NOVALIQ

Transforming Ocular Therapeutics

OVERCOMING THE CHALLENGES OF OPHTHALMIC DELIVERY USING AQUEOUS-FREE TECHNOLOGY: REDEFINING DRY EYE DISEASE

Traditional aqueous vehicles for topical ophthalmic medications suffer from a number of limitations. In this article, Christian Roesky, PhD, Chief Executive Officer and Managing Director, Novaliq, reviews the benefits of EyeSol®, a proprietary aqueous-free drug delivery technology, and findings from preclinical and clinical trials of marketed and investigational EyeSol®-based products.

Topical eye drops are the mainstay of therapy for many ocular diseases, but features of existing aqueous-based formulations create issues that can limit a product's efficacy and safety. The typical dispensed drop size of an aqueous-based ophthalmic preparation is 40-50 µL. This large volume exceeds the eye's external reservoir capacity, resulting in spill-over. The high surface tension of an aqueous-based drop further hinders its spreading on the ocular surface. In addition, the application of an aqueous-based eye drop can activate the defence mechanism of the eye, causing rapid blinking after instillation and tear secretion. Taken together, these factors reduce a drug's residence time and contribute to the low bioavailability of conventional topical ophthalmic medications, which is reported to be as low as 3-4%.[1]

> "As Novaliq advances its product development portfolio, it has the potential to redefine dry eye disease."

Another limitation of using aqueous-based formulations as a topical drug delivery platform relates to the fact that up to 60% of today's new chemical entities are lipophilic compounds or large molecules with poor water solubility.[1] The addition of oils and/or surfactants into aqueous-based formulations is a common strategy used to address this problem, but the presence of these agents can lead to visual disturbance and tolerability issues. Tolerability can also be affected by preservatives that must be included in aqueous-based ophthalmic products that are packaged in conventional multi-dose containers.

DISRUPTIVE DRUG DELIVERY TECHNOLOGY

Novaliq, a German speciality pharma company, has developed EyeSol®, a proprietary, aqueous-free platform that overcomes the aforementioned issues. Novaliq is leveraging this disruptive technology in an extensive development programme to create innovative products that address unmet needs in ophthalmology and, as the company advances its product development portfolio, it has the potential to redefine dry eye disease.

EyeSol® is the first and only aqueous-free technology for ocular drug delivery. Therefore, it is distinguished from aqueous based technologies by a host of physical characteristics that translate into enhanced stability, bioavailability, efficacy and tolerability (Figure 1).

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	Water-based Technologies	EyeSol®
Drop Size	Ca. 40-50 µL (Blink reflex activated)	<12 µL (Blink reflex not activated)
Bioavailability	Bioavailability topical formulations: 1-10%	Up to 4x higher
Drug residual time	Reduced to 3-5 min due to blink reflex	No rapid blink reflex at instillation
API Solubility	75% of NCEs are poorly soluble	Enables lipophilic drugs and biologicals
Spreading	High surface tension hinders spreading	Reduced vision impairment, less "spill-over"

Figure 1. Comparison of aqueous-based and aqueous-free EyeSol® drug delivery technologies.

EyeSol® is based on specific semi-fluorinated alkanes (SFAs). These compounds have the same refractive index as water and are transparent, inert, non-toxic, amphiphilic liquids that are able to formulate lipophilic and large molecules, such as biologic agents. Because they have very low surface tension and viscosity, SFAs dispense as a low volume drop (<12 µL) that does not stimulate blinking or reflex tearing. Having both low surface tension and low interface tension, EyeSol® products spread rapidly over the ocular surface and form a flat, transparent monolayer that enables clear vision without blurring. Because of their amphiphilic nature, EyeSol® products also interact with tear film lipids and have been shown to stabilise and restore the tear film (Figure 2).

Being aqueous-free, EyeSol® products avoid hydrolytic and oxidative reactions that can degrade active pharmaceutical ingredients, thus improving product stability. In addition, the aqueous-free EyeSol® technology platform does not support microbial growth, therefore allowing manufacturing of preservative-free formulations in multi-dose containers. It also avoids the tip clogging that can occur with suspensions.

> "Only about 2 million people with DED are being treated due to limited treatment options and a lack of robust non-contact diagnostics."

DRY EYE DISEASE

Dry eye disease (DED) is a very common disorder estimated to be diagnosed in more than 16 million adults in the US alone.[2] However, only about 2 million people with DED are being treated due to limited treatment options and a lack of robust non-contact diagnostics. Tear supplementation with ocular lubricants (artificial tears), with or without lipid-containing agents, remains the cornerstone of DED therapy. Such products primarily address aqueous deficiency in the tear film, and although they effectively improve comfort, they have not demonstrated a curative therapeutic effect.

A large majority of people with DED have evaporative disease, most often caused by Meibomian gland dysfunction (MGD).[3] These patients require both prevention of tear film hyperevaporation and improvement of Meibomian gland function.

TIERED FAMILY OF PRODUCTS

Novaliq's EyeSol®-based pipeline addresses this multifactorial disease across its clinical spectrum (Figure 3, next page). The core focus is DED, for which Novaliq has a tiered family of products that targets the spectrum of this condition's subtypes and severity.

NovaTears®, the first DED product from Novaliq, is a preservative free, surfactant free, non-aqueous, non-blurring formulation that particularly targets evaporative DED. Containing perfluorohexyloctane as its only ingredient, NovaTears® is the first eye lipid layer stabiliser. Marketed in Germany since October 2015, this innovative product has demonstrated clinical efficacy and safety in four clinical trials and has sold more than one million units. It is being launched in other European countries with reimbursement, as well as in Australia and New Zealand.

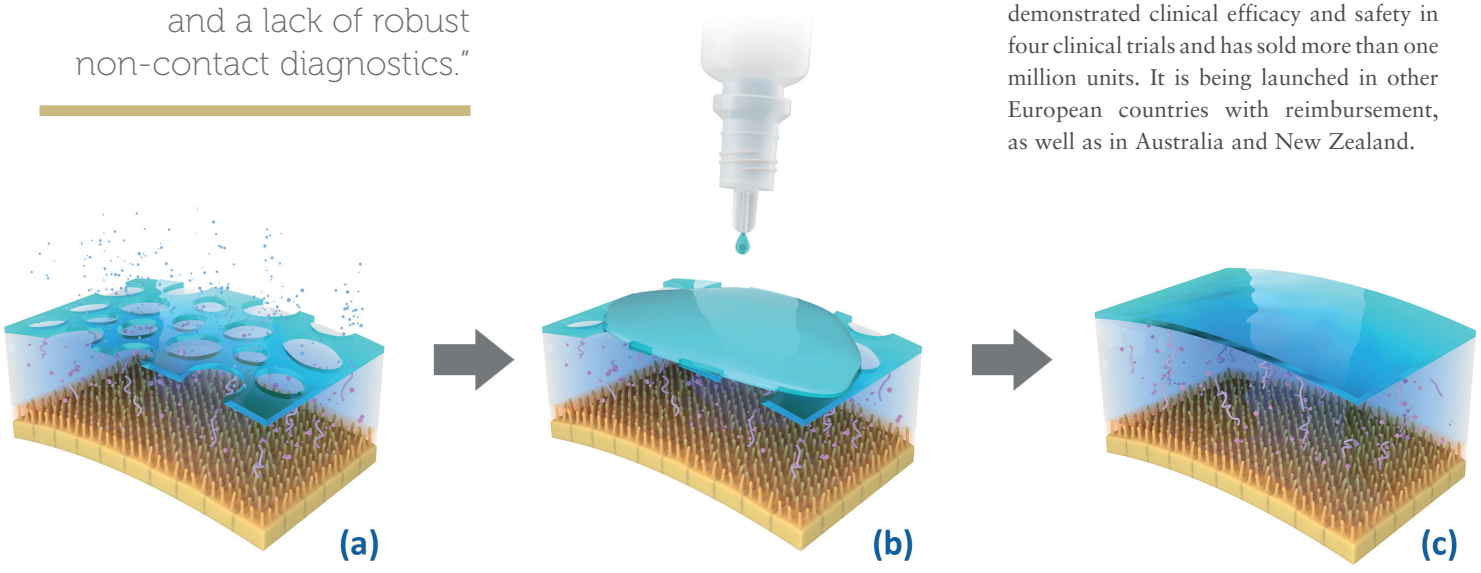

Figure 2: In dry eye, the tear film is unstable and breaks up rapidly (a). A single EyeSol® drop spreads rapidly across the cornea (b), restoring a smooth, uniform tear film layer (c). Image courtesy of Novaliq.

Dry Eye Disease Product Family

Product/ Program	Indication	Region	Disc.	Pre-clinic	Phase I	Phase II	Phase III	Reg.	Market
NovaTears® (NOV01)	Dry Eye, mild – moderate	EU/Med. Dev.							2015
NovaTears® +Omega-3	Dry Eye, mild – moderate	EU/Med. Dev.							2017
CyclASol® (NOV02)	Dry Eye, moderate – severe	US/EU						FPFV, Nov 2017	
NOV03	Dry Eye, evaporative, MGD*	US/CN/JP						IND granted, Nov 2017	
NOV07	Dry Eye, ocular pain, anti-inflamm.	US/EU					Successful pre-IND, Dec 2017		

Glaucoma & Retina Development Programs

Product/ Program	Indication	Region	Disc.	Pre-clinic	Phase I	Phase II	Phase III	Reg.	Market
NOV04	Glaucoma	Global							
NOV05	Retinal Diseases (Topical)	Global							
NOV06	Retinal Diseases (Back of the Eye)	Global							

Figure 3: Novaliq's pipeline has a major focus on dry eye disease, but it is also targeting other ocular diseases with unmet therapeutic needs.

In a six week, prospective, non-interventional clinical trial (NT-001), in patients with mild to moderate hyper-evaporative DED, NovaTears® four times daily was safe and effective for improving DED-related objective signs and subjective symptoms.[4] Statistically significant improvements from baseline were achieved in four of five outcome measures, including a clinically meaningful and dramatic decrease in the Ocular Surface Disease Index (OSDI) score from 55.0 at baseline to 34.3 at six weeks. Mean tear film breakup time (TFBUT) also improved significantly, reflecting increased tear film stability, as did mean scores for Schirmer 1 testing and corneal fluorescein staining (CFS).

A recent clinical trial (NT-004) showed statistically significant increases in total tear film and lipid layer thickness among patients with mild to moderate DED who used NovaTears® for four weeks.[5] These tear film improvements were documented with high-resolution optical coherence tomography (OCT) images acquired in the morning, before patients used their first daily dose.

A third clinical trial (NT-002) was designed to specifically investigate NovaTears® as treatment for DED related mild to moderate MGD.[6] Its results were consistent with those of the earlier study and showed benefits relating to Meibomian gland function. Specifically, patients using NovaTears® four times daily, as directed, for six to eight weeks achieved statistically significant improvements in OSDI, TFBUT and corneal and conjunctival fluorescein staining. In addition, improvements were seen in meibum quality and quantity (Figure 4), and there was a statistically significant increase in the number of expressible Meibomian glands reported.

> "It is known that NovaTears® is able to dissolve lipids and, in an animal model using radiolabelled product, it was shown to distribute into the Meibomian glands after instillation onto the ocular surface."

The improvements related to MGD are explained by the ability of NovaTears® to penetrate into and subsequently liquify the meibum within the Meibomian glands. It is known that NovaTears® is able to dissolve lipids and, in an animal model using radiolabelled product, it was shown to distribute into the Meibomian glands after instillation onto the ocular surface.[5]

Based on these new insights, Novaliq is pursuing regulatory approval of NovaTears® as a prescription medication in the US. SEECASE, a Phase II randomised, controlled, double-masked clinical trial, is now underway (NCT03333057). The study has a planned enrolment of 300 patients, and topline results are expected in the second half of 2018.

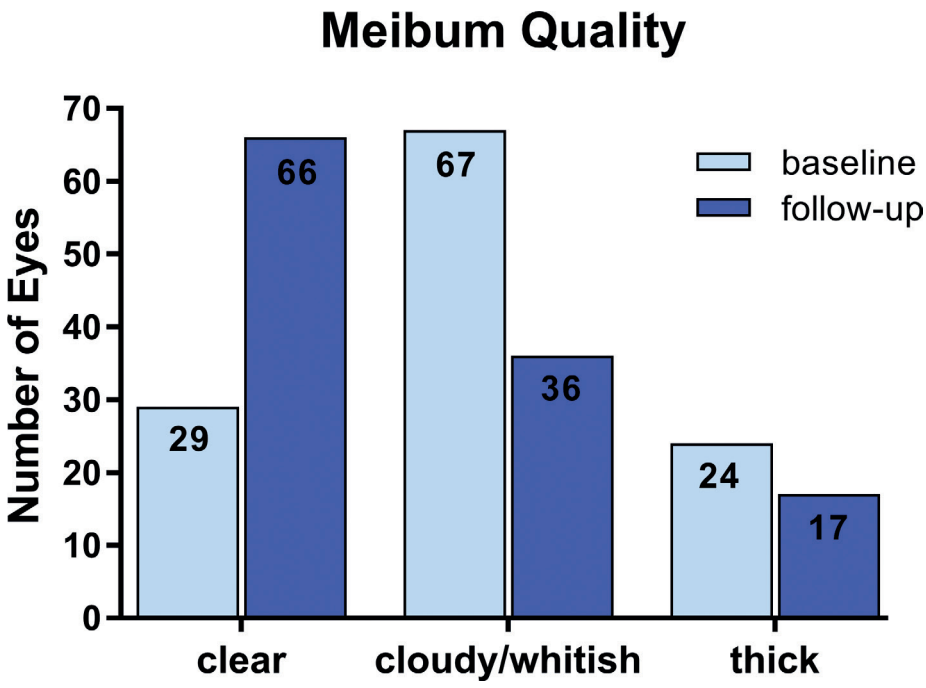

Figure 4: Findings from assessments of meibum quality at baseline and follow-up show improvement in patients with mild to moderate MGD who used NovaTears® for 6 to 8 weeks.

In addition, the NovaTears® line was recently extended when Novaliq received CE Mark for NovaTears®+Omega-3. Omega-3 fatty acids are considered to have a role in DED management because they have anti-inflammatory effects, and there is also evidence from *in vitro* studies that they affect the quality and quantity of intracellular lipids produced by Meibomian gland epithelial cells.[7,8]

For patients with moderate to severe DED with an inflammatory component, Novaliq is developing CyclASol® (0.1% cyclosporine A in perfluorobutylpentane) as a novel treatment for improving both signs and symptoms. Commercially available topical immunomodulatory treatments that target the etiological role of ocular surface inflammation in DED include two cyclosporine oil-based emulsions, Restasis® (cyclosporine A 0.05%) and Ikervis® (cyclosporine A 1 mg/mL), and an ophthalmic solution containing a novel integrin antagonist, Xiidra® (lifitegrast 5%). Based on available results from clinical trials, limitations of these products include delayed onset of benefit and unfavourable tolerability profiles that can affect patient compliance, or even lead to treatment discontinuation, and inconsistent efficacy for improving both signs and symptoms.

In a prospective, exploratory, unpowered, multicentre, vehicle-controlled, double-masked Phase II dose-ranging study, CyclASol® groups demonstrated earlier onset of efficacy compared with Restasis® for improving corneal and conjunctiva staining parameters (Figure 5).[9] With a model based approach, the CyclASol® effect was statistically significant over vehicle (total corneal staining $p<0.1$, central corneal staining $p<0.01$, conjunctival staining $p<0.01$).

In addition, CyclASol® further showed a greater benefit for improving visual function related symptoms (OSDI, OSDI Q6-9 and reading) compared with vehicle. In the model based analysis, the CyclASol® effect for OSDI as symptom parameter even reached statistical significance ($p<0.01$).

The treatment benefit of CyclASol® was seen particularly among patients with more significant ocular surface damage. CyclASol® also showed excellent safety, tolerability and comfort in this study where 98% of patients randomised to its use completed the four month treatment period.

The robust effects of CyclASol® on both the signs and symptoms of DED observed in the Phase II study are being validated in ESSENCE (NCT03292809), a pivotal Phase IIb/III trial. In ESSENCE, patients will be randomised to CyclASol® 0.1% or vehicle twice daily. Planned enrolment is 316 patients. Topline data is expected to be available in the second half of 2018.

Novaliq is also applying its unique EyeSol® drug delivery technology to develop a first-in-class therapeutic to simultaneously treat signs and symptoms in patients with DED associated with ocular pain. NOV07 contains an active pharmaceutical ingredient that targets the cannabinoid receptors in the cornea and has the potential to provide benefit through multiple mechanisms of action.

Cannabinoids are an attractive treatment for DED because they modulate pain and inflammation and have been shown to have neuroprotective activity. The formulation of a topical cannabinoid ophthalmic product, however, has been challenging because these compounds are extremely unstable in aqueous-based formulations.

Preclinical research, using a mouse model, conducted at the University of Cologne, Germany, found that NOV07 caused dose-dependent improvement in corneal staining and tear volume. The company is now working towards translating the evidence from the preclinical investigation to plan a clinical study.

PIPELINE BEYOND DED

Novaliq's pipeline is not limited to DED. NOV05 formulates tacrolimus, a highly potent anti-inflammatory agent and immunomodulator, in EyeSol®, and is being developed as a topical treatment for non-infectious uveitis of the anterior segment. Tacrolimus is poorly water soluble and a tacrolimus ophthalmic suspension is only commercially available in Japan, even then only indicated for the treatment of vernal keratoconjunctivitis. EyeSol® technology may enable delivery of therapeutic concentrations of tacrolimus into the anterior eye segment and fill an unmet therapeutic need for non-infectious uveitis.

Current local treatment for this inflammatory disorder involves corticosteroids that are associated with risks for intra-ocular pressure elevation, and cataract. NOV05 holds promise for providing a long-term effective topical therapy to avoid recurrences of the disease with a more favourable safety profile than existing options.

CONCLUSION

Available evidence supports the idea that aqueous-free EyeSol® technology has

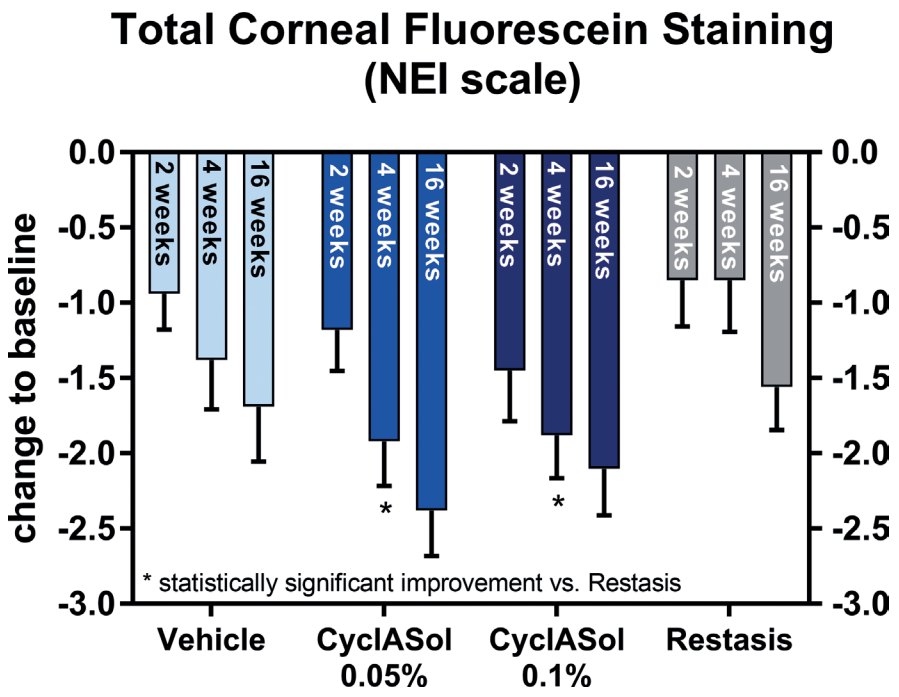

Figure 5: Improvement in total corneal fluorescein staining score was significantly greater after 4 weeks in eyes treated with CyclASol® 0.05% and 0.1% compared with active controls using Restasis®.

> "EyeSol® is distinguished from aqueous-based technologies by a host of physical characteristics that translate into enhanced stability, bioavailability, efficacy and tolerability."

great potential for overcoming the limitations of topical ophthalmic drug therapy and providing innovative products that are safer, better tolerated and more effective than existing gold standards. Backed by the leadership and guidance of a management team that brings tens of decades of experience in all areas of pharmaceutical development and a scientific advisory board comprised of renowned experts in both basic science and clinical ophthalmology, we are confident that Novaliq will be successful as it moves forward with its mission to transform topical therapeutics into highly effective products for both the front and back of the eye.

ABOUT THE COMPANY

Founded in 2007, Novaliq GmbH is a Heidelberg-based speciality pharmaceutical company focused on ophthalmology. Its mission is to transform poorly soluble drugs into effective ocular therapeutics for both the front and the back of the eye. Novaliq's proprietary EyeSol® technology enhances the topical bioavailability, stability and safety of traditionally insoluble or unstable drugs improving the delivery, efficacy and convenience of treatments for ocular surface diseases, including dry eye through preservative-free and multi-dose formulations. Novaliq has developed a tiered and long-term sustainable dry eye family of differentiated products that addresses the different needs of dry eye patients. The company's most advanced products are NovaTears® with CE-approval marketed under the brand name EvoTears® in Europe, and NovaTears®+Omega-3, which was just recently CE-approved in Europe. CyclASol® a second-generation prescription drug is currently in pivotal phase of clinical development.

REFERENCES

1. *Lallemand F et al "Successfully improving ocular drug delivery using the cationic nanoemulsion, Novasorb". J Drug Deliv, 2012, epub.*
2. *Farrand KF et al "Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older". Am J Ophthalmol, 2017, Vol 182, pp 90-98.*
3. *Craig JP et al, "TFOS DEWS II Definition and Classification Report". Ocul Surf, 2017 Vol 15, pp 276-283.*
4. *Steven P et al, "Semifluorinated alkane eye drops for treatment of dry eye disease – a prospective, multicenter, noninterventional study". J Ocul Pharmacol Ther, 2015, Vol 31, pp 498-503.*
5. *Novaliq data on file.*
6. *Steven P et al, "Semifluorinated alkane eye drops for treatment of dry eye disease due to meibomian gland disease". J Ocul Pharmacol Ther, 2017, Vol 33, pp 678-685.*
7. *Jones L et al, "TFOS DEWS II Management and Therapy Report". Ocul Surf, 2017, Vol 15, pp 575-628.*
8. *Liu Y, Kam WR, Sullivan DA, "Influence of omega 3 and 6 fatty acids on human Meibomian gland epithelial cells". Cornea, 2016 Vol 35, pp 1122-1126.*
9. *Torkildsen GL, Moreira HR, Lonsdale JD, "A clinical phase 2 study to assess safety, efficacy, and tolerability of CyclASol for the treatment of dry eye disease". American Academy of Ophthalmology, 2017, poster.*

ABOUT THE AUTHOR

Christian Roesky is chief executive officer of Novaliq GmbH. Dr Roesky holds a PhD in Chemistry, has been involved in eye care for more than 15 years and has extensive operational experience at multiple international pharmaceutical companies. Previously, Dr Roesky has served as general manager of Bausch + Lomb GmbH / Dr Mann GmbH in Berlin; managing director of the Diagnostics Division and general manager and speaker of the Country Management Board of Abbott GmbH & Co KG in Wiesbaden; and general manager of Alcon Germany & Austria (Novartis).