IN INTRAVITREAL INJECTIONS

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In this article, **Dr Reza Abedian**, Senior Medical Affairs Manager, **Marie Stockton**, Global Marketing Manager, and **Bernd Zeiss**, Head of Scientific Affairs & Applied Technologies, all of **Gerresheimer**, consider the complexities and clinical unmet needs of intravitreal injections and discuss how the company's syringe technology can help overcome these challenges.

Treatment of retinal disease has been revolutionised thanks to the development of protein-based liquid drugs delivered directly into the vitreous body via intravitreal injection (IVI). Such injections of precise drug concentrations directly to the posterior eye segment can minimise systemic side effects.[1] However, despite the clinical efficacy of these therapies, there are challenges associated with drug delivery via IVI, including precision and repeatability of the injection dose volume, procedural inefficiency and patient safety.[2]

To address these challenges Gerresheimer has conducted extensive research and testing to provide specific syringe technologies optimised for IVI. The company is also committed to ongoing innovation in this field to provide even greater support to clinicians and patients.

THE ROLE OF IVIs IN TREATING RETINAL DISEASES

IVIs have become the standard practice for administering anti-vascular endothelial growth factor (anti-VEGF) drugs, corticosteroids and antibiotics to treat retinal conditions. This approach is critical for managing a number of serious conditions. Wet age-related macular degeneration (AMD), one of the leading causes of vision loss in older adults, is treated through anti-VEGF therapies, which inhibit the action of VEGF, reducing neovascularisation and fluid leakage, thereby stabilising or improving vision in many patients. Similarly, diabetic macular oedema, diabetic retinopathy and retinal vein occlusion are commonly treated

"THE SYRINGE USED FOR THE IVI IS A CRITICAL FACTOR, BUT THE PHYSICIAN'S PRACTICAL EXPERIENCE ALSO HAS A SIGNIFICANT INFLUENCE ON ACCURATE DOSING."

through IVIs to reduce macular swelling and restore or maintain visual acuity. With a growing prevalence of patients with diabetes and an ageing population in most geographical regions, the number of IVIs is increasing year on year, and the demand for efficient and effective IVIs is growing accordingly.

CHALLENGES IN INTRAVITREAL INJECTIONS

Dose Volume Accuracy and Reproducibility

As IVIs are usually administered in volumes of between 20 to 100 µL, accurate and reproducible microlitre dosing is crucial. The syringe used for the IVI is a critical factor, but the physician's practical experience also has a significant influence on accurate dosing,[3] as moving the plunger the correct amount while removing the air bubble and priming the syringe can impact significantly on injected volume. This is particularly challenging with very small volumes, as the plunger only moves a tiny distance. Moreover, the user is only guided by a visual marking (usually a dark ring) on the outer syringe barrel to set the injection dose volume. In a study assessing 800 injections, results showed that up to 22% of injections with a prefilled syringe (PFS) deviated by 20% or more from the intended volume of 0.05 mL.[4]

Patient Safety and Treatment Outcome

As discussed, precise administration is a challenge when delivering small volumes. If too much of the drug is injected it could result in complications such as intraocular inflammation, haemorrhage and elevated intraocular pressure (IOP), also referred to as postoperative IOP spikes.[5] These risks

Figure 1: 0.5 mL glass syringes for ophthalmology with Luer lock adapter, available BOS or silicone-oil-free, ready-to-fill (RTF®) format, various elastomer components and dose mark options.

are compounded when repeated injections are required for chronic conditions, such as AMD. Underdosing as a result of variability in technique, as well as large dead space in some syringes, could also be problematic, as it may negatively impact the therapeutic effect while also leading to wastage of an expensive drug formulation.

Another concern is particles entering the vitreous body during injection. This is particularly relevant when treating conditions that require repeated injections, which could lead to a build-up of particles, often referred to as floaters, within the eye over time and potentially affect vision. Particle count is therefore subject to strict regulations in accordance with USP <789> and Ph Eur 2.9.19. One of the main causes of particles is migration into the eye is silicone oil used to lubricate the inside of the syringe. Other sources include the drug formulation, the administration process and the plunger stopper.

The frequently used process of transferring the drug from a vial to a regular spray-siliconised disposable syringe is an additional source of increased particle count. The use of a PFS contributes significantly to lower residual volume and lower particle loads while significantly reducing the risk of contamination and, consequently, endophthalmitis.[6,7]

Procedure Efficiency and Clinician Burden

The current practice of intravitreal injections can be time consuming, contributing to higher costs and resource burdens in clinical settings. If the therapeutic drug is stored in a vial, it first has to be transferred to a syringe and primed for the patient-intended dose prior to administration. This opens up the possibility of manual error and also impacts efficiency, which becomes ever more important with the increasing prevalence of retinal diseases requiring treatment delivery via IVIs.

SOLUTIONS TO ADDRESS CHALLENGES OF IVI

Gerresheimer is one of the leading suppliers of primary packaging to the ophthalmic market. The company is committed to investing in ongoing research and development of solutions to fulfil unmet needs in this field.

The first stage of eliminating workflow steps is to opt for a PFS (Figure 1). In this case, the drug is prefilled into a glass or cyclo-olefin-polymer (COP) syringe in the correct volume and dose concentration with no need to be transferred into a syringe from a vial. Not only does the use of a PFS streamline workflow but it also reduces potential errors and the possibility

of contamination. Most importantly, recent studies show that PFS use was associated with a significant reduction in the rate of endophthalmitis following IVIs.[7]

BOS Syringes

Unlike standard spray-siliconisation methods, which are suitable for many drugs and applications, only a special low-particle siliconisation, such as baked-on siliconisation (BOS), provides a very thin, more uniform and stable silicone layer as the silicone oil is bonded to the surface via hydrogen bonds and partly covalent bindings. This significantly reduces the risk of silicone oil droplets migrating into the drug over its shelf life and during injection and potentially causing aggregation, drug interaction and particle migration into the vitreous body. BOS has proven to support USP <789> requirements of the final ophthalmic drug product.

Silicone-Oil-Free Syringes

Gerresheimer's introduction of silicone-oil-free syringes marked a pivotal innovation in syringe technology. These syringes do not use silicone as a lubricant, which eliminates silicone-derived particle formation. Silicone oil can induce the formation of protein aggregates prior to IVI. The release of silicone from the syringe can exacerbate this process, leading to increased levels of protein particles in the formulation.[8] Therefore, elimination of silicone supports greater compatibility with sensitive protein-based drugs by reducing the likelihood of aggregation.[9]

Proven Syringe Performance

In a study evaluating BOS and silicone-oil-free syringes, particle levels were found to be significantly below USP <789> requirements, confirming their suitability for ophthalmic applications (Figure 2). Testing involved the use of water for injection in both glass and COP barrels under real-time and accelerated storage conditions. Results indicated consistently low particle counts across all scenarios. Comparative analyses between BOS and silicone-oil-free syringes revealed both options to be highly effective and compliant with USP <789> requirements.

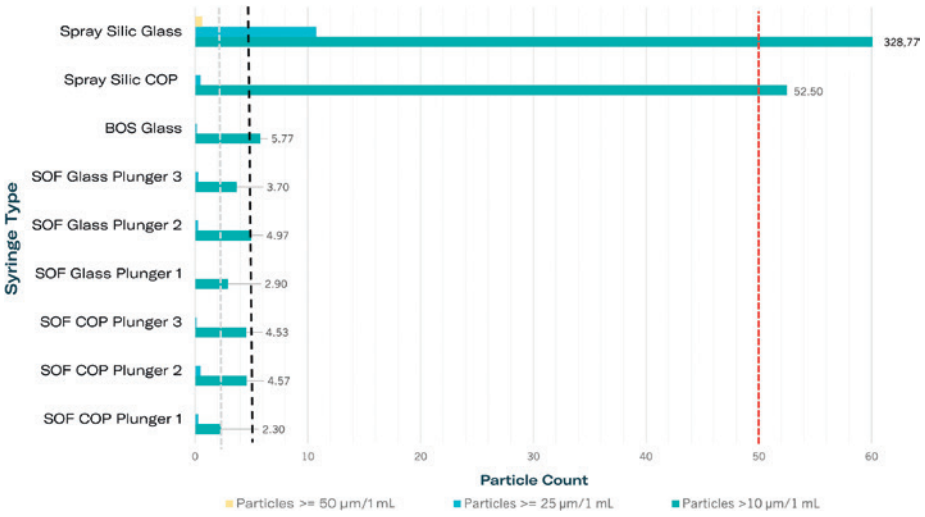

Figure 2: Particle measurements of silicone-oil-free 1-mL-long syringes compared with siliconised (Silic) systems in accordance with USP <789>. Dashed lines indicate limits for three particle classes in accordance with USP <789>. All syringes filled with water for injection. *Legend: COP/glass – syringe body material; Spray Silic – spray siliconised, BOS – baked-on siliconised, each with modern coated plunger stoppers; SOF with plungers 1–3 – silicone-oil-free syringes with various plunger stoppers.*

Dose Accuracy

For delivery of a precise microlitre dose, PFSs of 0.5 or 1 mL are required due to their small internal diameter. Tolerances for the internal dimensions of glass syringes can be set to ± 0.1 mm or even ± 0.05 mm to meet the most critical requirements. The moulding process used in manufacturing of the COP syringes means that these have even tighter tolerances contributing to higher dose-volume accuracies.

Dose marking is a key visual aid for retinal specialists when administering such small dose volumes. The visual dose mark helps to assess the stop position of the plunger for precise administration of the patient-intended dose. Gerresheimer employs a cutting-edge camera-based inspection system within its glass syringe production plants, which ensures accurate dose marking on its syringes with tolerances as low as ± 0.25 mm.

Break-Loose and Gliding Forces

Break-loose and gliding force (BLGF) tests further validate the functionality of these syringes for IVIs. After three months of accelerated ageing (equivalent to three years of real-time storage), all silicone-free glass syringes demonstrated BLGF values below 20 N, indicating excellent usability. The absence of ageing effects on gliding forces highlights the stability and reliability of the syringe systems (Figure 3).

Meeting Patient and Clinician Needs

A central focus on improving the experience of both patients and clinicians during IVI procedures while driving innovation is a top priority for Gerresheimer. By reducing or eliminating the presence of silicone particles and ensuring smooth injection by PFSs, the company's solutions contribute to higher safety levels for patients. For clinicians, the use of PFSs simplifies the preparation process, reducing procedural time, and the risk of dosing errors and contamination. This not only enhances workflow efficiency but also allows healthcare professionals (HCPs) to focus more on patient care.

CAN IVI PRACTICE BE FURTHER OPTIMISED?

Gerresheimer's syringes are shown to minimise the challenges of conventional

"GERRESHEIMER'S INTRODUCTION OF SILICONE-OIL-FREE SYRINGES MARKED A PIVOTAL INNOVATION IN SYRINGE TECHNOLOGY."

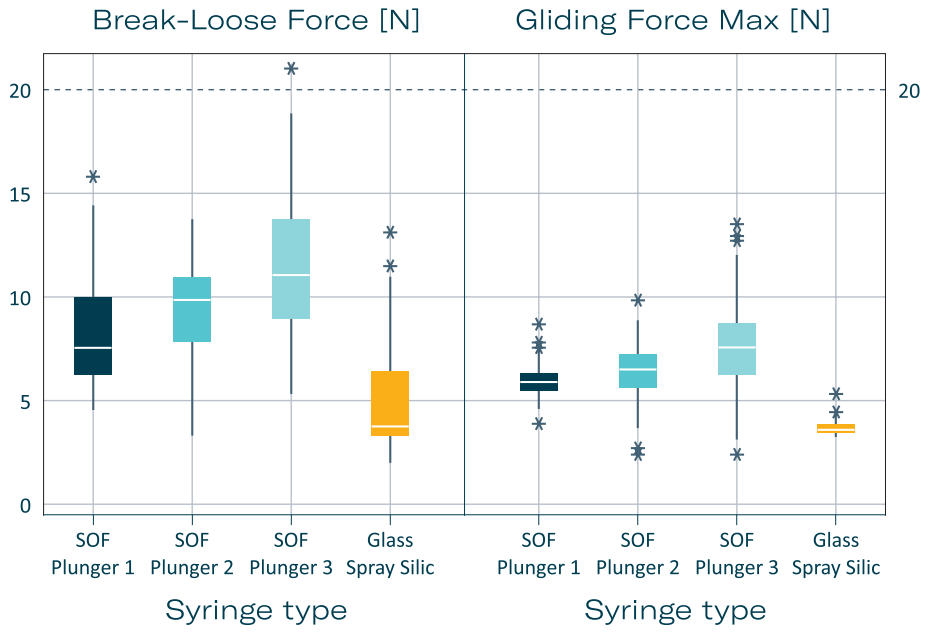

Figure 3: Break-loose and gliding forces of silicone-oil-free syringes compared with spray-siliconised syringes. Extrusion force 270 mm/min. Each syringe 1 mL long with 27 G needle syringe with standard ID, filled with water for injection. Measurement times each with N = 160: summed [T0 (3 days after filling), T1 3 months, T1 acc (3 months accelerated ageing in accordance with ICH), T2 acc (6 months accelerated ageing in accordance with ICH), T2 (6 months)]. *Legend: SOF with plungers 1–3: Silicone-oil-free syringes with three special plunger stoppers from different manufacturers; Glass Spray Silic – 0.5 mg silicone oil, coated plunger stopper.*

IVIs to a great extent. However, the judgement, dexterity and experience of the retina specialist continues to have an influence on the accuracy of microlitre dosing, reproducibility and patient comfort.[10] These variables are particularly critical with very small volumes – for example, the treatment of paediatric patients with retinopathy of prematurity is likely to involve volumes as small as 20 µL. In this case, patient comfort and safety is also of greater concern. Another consideration is the therapeutic window of the drug. If this is very narrow, over- or underdosing could have a greater influence on therapy effectiveness. Gerresheimer therefore instigated an innovation project to investigate the potential of an injection-aiding device to further optimise IVIs for patients and HCPs.

User-Centric Research

User centricity is a cornerstone of Gerresheimer's development process. Whenever a potential unmet need is identified, Gerresheimer's first step is to initiate a user preference study. In this instance, a combination of an online survey and in-person interviews were conducted with 25 retina experts to confirm challenges and identify further unmet needs.[11] This phase of research was followed by in-person interviews with international key opinion leaders (n = 5). The results confirmed that ease of handling, precise needle positioning, accuracy and consistency of dose delivery are viewed as critical factors by HCPs.

Initial Concept Testing

As a result of the initial research, several potential device concepts were generated that focused on the unmet needs of users, such as handling characteristics and accuracy of intended injection volume. Verification testing and user experience validation of potential device concepts were carried out. Both qualitative evaluation and statistical analysis were used to determine significant differences between the results of injection of a fixed intended dose with a chosen device concept compared with standard of care with a conventional PFS. Injection volumes, measured while using an injection-aiding device, demonstrated less dispersion around the intended dose volume compared with those performed with a PFS only (Figure 4).

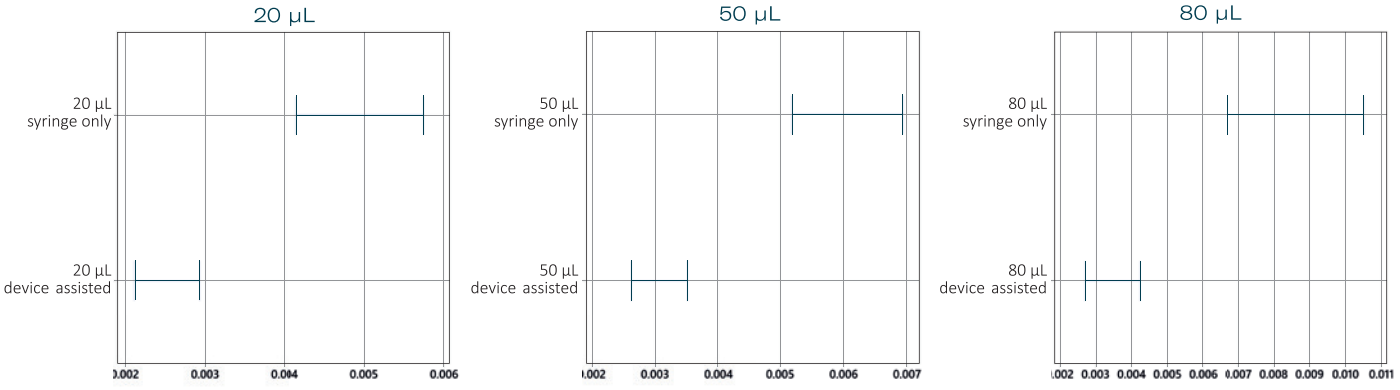

Figure 4: Results of tests for equal variances at target volumes of 20, 50 and 80 µL with standard practice using a PFS compared with an injection-aiding device. Multiple comparison intervals for the standard deviation, α = 0.05.

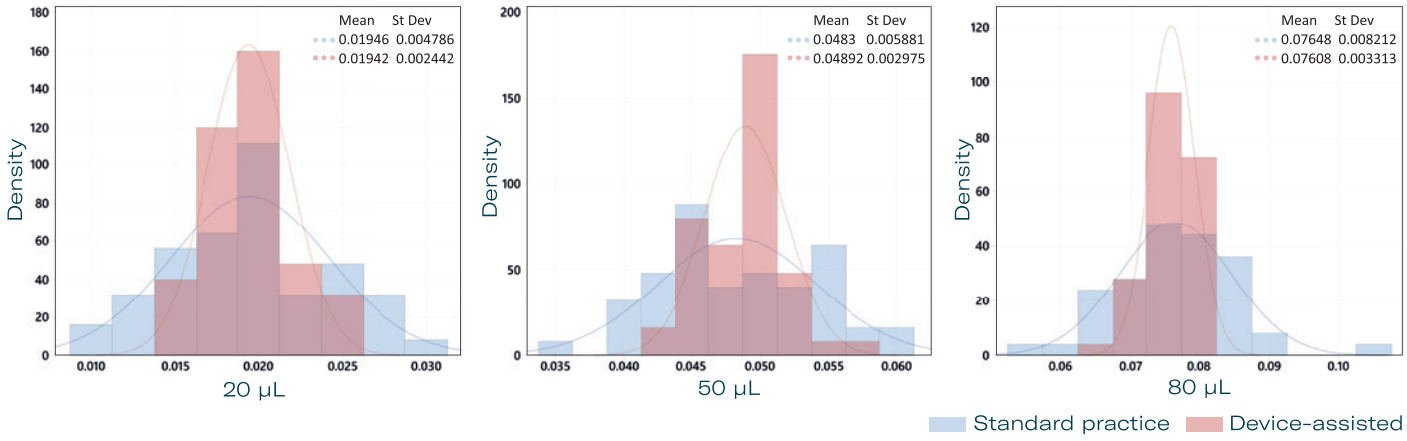

Figure 5: Histogram of injection volumes of 20, 50 and 80 µL with standard practice using a PFS compared with an injection-aiding device.

In-Depth Prototype Testing

An evolved prototype of the preferred device solution was then produced and subsequently underwent rigorous testing to assess injection accuracy and repeatability across target doses of 20, 50 and 80 µL. Five users performed injections of each of the target dose volumes using both the injection device prototype with PFS and the current standard of care in IVI with a PFS using a visual dose marker (n = 10 injections per user and target dose volume) (Figure 5).

Results showed reduced variability in delivered volume with the injection device compared with manual injection. Statistical analyses confirmed the superior consistency of device-assisted injections. The potential benefits of this device are manifold; by enhancing key aspects of the injection process, an injection-aiding device could increase patient safety by minimising dosage errors. It also has the potential to reduce procedural time, benefiting both patients and clinicians.

Gerresheimer remains committed to working closely with experts in the field to ensure that the final product meets the highest standards of safety and efficacy.[12]

"GERRESHEIMER REMAINS COMMITTED TO WORKING CLOSELY WITH EXPERTS IN THE FIELD TO ENSURE THAT THE FINAL PRODUCT MEETS THE HIGHEST STANDARDS OF SAFETY AND EFFICACY."

Future development steps include further testing to refine the device design and validate its performance under real-world conditions. The research project is ongoing and the next results have been accepted for presentation at the Association for Research in Vision and Ophthalmology annual meeting on May 4th–8th, 2025 in Salt Lake City (UT, US).

CONCLUSION

IVIs are indispensable in ophthalmology, yet challenges remain in ensuring precise, safe and efficient administration, particularly in demanding retinal therapies. Gerresheimer's ongoing commitment to patient and user-centric innovation ensures that the company continuously strives to identify and fulfil unmet needs. In this way, the company remains at the

forefront of solutions for intravitreal drug delivery, aiding healthcare providers and, ultimately, contributing to optimal outcomes for patients.

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Each issue of ONdrugDelivery focuses 100% on one specific topic *within* drug delivery.

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MAY/JUN Oral Drug Delivery DEADLINE: **Apr 17, 2025**	**JUN** Connectivity in Drug Delivery DEADLINE: **May 1, 2025**	**JUL** Industrialising Drug Delivery DEADLINE: **May 15, 2025**
SEP Wearable Injectors DEADLINE: **Aug 7, 2025**	**SEP/OCT** **NEW ISSUE TOPIC** Dual Chamber Delivery Systems DEADLINE: **Aug 14, 2025**	**OCT** Prefilled Syringes & Injection Devices DEADLINE: **Sep 4 , 2025**
OCT/NOV Sustainability in Drug Delivery DEADLINE: **Sep 18, 2025**	**NOV** Pulmonary & Nasal Drug Delivery DEADLINE: **Oct 2, 2025**	**DEC** **NEW ISSUE TOPIC** Delivering Gene & Cell Therapeutics DEADLINE: **Nov 6, 2025**
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A NEW DELIVERY PLATFORM FOR SUPRACHOROIDAL ADMINISTRATION USING WEST'S ADVANCEABLE MICRONEEDLE DEVICE

Dr Anu Prabhathachandran, **Menachem Peretz** and **Dr Manali Potnis** of **West Pharmaceutical Services** discuss the growing need for more effective delivery of therapeutics to treat ophthalmic conditions to meet the needs of the ageing population, including how delivery into the suprachoroidal space may present an appealing alternative to intravitreal injection, and go on to introduce West's Suprachoroidal Advanceable Microneedle Device, which offers several advantages for overcoming the challenges with suprachoroidal space.

As the population ages, the prevalence of eye diseases, such as age-related macular degeneration (AMD), geographic atrophy and diabetic retinopathy, is rising significantly. By 2040, AMD will affect 288 million patients worldwide.[1] By 2030, approximately 14 million patients globally will be treated with intravitreal injections (IVIs) for retinal diseases.[2] With a patient receiving around 4–8 injections per year, this translates to approximately 112 million injections annually.[2] Without proper adherence to these maintenance injections, patients face the risk of irreversible vision loss, and thereby their independence.

Since the approval of intravitreal ranibizumab (Lucentis®, Genentech) in 2014, intravitreal delivery has become a predominant method for ocular drug administration, with around 10 million IVIs administered annually in the US.[3] Despite its widespread use, intravitreal delivery has risks of intraocular inflammation when used to deliver newer therapeutics, such as gene therapies. IVIs risk systemic inflammation due to the leakage of drugs into systemic circulation and have limited efficacy in delivering therapies to the inner retina across restrictive biological barriers.[4] The alternative – sub-retinal injection – is effective but requires complicated, invasive surgical procedures that are not feasible for widespread use in a busy retina clinic.

Suprachoroidal delivery offers a promising alternative route of administration by enabling targeted drug

"SUPRACHOROIDAL DELIVERY OFFERS A PROMISING ALTERNATIVE ROUTE OF ADMINISTRATION BY ENABLING TARGETED DRUG DELIVERY THROUGH A MINIMALLY INVASIVE IN-OFFICE PROCEDURE."

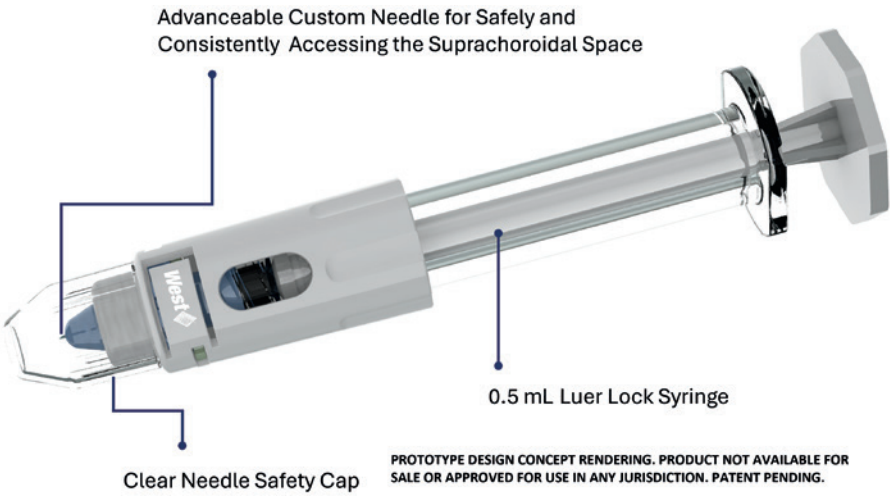


Figure 1: Render of West's Suprachoroidal Advanceable Microneedle Device.

delivery through a minimally invasive in-office procedure. This method involves delivering drugs into the potential space between the sclera and the choroid, enabling medication to travel posteriorly and circumferentially to the retina. Currently, only one small molecule drug is approved for suprachoroidal delivery, which offers comprehensive coverage of the choroid and the retina compared with conventional IVIs.[5]

Currently, several gene therapies and small molecule-based therapies targeting the suprachoroidal space are being evaluated in various clinical trials.[5] Small molecules can access the diseased area of the retinal pigment epithelium (RPE) and choroid, whereas large molecules cannot pass through Bruch's membrane and are therefore limited to the RPE side.[5] The apposition of the drugs on the choroidal layer may offer significant benefits in controlling inflammation in geographic atrophy, with specific advantages for extended delivery systems that can offer more durability to the therapy. The potential for improving therapeutic outcomes through better tissue access, physician training and patient education is significant in this route of administration.

Despite the potential advantages, accessing the suprachoroidal space is very challenging with current conventional practices due to the anatomical variability and the collapsed state of the suprachoroidal space. Notable challenges in accessing the suprachoroidal space include maintaining consistent pressure on the sclera to dimple the tissue during injections and the longer injection duration compared with intravitreal procedures – 5–10 seconds per eye for the suprachoroidal space versus approximately 1 second for an IVI.[5] The need for slow injection is to minimise the pain experienced by the patients during the injection. For suprachoroidal injection, dimpling is necessary to clear the conjunctiva and expand the suprachoroidal space.

These challenges result in injections failing in approximately 30% of patients, and a second injection with a longer microneedle is required to access the space.[6] Applying slightly greater pressure with the needle on the ocular surface prior to switching to a different quadrant or to a longer needle also increases patient discomfort during the injection.

"DESPITE THE POTENTIAL ADVANTAGES, ACCESSING THE SUPRACHOROIDAL SPACE IS VERY CHALLENGING WITH CURRENT CONVENTIONAL PRACTICES DUE TO THE ANATOMICAL VARIABILITY AND THE COLLAPSED STATE OF THE SUPRACHOROIDAL SPACE."

INTRODUCING THE SUPRACHOROIDAL ADVANCEABLE MICRONEEDLE DEVICE

To accommodate the anatomical variability of individual patients and find a solution for the challenges discussed above, West has introduced the Suprachoroidal Advanceable Microneedle Device (Figures 1 & 2). This device features firm dimpling followed by incremental needle advancement, allowing for more precise delivery of therapeutics into the

Figure 2: Suprachoroidal Advanceable Microneedle Device prototype and 0.5 mL prefilled syringe with surrogate drug product. *Prototype design not available for sale or approved for use in any jurisdiction.*

suprachoroidal space (Figure 3). The goal of the device and the advancement feature is to increase the precision and accuracy of suprachoroidal delivery by minimising the need for any unnecessary manoeuvring or excessive dimpling. This compensates for the depth needed in accessing the tissue, thereby avoiding the need for the second injection that arises in approximately 30% of cases using conventional practices.[6] The anticipated benefits of the new platform are summarised here:

- Single stick
- Faster injections
- Potential for reduced pain during injection
- Perpendicular access, which is easier to train and implement
- Potential to use the advancement feature to access the suprachoroidal space without rocking or twisting (manoeuvres that may increase the risk of choroidal haemorrhage)
- Potential to use a prefilled syringe with accurate dose marking
- Standard plunger rod platform similar to the devices used for IVIs, which may have a distinct advantage for both surgeon preference and drug manufacturer adoption.

In December 2024, West conducted a directional study with 13 participants, including retina consultants and trainees with varying levels of experience (Figure 4). The purpose of the study was to test the device's efficiency in performing suprachoroidal injections in terms of precision and accuracy and to assess whether the needle advancement feature can improve the success rate of injections when the free length of the needle is insufficient to access the suprachoroidal space. No formal training was conducted for the users.

Fresh porcine eyeballs (used within 48 hours post-euthanasia) were used for this study and were optimised to standard intraocular pressure using normal saline injections prior to the tests. Each participant performed four suprachoroidal injections in independent porcine eyeball samples, after which the success of the injection and the use of the advancement feature was assessed. The successful injections were determined based on the gross dissection

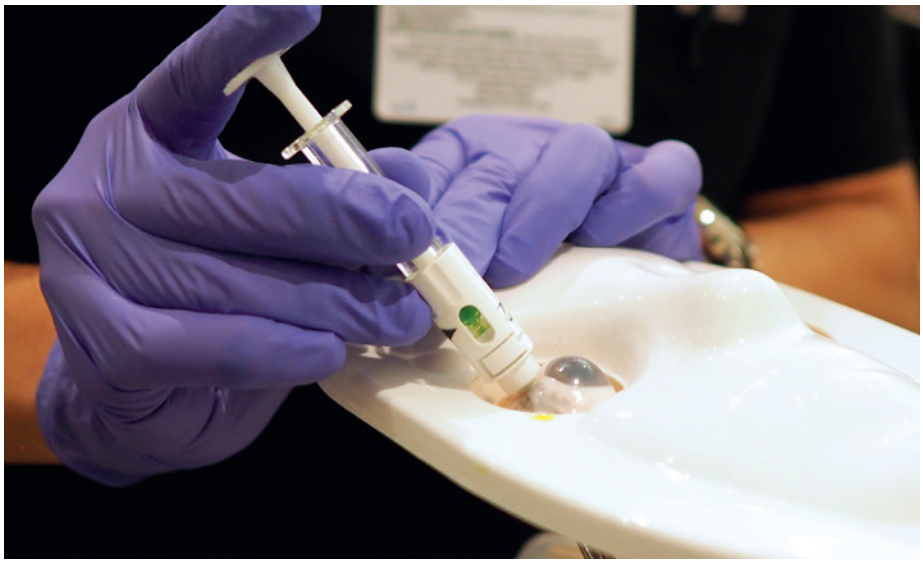


Figure 3: Demonstration of Suprachoroidal Advanceable Microneedle Device's dial rotation feature to advance the needle while performing injection. *Prototype design not available for sale or approved for use in any jurisdiction.*

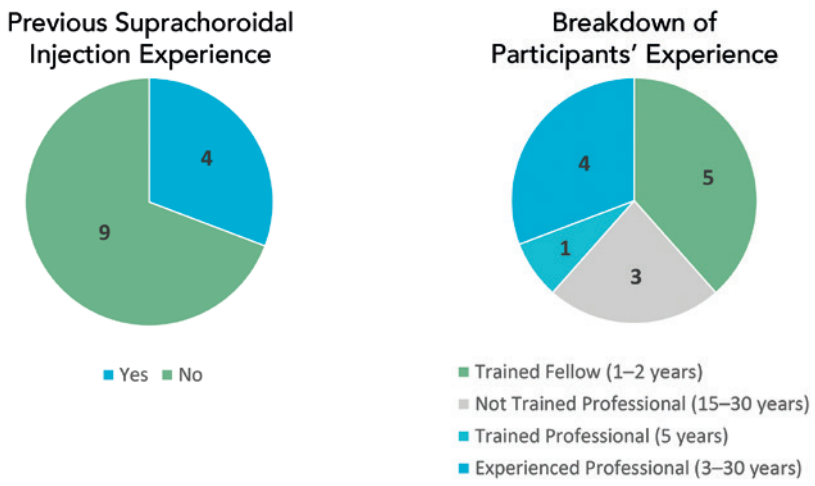


Figure 4: Distribution of participants involved in the early directional study.

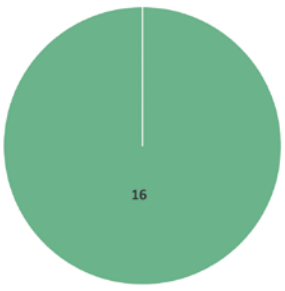
Figure 5: Demonstration of a failed versus successful suprachoroidal injection. In successful suprachoroidal injections, the potential space between the sclera and the choroid is seen expanded with the fluorescent drug surrogate, whereas in failed injections the dye is only seen on the surface of the sclera.

of the porcine tissue to qualitatively assess the expansion of the fluorescent dye in the suprachoroidal space (Figure 5).

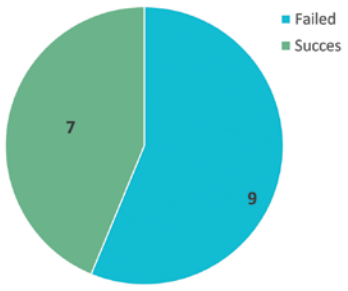
As seen in Figure 6A, the participants with experience injecting into the suprachoroidal space had a success rate of 100%. Within these successful injections, 75% were performed without using the extension feature, while 25% used the extension feature – a number consistent with the need seen in clinical cases where 25–30% of patients may have thicker sclera, necessitating the use of a longer needle.[6]

For inexperienced participants, the trained fellows with less than one year of retina experience were eliminated from the assessment, after which the success rate was 44%. The advancement feature was used successfully in 57% of the injections. Although extensions were applied more in failed injections than in successful ones, this was due to the lack of applied pressure, as inexperienced participants seemed unfamiliar with the baseline pressure and dimpling needed to conduct a suprachoroidal injection. Breaking down the results further, the inexperienced professionals showed failure even without extension in four cases, which was likely due to the lack of applied pressure in the injection (Figure 6B).

(A)



	Success	Failure
With Extension	4 (25%)	0 (0%)
Without Extension	12 (75%)	0 (0%)



	Success	Failure or no injection
With Extension	4 (57%)	5 (55%)
Without Extension	3 (43%)	4 (45%)

(B)

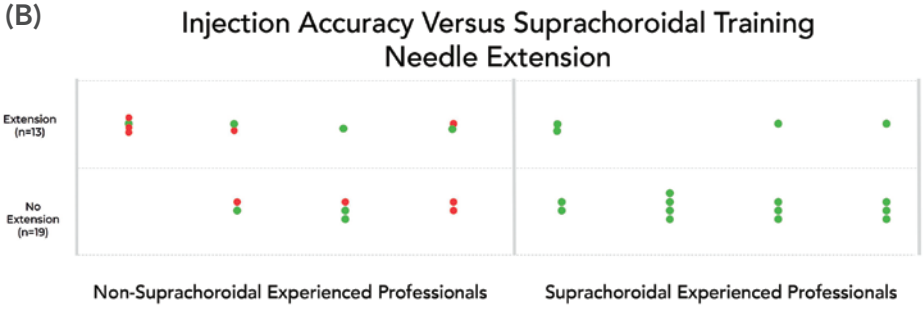


Figure 6: Success rate of suprachoroidal injection with participants who are experienced and inexperienced with suprachoroidal injections. Breakdown of success rate with and without extension feature.

SUMMARY AND FUTURE DIRECTIONS

Participants thought that accurately inserting the needle into the suprachoroidal space was primarily dependent on the needle lengths built into the device. West observed that needle depth accuracy was also highly dependent on the force applied by the user

and other techniques, such as twisting and pressing the needle into the eye.

Healthcare professionals with experience performing suprachoroidal injections knew that dimpling is critical for a higher success rate, which was reflected in the success rate of injections performed by this group. In thicker sclera, the extension feature was helpful in performing a successful injection, albeit only when constant pressure was applied to the surface of the eye. A goal for future research is to focus on device-dependent techniques that minimise injection time and discomfort, optimising both patient experience and procedural efficiency.

The suprachoroidal approach demands mastery of new techniques and collaboration between drug delivery device engineers, pharma companies and the retina community. Improving the comfort and timeliness of suprachoroidal injections is critical.

COLLABORATION AND ONGOING RESEARCH

Collaboration with pharmaceutical and ophthalmic device partners is crucial to advance the design and adoption of suprachoroidal delivery systems. West's expertise in container closure integrity provides valuable insights into clean, low-particulate packaging solutions with drug packaging solutions for low-volume injections, including for suprachoroidal delivery. West invites collaborations for drug-product specific optimisation and development of the Suprachoroidal Advanceable Microneedle Device for clinical trials.

Dr Anu Prabhathachandran

Anu Prabhathachandran, PhD, is a Principal Scientist at West. A biomaterials scientist and pharmacist by training, Dr Prabhathachandran is curious about devising and executing leading-edge research in drug delivery devices for various routes of administration, including in ophthalmology. In her current role in the Applied Research and Clinical Team at West, she executes research in emerging biologic and advanced therapy delivery with a highly interdisciplinary team of drug delivery engineers and scientists.

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Expert View

REVOLUTIONISING EYE CARE: THE POTENTIAL OF ANTISENSE OLIGONUCLEOTIDES

In this article, **Binbin Tian**, Senior Project Manager at WuXi AppTec, discusses antisense oligonucleotides and considers their potential as treatments for genetic and multifactorial ophthalmic diseases previously considered untreatable. The article considers how these therapies function as treatments, their current state of development, challenges in their delivery and the evolving regulatory landscape.

Ocular diseases are increasingly prevalent around the world due to ageing populations and unhealthy lifestyle choices. Many ocular conditions also have a genetic basis and require complex treatments.

Antisense oligonucleotides (ASOs) could become critical tools in the fight against genetic and multifactorial ophthalmic diseases. ASOs act at the RNA level, meaning that they can alter gene expressions regardless of the function of proteins encoded by their target. Subsequently, these drugs can zero in on disease-causing genes without affecting other cellular processes.

Although the use of ASOs in treating ophthalmic diseases is still in early development, researchers hope that they can relieve patients suffering from various conditions, including retinitis pigmentosa, macular degeneration and glaucoma. Their unique mechanisms of action and enhanced delivery systems offer significant advantages, but developers must first overcome considerable development challenges.

WHAT ARE ASOs?

Researchers worldwide are racing to develop oligonucleotides, colloquially called "oligos", due to their ability to treat conditions that have previously been thought undruggable, including genetic diseases, metabolic diseases and cancers. ASOs are small, single-stranded synthetic nucleic acid polymers capable of modulating gene expression.

ASOs can be tailored to target specific mutations or aberrant splicing events, making them suitable for treating conditions such as retinitis pigmentosa and other inherited retinal diseases (IRDs). They bind to their target RNA transcript in a sequence-specific manner using Watson-Crick base pairing, meaning that developers can design them to target specific genetic variants or distinct sequences. ASO molecules can alter protein expression by either knocking down transcripts or modifying pre-mRNA splicing, which enables either a reduction, modification or restoration of a specific protein.

Once delivered to the target cells, ASOs can have prolonged effects on gene expression, leading to sustained therapeutic benefits with less frequent dosing. Oligos can be designed for virtually any genetic target and present a low risk of side effects, making them an exciting option for precision medicine.

HOW ASOs WORK

ASOs can address genetic targets in ophthalmic conditions via different mechanisms. These include:

- **RNA degradation**: ASOs can bind to specific RNA, destroying it and preventing the production of proteins that cause disease.
- **Splicing modulation**: ASOs can be used to correct splicing defects or to skip faulty exons in genes associated with genetic disorders, such as retinitis pigmentosa or Usher syndrome. This technique is particularly effective in treating IRDs where traditional therapies are less beneficial.
- **Translational inhibition**: ASOs can block the process of translating RNA into protein, thereby preventing protein production.
- **Non-coding RNA targeting**: Some ASOs can be designed to target parts of the genetic code that do not make proteins but still play crucial roles in regulating gene activity linked with eye diseases.

"ASOs CAN BE TAILORED TO TARGET SPECIFIC MUTATIONS OR ABERRANT SPLICING EVENTS, MAKING THEM SUITABLE FOR TREATING CONDITIONS SUCH AS RETINITIS PIGMENTOSA AND OTHER IRDS."

"SUSTAINED-RELEASE FORMULATIONS AND NANOPARTICLE SYSTEMS OFFER PROMISING APPROACHES TO IMPROVE EFFICACY AND SAFETY BY OPTIMISING DRUG DELIVERY AND MINIMISING THE FREQUENCY OF ADMINISTRATION."

- **Allele-specific targeting:** ASOs can be designed to selectively target mutant alleles of genes while sparing the wild-type allele. This is useful when treating conditions where a specific mutation leads to disease, such as in certain forms of inherited retinal dystrophies.

For example, Leber congenital amaurosis (LCA) is a rare and severe hereditary retinal degeneration caused by mutations in more than a dozen genes. *RPE65*, a mutated gene, is highly expressed in the retinal pigment epithelium. It encodes the retinoid isomerase enzyme essential to produce chromophore, which forms the retina's visual pigment in rod and cone photoreceptors.[1] In LCA caused by mutations in the *RPE65* gene, ASOs can be tailored to target the mutant mRNA, reducing the expression of the dysfunctional protein while allowing the normal allele to function.

CURRENT STATUS OF ASO DEVELOPMENT

There are currently no ASOs approved for treating IRDs, but regulators have green-lit one aptamer (avacincaptad pegol) to treat geographic atrophy secondary to age-related macular degeneration. Three investigational RNA-based therapies for IRDs are in Phase I/II and II/III trials.

Sepofarsen is being developed to treat *CEP290*-associated IRD, more commonly called LCA10. This drug targets the retinal pigment epithelium-specific 65 kDa protein (RPE65) associated with LCA and retinitis pigmentosa. Clinical trials have shown that ASOs can effectively increase the expression of functional RPE65 protein, leading to improved retinal function and vision in patients.

Ultevursen aims to treat Usher syndrome and non-syndromic retinitis pigmentosa (nsRP) associated with biallelic *USH2A* mutations. ASOs such as ultevursen target the *USH2A* gene, which causes Usher syndrome and other retinal dystrophies. Studies have shown that they can correct splicing defects and restore the production of functional protein. QR-1123 is undergoing trials as a treatment for asRP associated with the c.68C>A mutation in *RHO*, leading to a proline-to-histidine substitution. All of these therapies are ASOs and are being developed by ProQR Therapeutics (Leiden, the Netherlands) and Ionis Pharmaceuticals (CA, US).[2]

CHALLENGES IN ASO DELIVERY

The unique anatomical and physiological properties of the eye present challenges for researchers aiming to develop ASOs for ophthalmic treatments, including the cornea, conjunctiva, blood-aqueous barrier, sclera and blood-retinal barrier. These barriers can limit the penetration of ASOs into the target tissues, such as the retina.

The delivery method for ASOs is crucial in determining their effectiveness and safety. Intravitreal injection allows direct access to the retina and provides high local concentrations, but it involves risks associated with invasive procedures. While topical delivery is less invasive, it can suffer from absorption challenges.[3]

Eye drops are the preferred method for treating anterior segment diseases, as they are convenient for the patient and deliver drugs locally. However, topical administration often results in poor drug absorption and low bioavailability.

Intraocular administration involves injecting medicine directly into the eye. It is an alternative approach demonstrating greater bioavailability, drug concentration and cell targeting. However, it causes a significant immune response. Using viral vectors to deliver ASOs can increase the likelihood of off-target toxicity; however, improper formulations and doses of these therapies can cause severe inflammation, unsafe toxicity levels and vision loss. Intravitreal injection involves directly injecting ASOs into the vitreous humour, allowing direct access to the retina and higher local concentrations.

Fortunately, improvements are on the horizon. Sustained-release formulations and nanoparticle systems offer promising approaches to improve efficacy and safety by optimising drug delivery and minimising the frequency of administration.[4] Ultimately, the ideal delivery method is determined by the unique properties of the ASO, the targeted disease and the patient demographic.

ADME AND BIOANALYSIS

The eye's anatomy also affects the absorption, distribution, metabolism, elimination (ADME) and bioanalysis of ASOs. For example, the cornea is a significant barrier to absorption as it has a multi-layered structure, which includes the epithelium, stroma and endothelium. The hydrophilic nature of ASOs makes penetrating the lipophilic corneal epithelium challenging when delivered topically.[5] As such, ASOs are often delivered via intravitreal injection to pass the corneal barrier. This allows direct access to the vitreous humour and subsequent distribution to the retina.

During the procedure, ASOs distribute a gel-like substance that fills the eye. They then diffuse to adjacent structures such as the retina and retinal pigment epithelium (RPE). The distribution is influenced by the size and charge of the ASOs and their formulation. The retina also has several layers, including the RPE, photoreceptors and inner retinal layers. ASOs must penetrate these layers to reach their target cells. The main barrier is the RPE, and ASOs can be affected by their ability to cross this hurdle. Distribution can be uneven, depending on the specific binding affinity of the ASO to the various retinal cell types.

The presence of enzymes in the vitreous humour and within retinal cells can lead to the metabolism of ASOs, which reduces their efficacy. Because nuclease

metabolises ASOs, they are not expected to be metabolised by cytochrome P450 (CYP) enzymes and thus have a low risk of drug–drug interaction. For elimination, the eye has several mechanisms for clearing substances, including tear drainage, aqueous humour drainage and lymphatic drainage. ASOs can be removed from the vitreous humour through these pathways, which can limit their half-life.

Bioanalysis of ASO levels in ocular tissues requires a diverse approach, using methods such as liquid chromatography-mass spectrometry, liquid chromatography-high-resolution mass spectrometry, quantitative polymerase chain reaction, liquid chromatography-fluorescence detection and ligand binding assay. High sensitivity is often needed because local delivery doses can be relatively small.

NAVIGATING REGULATION

Limited regulatory guidance on oligonucleotide therapies means that developers may face challenges navigating the approval process. However, regulators in the US recently released a draft of a non-clinical safety assessment for oligonucleotide drugs, and a handful of white papers have been written about the preclinical ADME evaluation of oligo drugs.

It is paramount to ensure safety and minimise immune responses when testing and developing ASOs for ophthalmic use. Fortunately, ASOs are well suited for treating the eye, as it is an immune-privileged closed compartment, and they should have limited off-target effects. However, it is important to follow regulatory guidance to assess immunotoxicity.

Many types of oligonucleotides are known to engage the innate immune system. Stand-alone, dedicated immunotoxicity assessments are not typically warranted, but evaluation of the effects on the immune system in general toxicity testing can provide helpful context for understanding observations in these studies.

Oligo drugs can also provoke the production of antidrug antibodies, and developers should consult ICH requirements and US FDA Guidance for Industry[6] to determine whether a non-clinical assessment of antidrug immunogenicity is warranted. The potential for immunogenicity in oligo drugs to impact patient safety or efficacy is best characterised during clinical testing.

A FINAL WORD ON ASOs

ASOs have the potential to revolutionise the treatment of many ocular diseases, offering a targeted, gene-based approach for previously untreatable conditions. Although few have been approved, many are currently in clinical trials and even more are on the horizon. The development of these drugs presents challenges, particularly in delivery and bioanalysis. However, with rigorous testing and specialised laboratory expertise, ASOs will soon be brought to market, where they can change patient lives.

ABOUT THE COMPANY

As a global company with operations across Asia, Europe and North America, WuXi AppTec provides a broad portfolio of R&D and manufacturing services that enable the global pharmaceutical and life sciences industry to advance discoveries and deliver groundbreaking treatments to patients. Through its unique business model, WuXi AppTec's integrated, end-to-end services include: contract research, development and manufacturing organisation (CRDMO) services for chemically synthesised drugs; biology discovery; preclinical testing and clinical research services; and contract testing, development and manufacturing organisation (CTDMO) services for advanced therapies. The company's cost-effective and efficient solutions combine to help customers improve the productivity of advancing healthcare products. WuXi AppTec received an AA ESG rating from Morgan Stanley Capital International for the fourth consecutive year in 2024. Its open-access platform enables more than 6,000 customers from over 30 countries to improve the health of those in need.

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Expert View

GENE THERAPY IN OPHTHALMOLOGY: ADVANCES AND CHALLENGES

In this article, **Dr Joe Batley**, Principal Physicist, and **Dr Lorna Barron**, Mechanical Engineer, both at Springboard, provide an overview of the latest cutting-edge ophthalmic delivery methods and discuss possible future developments.

"THROUGH A TARGETED APPROACH OF MODIFYING EXISTING OR INTRODUCING NEW GENETIC MATERIAL INTO A PATIENT'S CELLS, GENE THERAPIES AIM TO CORRECT THE UNDERLYING CAUSES OF THE DISEASE, RATHER THAN MERELY MANAGING SYMPTOMS – SOMETIMES WITH JUST A SINGLE INJECTION."

Gene therapy has emerged as a promising frontier in modern medicine, offering potential cures for previously untreatable genetic disorders. These therapies target the rarest of diseases, collectively afflicting millions of people worldwide, where a genetic defect modifies or prevents the proper functioning of cells, often leading to life-threatening conditions. Through a targeted approach of modifying existing or introducing new genetic material into a patient's cells, gene therapies aim to correct the underlying causes of the disease, rather than merely managing symptoms – sometimes with just a single injection.

Cell, gene and RNA therapies are gaining significant momentum as a novel branch of medicine. Following the first approval of Vitravene (fomivirsen, Novartis) in 1998,[1] more than 20 therapies were approved in the following 20 years, compared with more than 30 therapies in the last five years.[2,3] One target is ophthalmology, where genetic conditions such as inherited retinal diseases (IRDs), which are thought to affect 5.5 million people worldwide,[4] have long posed significant therapeutic challenges. The success of therapies such as Luxturna (voretigene neparvovec-rzyl, Spark Therapeutics, PA, US) – the first US FDA-approved gene therapy for an eye-related condition – has spurred rapid advancements in the field.

GENE THERAPIES

Gene therapies cover a broad class of treatments with the same underlying goal – manipulating the DNA of a patient's cells to treat a disease at its root cause. In general, these diseases cannot be treated or managed through conventional drugs and, in the case of inherited retinal diseases, often lead to blindness.

"THE OPHTHALMIC GENE THERAPY PIPELINE IS EXPANDING, WITH MULTIPLE CANDIDATES EXPLORING SEVERAL KEY APPROACHES TO DELIVERY."

As a class of treatments that specifically targets a genetic defect and the individual cells that are affected, the variation in different genetic diseases leads to a varied approach for transfecting the new genetic material. Broadly, these can be categorised into two methods with different requirements for the delivery device used:

- ***In Vivo***: The genetic material is delivered directly into the patient's body, typically enclosed in a carrier, and interacts with the target cells.
- ***Ex Vivo***: Cells are modified outside the body before being delivered to the patient. These may be from the patient or a donor.

With many different approaches under development, competition is intense. This article will focus on the *in vivo* approach.

EMERGING THERAPIES AND CLINICAL PIPELINE

The ophthalmic gene therapy pipeline is expanding, with multiple candidates exploring several key approaches to delivery (Figure 1). Therapies often use adeno-associated viruses (AAVs) as a delivery

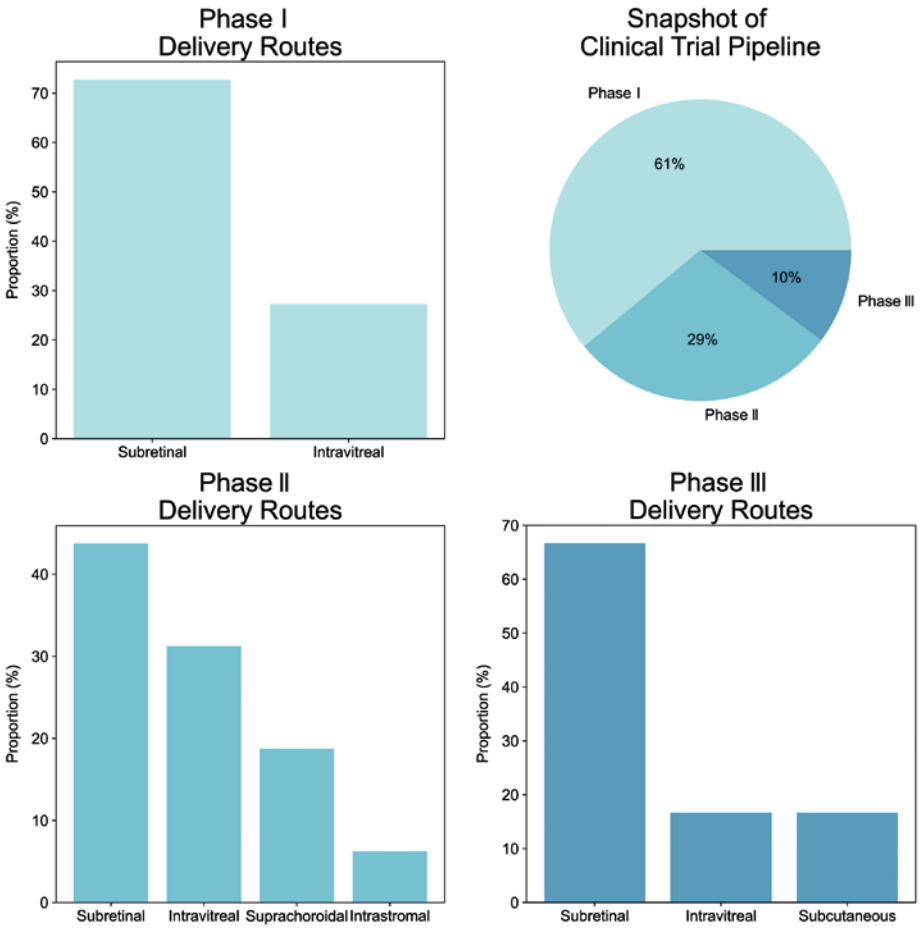

Figure 1: Snapshot of clinical trial pipeline. Subretinal injections are currently the primary delivery mode across all clinical phases, with intravitreal secondary. Recent years have seen a growth of a new method using the suprachoroidal space.

vector to introduce a corrected copy of a single gene but monoclonal antibodies, genetic modifiers or even novel optogenetic approaches are also used.

A key AAV-based therapy is Luxturna to treat *RPE65* mutation-associated retinal dystrophy (RD). The ongoing PERCEIVE study has reported results up to two years demonstrating the safety and effectiveness of the treatment in real-world settings.[5] After this first success for RD patients, AAV-based gene therapy is now being applied to other diseases. Notably, MeiraGTx (NY, US), through subretinal injection, has demonstrated significant vision improvement in treated children, all of whom were legally blind before therapy.[6]

AbbVie and REGENXBIO (MD, US) are taking gene therapy to new heights with their Phase III trial, ASCENT, for neovascular age-related macular degeneration (nAMD). The treatment comprises a one-time subretinal injection of an AAV-based vector to deliver a gene encoding for a monoclonal antibody fragment to inhibit the formation of abnormal blood vessels.[7] They are also exploring a suprachoroidal approach, enabling in-office delivery of the therapy in their Phase II trial, AAVIATE, which has reported positive interim results.[8]

Occugen's (PA, US) OCU400 takes a different approach. As an AAV-based gene-agnostic modifier therapy, it delivers the protein encoding gene *NR2E3*, regulating multiple gene networks to restore retinal homeostasis.[9] The liMeliGhT Phase III trial reports that 89% of patients experienced vision preservation or improvement, and this approach may be beneficial for multifactorial diseases such as AMD.

While AAV-based therapies require viable cells for transfection, optogenetic therapies offer an alternative that seeks to restore vision independent of the underlying genetic defect by introducing light-sensitive proteins into surviving retinal cells, enabling them to function as photoreceptors. GenSight Biologics' (Paris, France) GS030 introduces a light-sensitive protein into retinal ganglion cells and stimulates them with intense light. PIONEER Phase I/II results show patients transitioning from low light perception to object recognition after one year.[10] As optogenetics does not require viable photoreceptors, it is a promising option for late-stage retinal diseases.

CHALLENGES IN OPHTHALMIC GENE THERAPY

IRDs, genetic mutations affecting the photoreceptors or retinal pigment epithelium, are a key target for ophthalmic gene therapies. Over the years, researchers have identified many key genes associated with IRDs but, since these diseases are rare, developing this knowledge is difficult and time-consuming.

Despite significant advancements in the field, and the success of drugs such as Luxturna, there are still fewer approved therapies for ophthalmology than other therapeutic areas.[3] There are many general challenges to gene therapies – developing customised therapies for rare mutations remains costly, time-intensive and with impacts on manufacturing scalability. However, some challenges specific to ophthalmic therapies include:

1. **Disease Progression**: Therapy is most effective when sufficient retinal cells remain. Late-stage diseases may require stem cell transplantation or retinal implants.
2. **Safety Concerns**: Viral vectors can trigger inflammation, while invasive techniques risk retinal detachment and infection.
3. **Targeted Delivery**: The blood-ocular barrier limits the effectiveness of systemic therapies, requiring local delivery.

DELIVERY METHODS FOR OPHTHALMIC GENE THERAPY

Targeted delivery of gene therapies to the eye can be a significant challenge. The eye is a highly sensitive and complex organ, composed of various layers, internal membranes and barriers that can impede drug efficacy. The blood-retina barrier restricts transport to water, ions

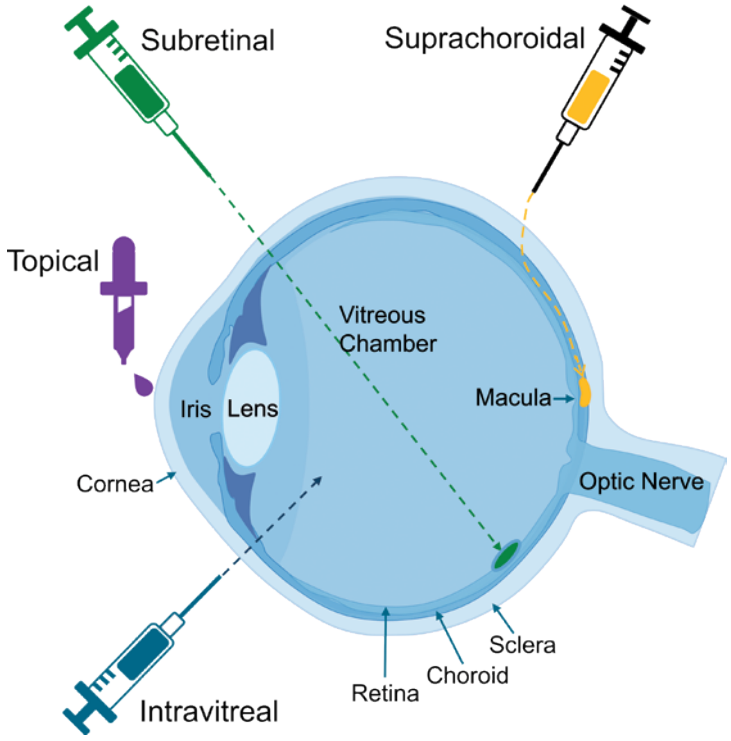

Figure 2: Key parts of the eye and the modes of delivery for ophthalmic therapies.

and proteins, limiting the effectiveness of systemic infusion therapies. Additionally, internal barriers, such as the internal limiting membrane, hinder the movement of therapeutic agents between the vitreous humour and retinal cells.

"GENE THERAPY REQUIRES DIRECT ACCESS TO TARGET CELLS FOR EFFICIENT GENETIC MATERIAL TRANSFER AND, AS MANY OCULAR DISEASES AFFECT THE MACULA AND RETINA AT THE BACK OF THE EYE, THIS NECESSITATES LOCALISED DELIVERY METHODS RATHER THAN SYSTEMIC INFUSION."

Gene therapy requires direct access to target cells for efficient genetic material transfer and, as many ocular diseases affect the macula and retina at the back of the eye, this necessitates localised delivery methods rather than systemic infusion. Since topical drug delivery lacks the bioavailability needed for effective gene therapy,[11] more invasive techniques are required. As the field evolves, emerging technologies aim to enhance precision, minimise invasiveness and improve therapeutic outcomes.

Several delivery methods are being explored to ensure effective and targeted gene transfer (Figure 2). Historically, the first gene therapies, such as Luxturna, have used extremely delicate surgical approaches to delivering genetic materials to the eye. However, as is a common trend in drug delivery, more recent years have seen a focus on methods that can be delivered in a clinic or office setting, aimed at reducing costs and risks. Each approach is presented here to help understand the challenges involved.

Surgical Based

A widely used delivery method (Figure 1), most notably for Luxturna, subretinal injection involves creating a localised retinal detachment or "bleb" to facilitate direct gene transfer to the photoreceptors. This technique ensures precise targeting of affected cells but requires a complex surgical procedure known as pars plana vitrectomy, in which the vitreous of the eye is removed to gain access to the back of the eye. While subretinal injection has demonstrated long-term efficacy, its invasiveness necessitates highly specialised surgical expertise.

To produce a bleb retinal detachment, the surgeon will push the cannula through the retina before injecting fluid. Complications can occur, including neurosensory retinal trauma and damage to delicate subretinal structures.[12] Surgeons often control the delivery of the therapy by using foot-pedal control of pneumatic pressure to drive the syringe plunger. However, this technique lacks direct control of flow rate and volume, which may lead to unintended bleb propagation or damage to retinal cells.

As the sub-retinal approach is the most common delivery method seen across therapeutic pipelines (Figure 1), many alternative devices are in development. One such device is Altaviz's Advent (CA, US), which aims to control flow rates and dose while providing a low force actuation. However, shifting to simpler, in-office approaches may offer improved accessibility and lower costs.

Clinic Based

In-office treatment at local clinics eliminates the need for large surgical suites and specialised equipment. Intravitreal injection (IVI), a common ophthalmic delivery method routinely employed for a range of conditions, has shown promise for gene therapy, thanks to its relative simplicity and cost effectiveness. Compared with subretinal injections, IVIs are less invasive and do not necessitate extensive surgical equipment. Injection guides, such as Precivia (FCI, MA, US) and SP.eye™ (Andersen Caledonia, Strathclyde, Scotland), help standardise depth and positioning, improving precision.

Since gene therapies are typically produced in small quantities and require extreme cold storage, they are commonly shipped in vials. Standard injection syringes are a well-established method for

transferring and administering these doses but their accuracy can be a limitation – especially for the typical 50 µL doses. To address this, companies such as Credence MedSystems (CA, US) and Congruence Medical Solutions (MD, US) are developing devices that improve dosing precision. However, prefilled syringe solutions, such as those from Credence, may not be suitable for gene therapies due to the need for ultra-cold storage.

Despite its advantages, IVI presents some challenges. Potential complications include floaters, intraocular pressure fluctuations, inflammation and infection. While IVI remains the preferred in-office method (Figure 2), its limitations have driven interest in alternative approaches, particularly suprachoroidal injection.

The suprachoroidal space lies beneath the sclera and encircles the posterior eye. Unlike IVIs, this approach does not penetrate the vitreous, reducing the risks of vitreous haemorrhage and intraocular pressure fluctuations. Additionally, the natural fluid dynamics of the suprachoroidal space help distribute the delivered therapy more evenly across the retina. Clearside Biomedical (GA, US) has pioneered the development of suprachoroidal injection devices, introducing a custom microneedle injector currently being tested in multiple gene therapy trials.

Although promising, suprachoroidal injection presents challenges. Determining the exact thickness of the sclera can be difficult, making depth control a key concern. The Clearside device has both 900 µm and 1,100 µm microneedles, with studies showing the former is suitable for 78% of injections[13] and so, in some cases, a second attempt is required. As a result, other companies, such as Oxular (recently acquired by Regeneron, NY, US), are developing microcatheter-based techniques, while early-stage research explores adjustable microneedle devices. Additionally, the procedure takes longer than IVI, which can cause discomfort. However, with increasing clinical adoption and a growing research pipeline, suprachoroidal injection is one to keep an eye on.

Finally, a major challenge in gene therapy is the immune response triggered by viral vectors. To address this, researchers are investigating non-viral approaches such as electroporation and optogenetics. Electroporation uses electric fields to enhance the uptake of genetic material, while optogenetics employs light pulses to activate gene expression. Both methods still require local injection for delivery, but they offer the potential for safer, more flexible gene transfer. While these technologies require further optimisation, they represent a promising evolution in ophthalmic gene therapy.

THE FUTURE OF OPHTHALMIC GENE THERAPY

The field of ophthalmic gene therapy continues to evolve, driven by advances in vector design, delivery technologies and gene-editing tools. As research progresses, the development of mutation-independent therapies, improved non-viral delivery systems and personalised medicine approaches will likely enhance treatment efficacy and accessibility.

With ongoing clinical trials and increasing regulatory approvals, gene therapy holds the potential to revolutionise

"WITH ONGOING CLINICAL TRIALS AND INCREASING REGULATORY APPROVALS, GENE THERAPY HOLDS THE POTENTIAL TO REVOLUTIONISE THE TREATMENT LANDSCAPE FOR INHERITED AND ACQUIRED OCULAR DISEASES."

the treatment landscape for inherited and acquired ocular diseases. However, the costs to develop and manufacture these therapies can be extremely high, making effective delivery of the dose to a complex organ, such as the eye, a critical requirement. Meeting optimal clinical efficacy and safety will require dual development of the therapies and delivery methods, avoiding generic methods for a bespoke treatment. However, by addressing these challenges and refining delivery techniques, researchers and clinicians can pave the way for a future where vision loss due to genetic disorders becomes a thing of the past.

ABOUT THE COMPANY

Springboard, part of Sanner Group since 2024, is an engineering company that specialises in the design and development of new products and technologies in the field of medtech and drug delivery devices, resolving technical challenges and decreasing time to market.

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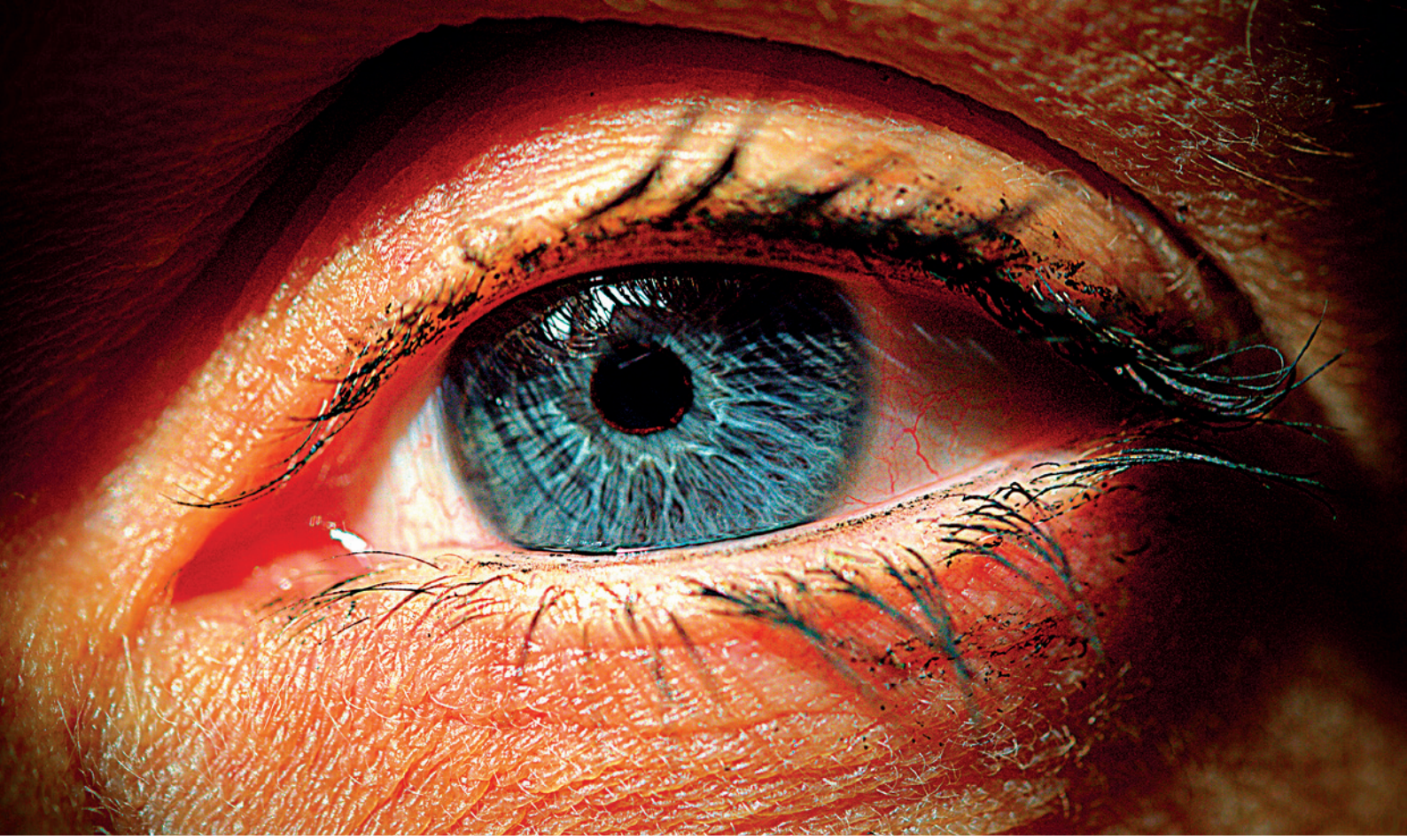

GLAUCOMA IN VIEW: IMPROVING PATIENT ADHERENCE WITH MULTIDOSE EYEDROPPERS FOR PRESERVATIVE-FREE SOLUTIONS

Nemera
we put patients first

Zoë Davidson of **Nemera** considers the impact of glaucoma on global health and the challenges presented by the increasing prevalence of this disease in the ageing global population, discussing how Novelia®, Nemera's multidose eyedropper for preservative-free formulations, is well-positioned to address many of the challenges presented by glaucoma treatments, from ease of use to sustainability.

INCREASING PUBLIC AWARENESS AND EDUCATION AROUND GLAUCOMA

Glaucoma Awareness Day, observed annually on March 12, serves as a vital reminder of the importance of the early detection and treatment of glaucoma, a leading cause of irreversible blindness worldwide. This day aims to educate the public about the silent progression of glaucoma, which often presents no early symptoms, making regular eye exams crucial for early diagnosis. By raising awareness, Glaucoma Awareness Day encourages individuals, especially those at higher risk, to prioritise their eye health and seek timely medical advice.[1]

GLAUCOMA MARKET GROWTH PROPELLED BY AN AGEING DEMOGRAPHIC

The growing global ophthalmic eyedroppers market is expected to be driven by the increasing prevalence of eye disease and disorders such as glaucoma, dry eye disease and age-related macular degeneration. Moreover, the increasing ageing population further propels market growth due to a higher incidence of age-related eye conditions.[2]

Glaucoma represents a group of optic neuropathies characterised by the progressive degeneration of retinal ganglion cells (RGCs). Open-angle glaucoma (OAG) is the most common form of glaucoma, carrying a chronic prognosis and making

up 75–95% of primary cases.[3] Angle-closure glaucoma (ACG) can either be acute or chronic, but typically has a faster progression than OAG and therefore requires more drastic interventions. These two main types often require the use of eyedrops to reduce intraocular pressure and prevent further damage.

As the population ages, the demand for glaucoma medications administered via eyedroppers is also expected to increase, thereby driving market growth. For example, people are six times more likely to develop glaucoma after the age of 60.[4] Given the growing ophthalmic eyedroppers market, drug delivery device designers and manufacturers must strive to not only understand but also provide solutions for patients encountering challenges administering their medication and to improve at-home eyecare management.

A SAFE PRESERVATIVE-FREE SOLUTION FOR PATIENTS

The majority of eye drops today contain preservatives to maintain the sterility of the eye drop formulation. The most commonly used preservative is benzalkonium chloride (BAK), which has been known to damage the cornea over long-term use. Despite consistent data confirming its potential toxic effects, especially for chronic use such as for glaucoma, BAK is still used as the main preservative in eye drops.[5]

Glaucoma patients have set regimens as prescribed by their healthcare provider and commonly have to fit this regimen into their morning/nightly routine. However, some patients may also use over-the-counter (OTC) dry-eye eye drops in addition, as irritation can be a side effect of some glaucoma medications. According to a 2008 survey conducted in Germany, over 50% of all glaucoma patients have dry eye. Furthermore, dry eye was found to be more common if more than three or more anti-glaucoma agents were used, suggesting that preservatives have an influence on the development of dry eye.[6]

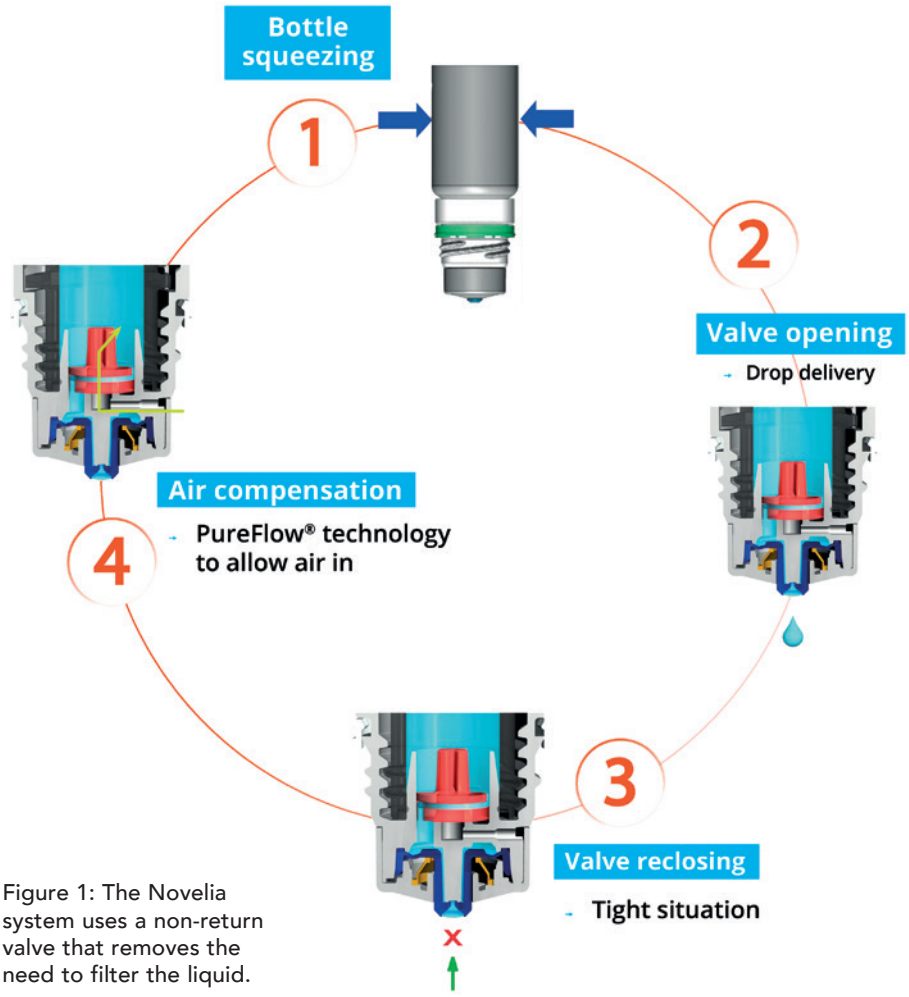

Figure 1: The Novelia system uses a non-return valve that removes the need to filter the liquid.

There has been a lot of effort to improve the primary container closure systems of topical ophthalmic products – for example, multidose bottles have been improved to multidose preservative-free (MDPF) bottles. As science and technology evolves, there is a greater need to further understand and "preserve" the complex organ that is the eye[7] and to ensure that the patient is put first.

To prevent the entry of bacteria into the bottle and/or to filter air, more than half of the bottles designed for multidose preservative-free eye drops on the market rely on a filtering system, with 0.22 µm sterile mesh filters being the industry standard. Significant research has been carried out that challenges their effectiveness.[8] Due to their porous structure, bacterial filters do not provide a continuous barrier to contamination.

Nemera's alternative to the use of sterile filters for multidose eye droppers for preservative-free formulations is a non-return valve system used in conjunction with a silicone membrane to process the returning air (Figure 1). The non-return valve ensures that no liquid can be re-introduced to the container after the drop has been dispensed, completely removing the need to filter the liquid. The intake of air into the dispenser takes place via a separate venting system with a silicone membrane called the PureFlow™. The silicone membrane is a solid, non-porous (unlike bacterial filters) material. It is homogenous and does not contain any holes, meaning that its characteristics can be precisely engineered.

"THERE HAS BEEN A LOT OF EFFORT TO IMPROVE THE PRIMARY CONTAINER CLOSURE SYSTEMS OF TOPICAL OPHTHALMIC PRODUCTS – FOR EXAMPLE, MULTIDOSE BOTTLES HAVE BEEN IMPROVED TO MDPF BOTTLES."

Figure 2: Cosopt iMulti® for the treatment of intraocular pressure in patients with OAG using Novelia, marketed by Santen (image courtesy Santen).

Novelia® has the largest amount of published information regarding the safety and sterility of these MDPF packages and is able to withstand both the likely microbial challenges in real-world scenarios and the more significant and severe challenges that can occur (Figure 2).[9]

PATIENT CHALLENGES FROM THE HEALTHCARE PROFESSIONAL'S PERSPECTIVE

Self-administration can be challenging for patients with arthritis, tremors and/or hand strength/dexterity issues that can make removing the cap, gripping and squeezing the bottle and holding the hand steady during administration challenging. Additionally, as described by physicians, there is a subset of patients who don't do well putting things into their eyes. These patients may require aiming techniques and ways to hold the eyelid steady (to avoid blinking). In a worst-case scenario, these limitations may preclude self-administration, requiring a caregiver.

Compliance is often recognised as a challenge by healthcare professionals (HCPs), especially with more complex treatment regimens. Nearly nine out of ten glaucoma patients are unable to instil eye drops correctly and therefore an easy-to-use system that is appreciated by patients could contribute to improving their compliance with their treatment.[10] In a study conducted by Nemera's Insight Innovation Centre, one participant (an ophthalmologist) commented that when you have one drop, compliance is 75–80%, when you use two drops, it drops to 65%, and if you need three drops, it drops below 50%. Additionally, patients (especially those with cognitive issues) may not always remember or follow storage and administration instructions, such as refrigerating the medication or shaking before use.

PRECISION MATTERS FOR PATIENT-CONTROLLED EYE DROP DELIVERY

Patients and HCPs alike desire a bottle that allows patients to control the number of drops delivered, consistently delivering a single drop with each actuation. A study of glaucoma patients found that 90% used an erroneous technique, with many patients missing the eye entirely.[11]

Novelia's patented PureFlow technology not only serves as a venting system but also controls the medication flow. Nemera has adapted the flow control within Novelia to avoid delivery of multiple drops into the eye and ensures that only one calibrated drop is dispensed at a time. Nemera offers three different PureFlow versions, each tailored to formulations of differing viscosities, from highly liquid to highly viscous. In addition, five different valve sizes are available, each one delivering a different calibrated drop size. This allows Nemera's team to customise the drop size depending on specific product requirements. This improved control leads to increased patient confidence that they are delivering an accurate dose, reducing frustration and medication waste.

Patients, even those with dexterity issues and tremors/shaking, must be able to effectively handle/manipulate the delivery system and administer a drop. According to a study conducted for Nemera by GfK (Nuremberg, Germany) in 2015, contributing factors to Novelia being the multidose eyedropper for preservative-free formulations preferred by 76% of patients included the intuitiveness of the screw-on cap and the associated reassurance, as well as the squeeze force required towards the end of the product's life. Novelia required only 6% more pressure to squeeze the bottle from the beginning to the end of the treatment, compared with 35% for the other devices. Novelia's patented blue tip is also a favourite feature of the device, as it helps patients target the eye before drop administration and anticipate the angle of the drop on to the ocular surface.

A full range of bottles is available in low-density polyethylene (LDPE) and

Figure 3: A full range of bottles is available in LDPE and PP in 5 mL, 7.5 mL, 11 mL and 15 mL formats.

Figure 4: Nemera has recently commercialised a new vented cap version as part of the Novelia platform.

polypropylene (PP), in 5 mL, 7.5 mL, 11 mL and 15 mL formats (Figure 3). Novelia has been validated using both gamma and ethylene oxide (EtO) sterilisation. Offering two options for sterilisation allows Nemera to better meet customers' compatibility needs. Nemera can also develop additional coloured Novelia caps for specific demands. Finally, Nemera has recently commercialised a new vented cap version as part of the Novelia, aiming to combat challenging formulations and target selected highly regulated markets, thus expanding the scope of ophthalmic treatments served by the MDPF system (Figure 4).

SUSTAINABILITY IN FOCUS FOR TOPICAL OPHTHALMIC APPLICATIONS

When considering unit dose eyedroppers, patients have reported concerns that include cost, as more packaging and eye drop solution is required per dose; waste; and convenience, as it is easier to store a multi-use bottle in a preferred location than it is for a patient to ensure that they have the correct number of unit dose pipettes with them every day.[12] Difficult handling has also been pointed out regarding unit doses and their use by elderly patients – inappropriate finger manipulation could be associated with an increased risk of contamination.[9] Due in part to the rapidly ageing population, the number of people with glaucoma is expected to increase to over 111 million worldwide by 2040.[13]

A comparison analysis was conducted by Nemera comparing Novelia with unit-dose packaging for a glaucoma-type regimen (one drop per eye twice per day) over a one-month treatment. The results conveyed that, with Novelia, there is eight times less plastic used, 25 times less drug waste and nine times less energy needed for transportation compared with a unit-dose regimen.

In 2021, Nemera subscribed to the Science-Based Target initiative (SBTi) to define and develop best practices for carbon reduction. One of Nemera's first objectives is to reduce Scope 1 and 2 emissions by 90% by 2030 (from a 2019 base year). In addition, since February 1, 2024, Nemera's manufacturing facility in La Verpillière, France, where Novelia is manufactured, has been certified ISCC Plus. This certification scheme for bio-based, renewable and circular raw materials reinforces Nemera's implementation of sustainability goals. Furthermore, in November 2024, Nemera was awarded the EcoVadis Gold Medal (Figure 5), marking a significant milestone in the company's sustainability journey. With an impressive score of 79/100, Nemera has not only improved by 12 points since last year but also ranked in the top 1% of companies in the industry for social and environmental responsibility.

"WITH NOVELIA, THERE IS EIGHT TIMES LESS PLASTIC USED, 25 TIMES LESS DRUG WASTE AND NINE TIMES LESS ENERGY NEEDED FOR TRANSPORTATION COMPARED TO A UNIT DOSE REGIMEN."

Figure 5: In November 2024, Nemera was awarded the EcoVadis Gold Medal, marking a significant milestone in the company's sustainability journey.

ENABLING CUSTOMERS TO SERVE PATIENT NEEDS WORLDWIDE

Nemera offers a range of laboratory services for Novelia, including testing of customers' bulk formulation. This testing comprises usage simulation over a two-week period, drop size analysis (variable depending on valve diameter), flow control and squeeze force testing (beginning and near end of life). These tests enable Nemera to determine the best Novelia configuration for a particular customer formulation. Nemera can recommend the most suitable PureFlow control, bottle type and valve size to achieve the desired drop calibration.

Nemera's regulatory team is on hand to support customers with their submission filing, providing guidance on supportive documents for registration. Nemera can also assist customers in finding the right ready-to-go dossier available for private labelling of certain molecules with the Novelia delivery system. Nemera has a substantial list of partners, formulation licensors and fillers, all working in collaboration to bring to customers a finished drug-device combination product with Novelia.

While it's important that containers be user friendly, it has been found that educational resources instructing patients to apply their eye drops correctly mitigate many issues with unintentional noncompliance.[14] Nemera can support customers with product market launch, for example, by educating sales teams and HCPs on the delivery device, offering dedicated training and providing materials to assist in promotional material creation. Customisable patient guidance videos are also available in several languages to increase patient compliance around the world.

Today, Novelia has approximately 400 references on the market for prescription and OTC products in over 60 countries across Europe, Latin America, North America, Oceania, the Middle East and Asia Pacific. To serve customers in supporting patient needs, Nemera is once again increasing its manufacturing capabilities, this time in France. This capacity increase comes shortly after Nemera's US expansion in 2023, which saw the company double its capacity to produce Novelia® multidose eyedropper for preservative-free formulations.

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Zoë Davidson

Zoë Davidson has held the position of Global Category Marketing Manager for Nemera's ophthalmic franchise since 2019. In this role, Ms Davidson is responsible for the strategy management of Novelia® – Nemera's flagship own-IP multidose eyedropper for preservative-free formulations. With over eight years' experience in the pharmaceutical and medical device industry, Ms Davidson is motivated about gaining insights into patients' needs and wants within the ophthalmic space.

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Nemera is a global drug delivery device solutions provider that designs and manufactures devices that maximise treatment efficacy and put patients first. The company is a holistic partner and helps its customers succeed in the sprint to market of their combination products. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards.

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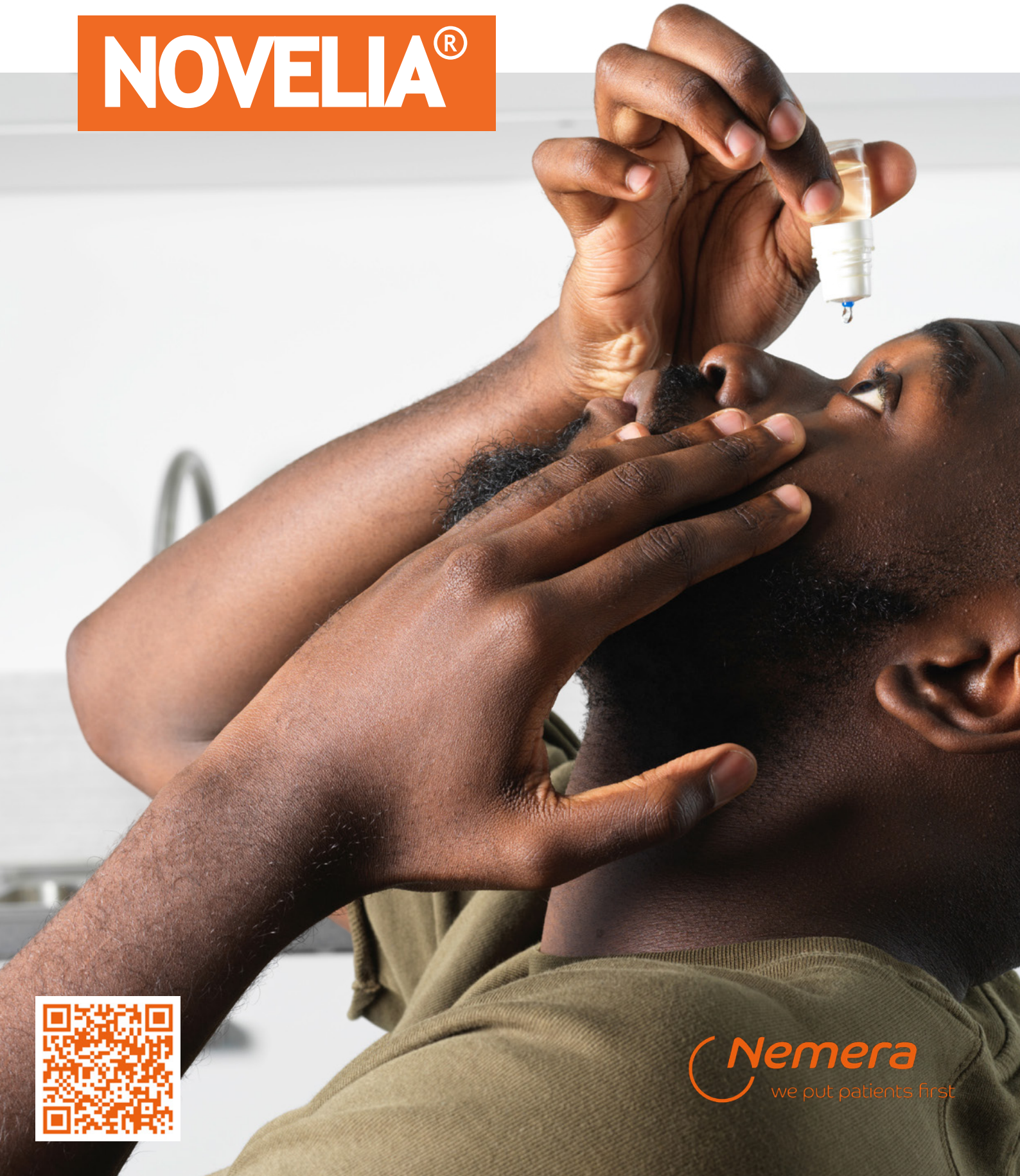

Nemera
we put patients first