NOVALIQ

Transforming Ocular Therapeutics

BREAKING THE VICIOUS CIRCLE OF DRY EYE DISEASE

In this article, Christian Roesky, PhD, Chief Executive Officer, Novaliq, discusses the underserved condition of dry eye disease, and presents two products in Novaliq's pipeline, based on the company's water-free, preservative-free EyeSol® technology, for the treatment of different types of DED.

DRY EYE DISEASE IS OFTEN UNDERESTIMATED

Dry eye disease (DED) is a chronic disease, negatively impacting a patient's quality of life in a manner comparable with other chronic diseases.[1] Symptoms of DED, such as feeling of dryness, burning, foreign body sensation or pain, are often quite debilitating. More recently, visual function related symptoms, such as fluctuating vision with blinking, blurred vision and difficulty with reading despite normal visual acuity, are coming into focus as an important and underestimated aspect of the disease.[2] In addition, adverse effects on mental health, such as depression and anxiety, have been observed.[3] DED is a serious disorder that, if left untreated or undertreated, progressively damages the ocular surface and may lead to vision loss due to corneal complications.[4]

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As many as 5–35% of patients visiting an ophthalmologist report symptoms of DED, making it one of the most common conditions seen by ophthalmic specialists.[5] In the US, more than 16 million patients are diagnosed with DED,[6] however approximately only 10% are receiving treatment. In the EU the ratio is similar. This significant gap between diagnosed and appropriately treated patients indicates that new DED therapies are needed.

Treatment of DED has traditionally started with artificial tears and topical lubricants. For more moderate to severe cases topical anti-inflammatory medications, including short 2–4 week courses of corticosteroids and longer-term therapies of cyclosporine A and lifitegrast, are used.[7] Tear film instability can induce ocular surface stress and damage, also potentially initiating an inflammatory cascade that generates innate and adaptive immune responses. These immuno-inflammatory responses lead to further ocular surface damage and the development of a self-perpetuating inflammatory cycle.[8]

Current prescription drugs have seen limited market penetration for two reasons:

- Efficacy of current DED treatments is limited while tolerability is low
- Patients often fail to get a satisfactory response.

As DED is a multifactorial disease, identification of the underlying root cause or disease pathogenesis for a specific patient provides valuable mechanistic guidance to develop targeted and effective treatments addressing different categories.

The International Dry Eye Workshop classifies DED into two major categories:[9]

- Aqueous tear deficient (keratoconjunctivitis sicca)
- Evaporative (=tear-lipid deficient).

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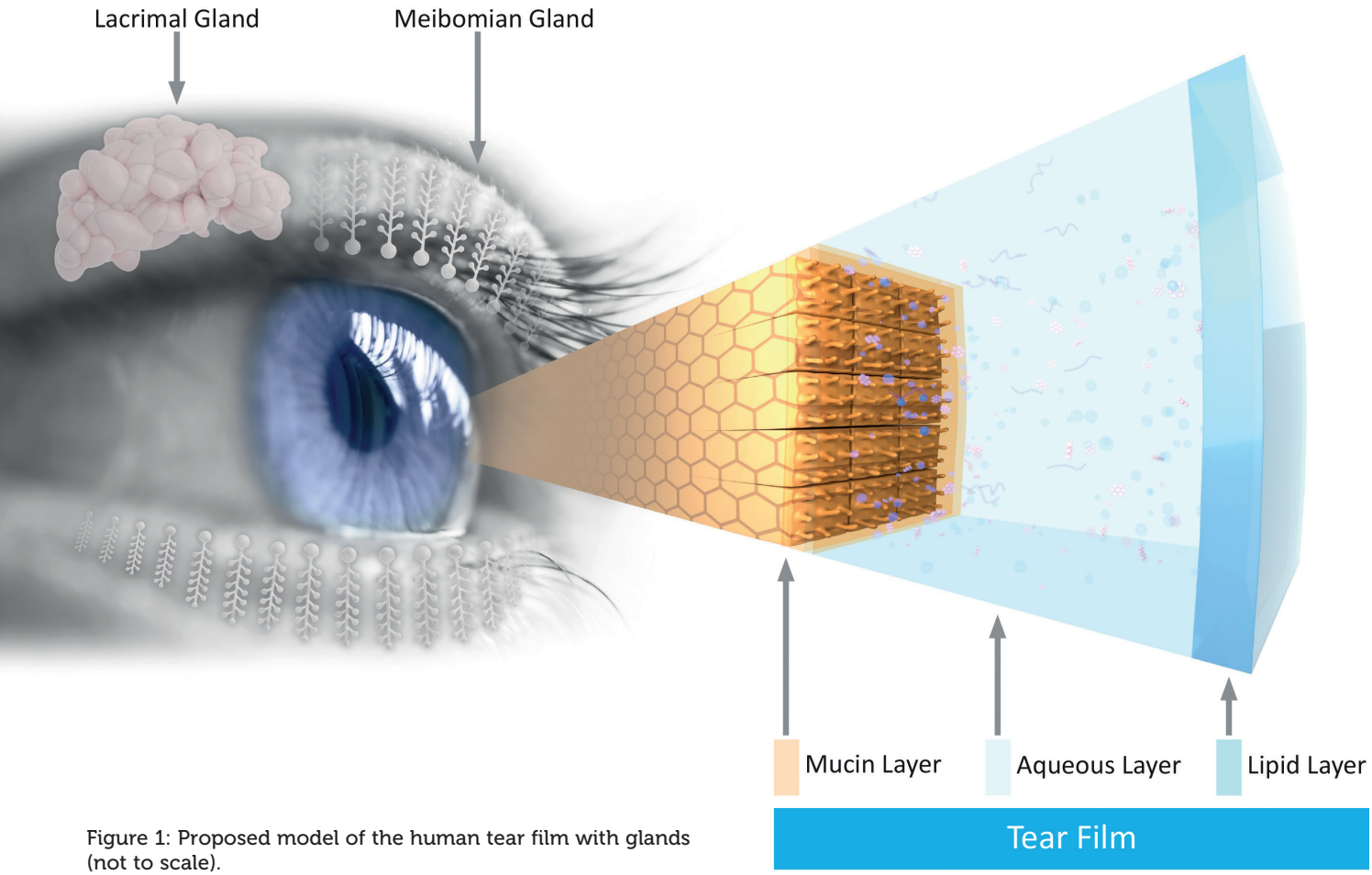

Figure 1: Proposed model of the human tear film with glands (not to scale).

> "Treatment options for patients with evaporative DED are limited, as tear supplementation or anti-inflammatory medications often do not address the underlying root cause of excessive evaporation."

In aqueous-deficient DED, reduced tear production leads to tear film instability. Around 10% of patients with dry eye have a solely aqueous-deficient disorder, and up to 40% have a predominantly aqueous deficiency. In evaporative DED an altered lipid layer leads to tear film instability. The evaporative form of dry eye is more prevalent, 60–90% of patients have predominantly evaporative DED.[10] Meibomian gland dysfunction (MGD) is the leading cause of evaporative DED. Meibum glands play an important role as the main source of lipids for the human tear film. The meibum spreads onto the tear film, promotes its stability and prevents its evaporation.[11,12]

Treatment options for patients with evaporative DED are limited, as tear supplementation or anti-inflammatory medications often do not address the underlying root cause of excessive evaporation. Patients suffering from DED with imbalanced tear conditions due to significant MGD represent a large population with high unmet medical needs in today's clinical care.

This mechanistic understanding of the tear film layers and gland interaction (Figure 1), together with new treatment strategies has led to the modified "vicious circle of DED" (Figure 2), highlighting the pathology and key drivers of the disease.[13]

OVERCOMING THE LIMITATIONS OF WATER-BASED EYEDROPS

Recently, data has emerged from two clinical trials of novel topical drugs utilising a non-aqueous, preservative-free technology

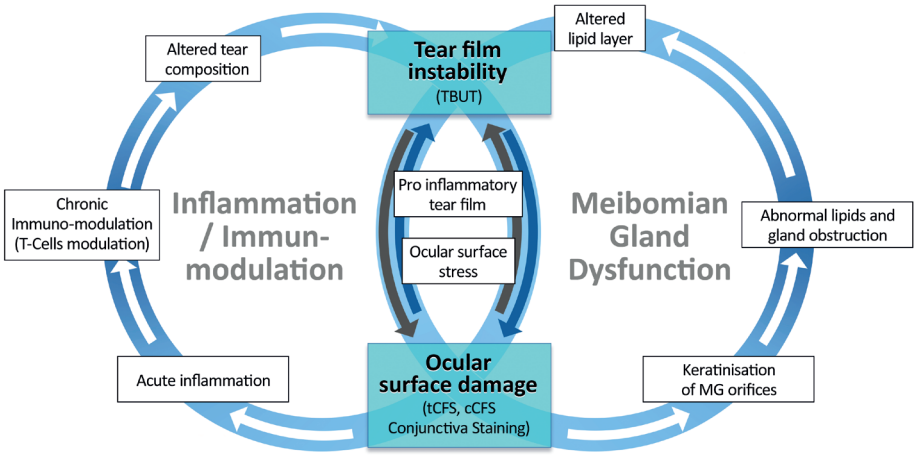

Figure 2: The modified vicious circle of dry eye disease.

that may offer new and promising treatment approaches to improve the quality of life for DED patients in both segments of the disease.

Novaliq is focusing on the development of first- and best-in-class ocular therapeutics based on EyeSol®. As the world's first water-free DED treatment technology, EyeSol® overcomes the traditional limitations of water-based formulations. EyeSol® is a novel odourless and colourless liquid with low surface tension and the same refractive index as water. Due to its unique physicochemical properties, EyeSol® spreads immediately over the ocular surface after instillation. Treatments use a small drop size of 10 µL that does not overfill the eye or initiate a blink reflex, which are common issues with water-based eyedrops. Due to EyeSol's water-free nature, EyeSol® products are preservative-free and surfactant-free, which is believed to greatly improve their tolerability compared with water-based drugs. The technology has been proven to be safe and well accepted, with one product already on the market in Europe and Australia.

Novaliq's late-staged products and pipeline in DED have the potential to break the vicious circle and redefine how DED is treated.

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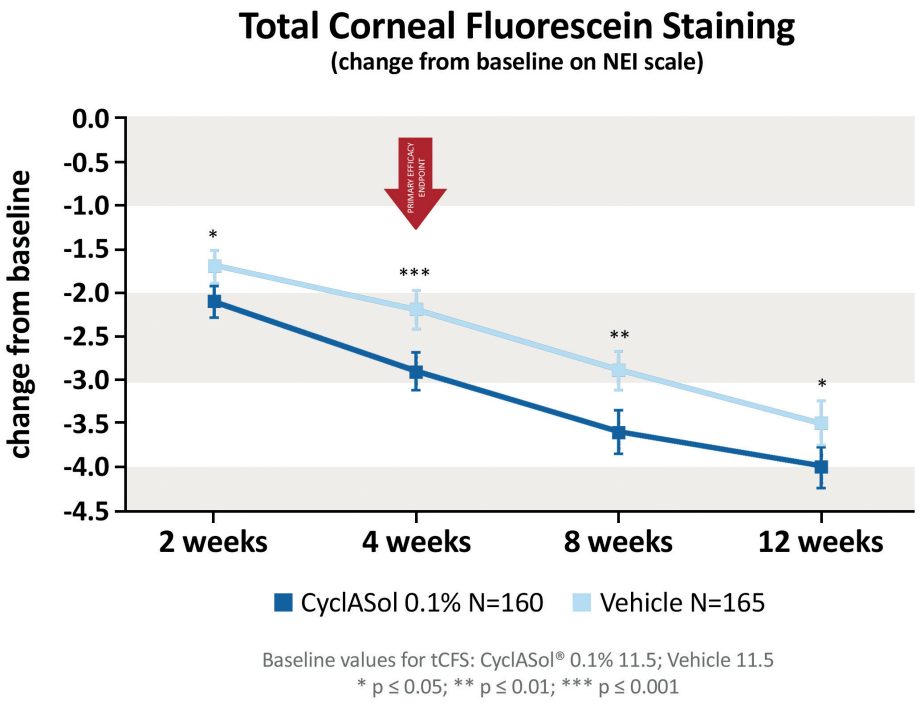

Figure 3: Primary efficacy endpoint of CyclASol® "ESSENCE" trial.

CYCLASOL® – AQUEOUS-DEFICIENT DED

CyclASol® 0.1% is a clear ophthalmic solution of 0.1% cyclosporine A, an anti-inflammatory and immunomodulating compound, developed in EyeSol® for the treatment of predominantly aqueous-deficient DED. Advantages over other cyclosporine-containing ophthalmic treatments are CyclASol's improved efficacy and a fast onset of effect, combined with an excellent tolerability profile. The ESSENCE Phase IIb/III clinical trial, which comprised 328 patients across nine clinical sites in the US, was designed to confirm the results of the CYS-002 proof-of-concept trial, in which CyclASol® demonstrated beneficial effects versus its vehicle and the active control, Allergan's Restasis™, with excellent safety and tolerability.[14]

ESSENCE evaluated the efficacy, safety and tolerability of topical CyclASol® 0.1% for the treatment of patients with aqueous-deficient DED, with its primary efficacy endpoint at four weeks and continued dosing for efficacy and safety evaluations over a period of three months (Figure 3).

The ESSENCE trial met its primary efficacy endpoint, improvement of total corneal fluorescein staining over vehicle at four weeks, with high statistical significance ($p = 0.0002$). The effect began as early as two weeks after start of treatment and was maintained for the full duration of the study. Consistent with the previous clinical study, the central area of the cornea benefitted most. The clinical significance of these outcomes is further shown by a high responder rate (>50%) on both corneal (at four weeks) and conjunctival (at three months) staining.

The second primary endpoint Ocular Surface Disease Index® (OSDI®) assessment indicated that all patients benefitted from the treatment. Secondary endpoints on DED symptoms, as measured by the visual analogue scale (VAS), reached statistical significance over vehicle at four weeks. The study further confirmed the excellent safety and tolerability profile of CyclASol®. Adverse events occurred as a reaction at the treatment instillation site in 2.5% of the CyclASol®-treated group.

Novaliq believes that CyclASol® 0.1% unfolds the full potential of cyclosporine A for the first time in the treatment of DED and demonstrates the superior benefits of its non-aqueous, preservative-free, multidose formulation, allowing clinicians to treat more of their patients suffering from predominantly aqueous-deficient DED.[15]

NOV03 – EVAPORATIVE DED ASSOCIATED WITH MGD

NOV03 (100% 1-perfluorohexyloctane) is a preservative-free, multidose ophthalmic solution and the first drug developed to treat evaporative DED associated with MGD. NOV03 uniquely treats DED associated with MGD based on a novel mode of action that balances the tear condition. Due to its low surface tension, NOV03 rapidly spreads across the ocular surface forming a layer at the tear film-air interface that prevents evaporation of the aqueous phase. Furthermore, it has the ability to penetrate meibomian glands and potentially dissolve thickened meibum, thereby improving meibomian gland function.

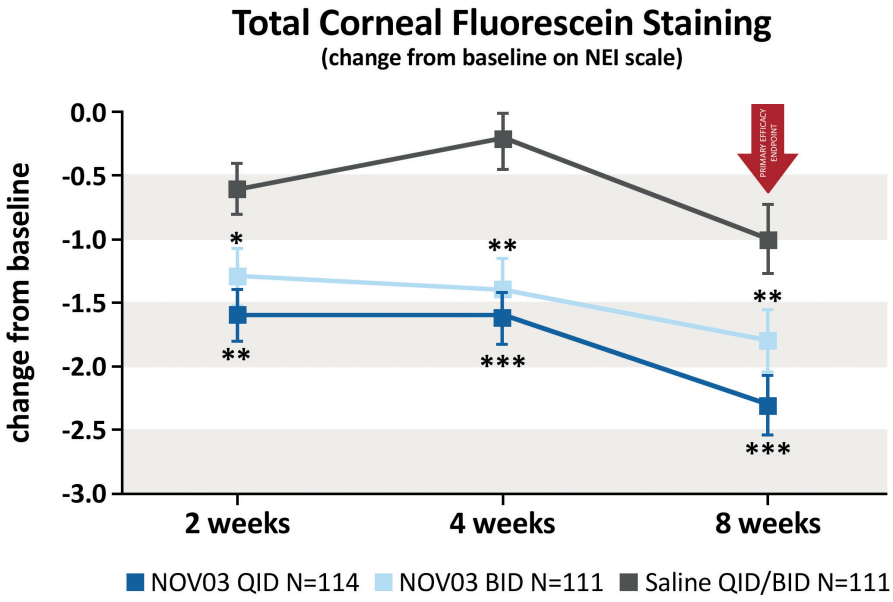

Figure 4: Primary efficacy endpoint of NOV03 in "SEECASE" trial.

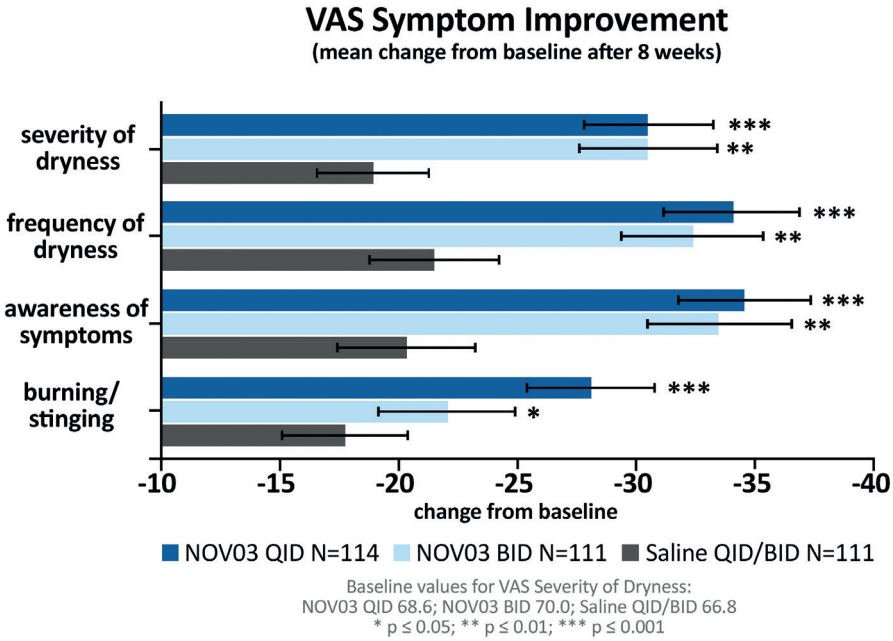

Figure 5: Symptom improvement by NOV03 in "SEECASE" trial.

Novaliq conducted the SEECASE Phase II clinical trial, which comprised 336 patients across 10 clinical sites in the US. SEECASE was a multicentre, randomised, double-masked, saline-controlled clinical trial. The trial was designed to evaluate the effects of NOV03 according to two different dosing regimens on signs and symptoms of DED. SEECASE evaluated its primary efficacy at eight weeks.

The SEECASE trial met its pre-specified primary endpoint, improvement of total corneal fluorescein staining over control at eight weeks, with high statistical significance for both dosing regimens, four times daily (qid) and twice daily (bid) ($p<0.001$ and $p=0.009$, respectively) (Figure 4). The effect started as early as two weeks after start of treatment and was maintained over the full duration of the trial for both treatment regimens. In addition, NOV03 showed pronounced, statistically significant improvement in various symptoms over control (Figure 5). In particular, the magnitude of effect on symptoms was impressive: patients reported on average a 40–50% improvement over their baseline depending on the parameter examined at eight weeks. Thus, this first-in-class treatment shows great promise for patients with evaporative DED associated with MGD.[15]

For both drugs, final clinical trials will start in 2019, leading to NDA filings in 2021.

CONCLUSION

DED is a chronic, multifactorial disease that impacts the functional vision and quality of life of patients. Due to different underlying root causes and pathogeneses, targeted therapies for the different disease segments are required to improve patient outcomes.

- Predominantly evaporative DED associated with MGD is regarded as the primary cause of DED, but therapeutic options for its treatment are limited. NOV03 is a promising treatment option specifically targeting and treating this form of DED.
- CyclASol® addresses predominately aqueous-deficient DED for patients requiring an anti-inflammatory treatment.

Targeted treatment options like CyclASol® and NOV03 based on a non-aqueous, preservative-free technology give hope that new drugs can help provide more patients with a satisfying treatment solution, improving and preserving their vision and quality of life.

ABOUT THE COMPANY

Novaliq is a pharmaceutical company focusing on the development and commercialisation of first- and best-in-class ocular therapeutics based on EyeSol®, the world's first water-free technology for ophthalmology products. With an initial focus on dry eye disease (DED), Novaliq offers an industry-leading portfolio addressing the unmet medical needs of millions of patients with DED. Novaliq's lead assets in late-stage clinical development are:

- CyclASol®, an anti-inflammatory and immunomodulating drug for the treatment of DED with a demonstrated early onset of action and excellent tolerability.
- NOV03, the first drug addressing evaporative DED associated with meibomian gland dysfunction (MGD).

NovaTears® water-free eyedrops for DED are CE marked and are commercialised in Australia/New Zealand by AFT Pharmaceuticals and in Europe as EvoTears® by Ursapharm.

Novaliq is headquartered in Heidelberg, Germany and has an office in Cambridge, MA, US. The long-term shareholder is dievini Hopp BioTech Holding (Walldorf, Germany), an active investor in life and health sciences companies.

REFERENCES

1. *Schiffman RM et al, "Utility assessment among patients with dry eye disease". Ophthalmology, 2003, Vol 110(7), pp 412–419.*
2. *Koh S, "Mechanisms of Visual Disturbance in Dry Eye". Cornea, 2016, Vol 35(Suppl 1), pp S83–S88.*
3. *Le Q et al, "Impact of Dry Eye Syndrome on Vision-Related Quality of Life in a Non-Clinic-Based General Population". BMC Ophthalmol, 2012, Vol 12(22).*
4. *Lemp MA, "Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes". CLAO J, 1995, Vol 21(4), pp 221–232.*
5. *McCarty CA et al, "The epidemiology of dry eye in Melbourne, Australia". Ophthalmology, 1998, Vol 105(6), pp 1114–1119.*
6. *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.*
7. *Foulks GN et al, "Clinical guidelines for management of dry eye associated with Sjögren disease". Ocul Surf, 2015, Vol 13(2), pp 118–132.*
8. *Stevenson W, Chauhan SK, Dana R, "Dry eye disease: an immune-mediated ocular surface disorder". Arch Ophthalmol, 2012, Vol 130(1), pp 90–100.*
9. *Sharma A, Hindman HB, "Aging: A Predisposition to Dry Eyes". J Ophthalmol, 2014, Vol 2014.*
10. *Lemp MA et al, "Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study". Cornea, 2012, Vol 31(5), pp 472–478.*
11. *Nichols KK et al, "The International Workshop on Meibomian Gland Dysfunction: Executive Summary". Invest Ophthalmol Vis Sci, 2011, Vol 52(4), pp 1922–1929.*
12. *Behrens A et al, "Dysfunctional tear syndrome: a Delphi approach to treatment recommendations". Cornea 2006, Vol 25(8), pp 900–907.*
13. *Baudouin C et al, "Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction". Br J Ophthalmol, Vol 100(3), pp 300–306.*
14. *Torkildsen GL et al, "A Clinical Phase 2 Study to Assess Safety, Efficacy, and Tolerability of CyclASol® for Treatment of DryEye Disease". Poster presented at AAO 2017.*
15. *Novaliq data on file.*

ABOUT THE AUTHOR

Christian Roesky is Chief Executive Officer of Novaliq. He holds a PhD in chemistry and has been involved in eyecare for more than 15 years. Dr Roesky has extensive operational experience at multiple international pharmaceutical companies, having worked in the US, Spain and Switzerland. He has served as General Manager for Bausch + Lomb GmbH; as Commercial Director, Central Europe of Abbott's Diagnostics Division; as General Manager and Speaker of the German Country Management Board of Abbott in Wiesbaden; and as General Manager of Alcon Germany & Austria (Novartis).