Semifluorinated Alkane Eye Drops for Treatment of Dry Eye Disease—A Prospective, Multicenter Noninterventional Study

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Abstract

Purpose: Evaporation of the tear film is heavily discussed as one core reason for dry eye disease (DED). Subsequently, new artificial tear products are developed that specifically target this pathomechanism. Perfluorohexyloctane (F6H8, NovaTears[®]) from the family of semifluorinated alkanes is a novel substance that has been approved as a medical device, as a nonblurring wetting agent for the ocular surface.

Methods: Thirty patients with hyperevaporative dry eye received F6H8 during a prospective, multicenter, observational 6-week study. Patients were advised to apply 1 drop 4 times daily in both eyes. Parameters assessed included best corrected visual acuity, intraocular pressure, Schirmer I test, tear fluid, tear film breakup time (TFBUT), corneal staining, meibum secretion, and Ocular Surface Disease Index (OSDI[®]).

Results: From the 30 patients recruited, 25 completed the trial per protocol. Four patients discontinued F6H8 and 1 patient did not present for follow-up. F6H8 treatment led to significant reduction of corneal staining and significant increase of Schirmer I and TFBUT. In addition, OSDI score dropped significantly from a mean of 55 (± 23.0) to 34 (± 22.4). Visual acuity and ocular pressure did not change.

Conclusions: This prospective observational study shows significant beneficial effects in patients suffering from evaporative DED, using F6H8 in all the relevant parameters tested. The decrease of the OSDI by a mean of 21 points was particularly remarkable and clearly exceeds minimal, clinically important differences for mild or moderate and severe disease. Overall, F6H8 (NovaTears) seems to be safe and effective in treating mild to moderate hyperevaporative DED.

Introduction

DRY EYE DISEASE (DED) belongs to the most common pathological conditions in ophthalmology with tens of millions of individuals affected worldwide.¹ Extensive clinical and basic scientific studies have led to the concept of dysfunctional tear syndrome² that proposes complex pathomechanisms affecting not only the cornea and the lacrimal gland but also the conjunctiva, eyelids, lacrimal apparatus, blood vessels, lymphatics, and nerves of the ocular surface. It is well established that 3 major pathomechanisms are the key players in

this disease: (1) evaporation of the tear film, (2) hyperosmolarity, and (3) inflammation. These key players form a vicious circle³ that drives disease progression, if not treated adequately. Currently, in particular, evaporation and meibomian gland dysfunction are heavily discussed as the core reasons for DED,⁴ leading to new therapeutic approaches supplementing the generally accepted stepwise treatment regimen.

These novel approaches include topically applied substances to substitute lipid components that are lacking or malsecreted by dysfunctional meibomian glands,^{5,6} supplement of Omega-3 fatty acids,^{7–9} or the direct treatment of

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meibomian glands by mechanical force (lid margin hygiene, debridement, etc.^{10–12}).

The substances used for supplementing the lipid layer include different oils such as castor oil and mineral oil or other stabilizing compounds such as polyethylenglycol, which have been demonstrated to stabilize the tear film in clinical trials.^{13–16} Nevertheless, intolerance against the stabilizing agent or contained preservatives may lead to inflammation, deterioration of tear film stability, and derogation of the therapy.^{17,18}

Recently, the novel substance perfluorohexyloctane (F6H8, NovaTears®), from the family of semifluorinated alkanes (SFAs¹⁹), has been introduced as a nonblurring wetting agent for the ocular surface that does not need to be combined with a preservative, since it is a completely nonaqueous liquid, and therefore, microbial growth is not possible. At the same time, F6H8 demonstrates significant spreading abilities that reduce shearing forces between surfaces and enables to dissolve lipids due to its amphiphilic nature without the necessity to form water–oil suspensions. After successful preclinical testing, NovaTears underwent a conformity assessment procedure according to the European Medical Device Directive and was CE marked in July 2013. The objective of this observational study, in 30 patients with DED, was to confirm that F6H8 is able to stabilize the tear film and relieve symptoms. Moreover, local tolerability and safety of F6H8 was assessed.

Methods

Study design

This was a prospective, multicenter, observational 6-week study of patients with DED receiving F6H8 in routine clinical care at 2 centers in Germany, University of Cologne or the Augenarztpraxis Heidelberg. The study was reviewed and approved by the ethics committees of the University of Cologne (13-339) and the Landesärztekammer Baden-Württemberg (F-2013-078) adhered to the tenets of the Declaration of Helsinki and was registered at clinicaltrials.gov (NCT02111928).

After informed consent was obtained, patients were trained on how to use F6H8 according to the instructions for use. Patients were advised to apply 1 drop 4 times daily in both eyes and report any adverse event (AE) immediately. Patients returned after 6 (window: 5–7) weeks for follow-up. Data were collected between December 2013 and April 2014.

Patients and examination parameters

Thirty patients with mild to moderate evaporative DED were selected from daily dry eye outpatient clinics of the 2 centers according to the inclusion criteria demonstrated in Table 1.

Parameters that were assessed both at the baseline and at the follow-up visit included best corrected visual acuity (BCVA), intraocular pressure, Schirmer I test, tear fluid osmolarity (using Tearlab Osmometer), tear film breakup time (TFBUT), corneal staining, and meibum secretion. Corneal staining was graded according to the Oxford Grading Scheme,²⁰ and meibum secretion was examined by compressing the lower and upper eyelid using a Q-tip and differentiating meibum quality (clear, whitish, thick, or none). In addition, each patient filled in a questionnaire

TABLE 1. INCLUSION CRITERIA

Criteria	Details
Gender	Male and female
Tear film breakup time	<10 s
Best corrected visual acuity	>0.4
Corneal Fluorescein Staining (Oxford Grading Scheme)	≤2
Schirmer I test	<15 mm
OSDI®	>20

OSDI, Ocular Surface Disease Index.

(Ocular Surface Disease Index, OSDI^{®21}), and physicians monitored AEs. Patients were also asked for usability and subjective treatment satisfaction. Furthermore, patients were asked to report AEs throughout the study; any serious deterioration in health had to be reported immediately. All patients reporting problems were called and interviewed by the physicians and were offered an immediate visit at the study site.

Statistical analysis and study analysis populations

Two analysis populations were defined:

- Full analysis set: All patients who completed the 5–7-week observation period and returned to the follow-up visit. As 1 patient was lost to follow-up for unknown reasons, data for 29 patients are included in this dataset.
- Compliant patient set: All patients who applied NovaTears constantly throughout the study, that is, patients who applied F6H8 almost daily, daily as per the recommended dose, or daily, but less than the recommended dose, based on the assessment at the follow-up visit. As 4 patients discontinued the use of F6H8 (for details, see the Discussion section), this dataset includes 25 patients.

Statistical analysis of visual acuity, intraocular pressure, Schirmer I test, TFBUT, osmolarity, OSDI, and corneal staining was performed retrospectively to identify statistically significant differences between the baseline and follow-up. For all parameters, except for corneal staining, a paired 2-sided *t*-test, testing the null hypothesis that the mean change from the baseline equals zero, was used. The change in corneal staining was analyzed using the Wilcoxon signed-rank test for location shifts between the baseline and follow-up. Statistical analysis was performed using SAS[®] (version 9.3 for Microsoft Windows). A *P* value of <0.05 was used to declare significance.

A retrospective power calculation revealed that with a standard deviation of 13 this study provided an 80% power to detect differences of at least 7.3 points on the OSDI score, if at least 29 patients were enrolled.²²

TABLE 2. SUMMARY OF DEMOGRAPHIC DATA (FAS, *N* = 29)

Age (years, mean ± SD)	Body weight (kg, mean ± SD)	Height (cm, mean ± SD)
63.4 ± 16.5	69.1 ± 11.8	169.3 ± 7.3

FAS, full analysis set; SD, standard deviation.

TABLE 3. SUMMARY OF VISUAL ACUITY ANALYSIS AND INTRAOCULAR PRESSURE (CPS, $N=25$)

Parameter	Baseline	Follow-up	Data	P-values
Visual acuity	Right eye: 0.8 (0.5–1.0) Left eye: 0.8 (0.5–1.3)	Right eye: 1.0 (0.4–1.1) Left eye: 0.8 (0.5–1.0)	Median (minimum to maximum)	OD: $P=0.060$ OS: $P=0.85$
Intraocular pressure (mmHg)	Right eye: 14.7 ± 2.8 Left eye: 14.9 ± 2.8	Right eye: 14.4 ± 3.5 Left eye: 14.7 ± 3.5	Mean $\pm$ SD	OD: $P=0.45$ OS: $P=0.64$
Osmolarity (mOsm)	Right eye: 317.0 ± 13.5 Left eye: 313.6 ± 15.0	Right eye: 307.2 ± 19.0 Left eye: 316.1 ± 17.1	Mean $\pm$ SD	OD: $P=0.024$ OS: $P=0.50$

CPS, compliant patient set; OD, oculus dexter (right eye); OS, oculus sinister (left eye).

Results

Demographic data

In total, 30 patients were included in the study with 15 patients per site. The according demographic data are presented in Table 2. More female patients were recruited than males (25 females, 5 males). One female patient did not complete the study (lost to follow-up for unknown reasons, data not included in this article).

Clinical findings

Visual acuity, intraocular pressure, and tear osmolarity. As can be seen in Table 3, BCVA and intraocular pressure did not change over the study period. Tear osmolarity decreased significantly in the right, but not in the left, eyes during the observation period.

Schirmer I and TFBUT. Tear secretion and tear film stability improved significantly over the study period, as can be seen in the increase in Schirmer I and the TFBUT. Retrospective statistical analysis is strengthening this observation, as the difference at the baseline and follow-up is highly significant for both parameters (Table 4).

Subjective dry eye symptom questionnaire (OSDI). The mean OSDI decreased significantly from 55 to 34 after the use of F6H8 over a 5–7-week period, indicating a decrease in subjective symptom severity (Table 5).

Corneal staining. Corneal staining decreased significantly after 5–7 weeks of treatment, as can be seen in the shift of the numbers of patients diagnosed with Grade 1 or 2 at the baseline and toward Grade 0 at follow-up [Table 6, Wilcoxon

signed rank test: $P=0.0013$ (right eyes) and $P=0.0041$ (left eyes); $n=24$].

Symptom assessment physician. Patients were asked by the physician whether they currently suffer from typical dry eye symptoms, both at the baseline and at the follow-up visit. As can be seen in the Table 7, a lower number of DED-associated symptoms were reported after 5–7 weeks of treatment.

Meibum secretion analysis. Patient meibum was descriptively examined at both the baseline and the follow-up visit. According to the data obtained, meibum quality improved in some cases. In 7 cases, no expressible meibum was reported at the end of the study period (Table 8).

Usability and overall satisfaction

Patients' opinion about the usability of F6H8 and treatment satisfaction was obtained by a questionnaire at the end of the study (follow-up visit). The majority of patients' responses were very positive. The responses of the full population ($n=29$, including the 4 patients who discontinued the use of F6H8 during the study) are shown in Table 9.

Adverse events

A total of 5 AEs were reported during the course of this study; none of them was classified as serious adverse device effects (=incident according to applicable legislation) (Table 10). Relapse of rheumatoid arthritis and seasonal allergy was either unlikely related or not related to the use of F6H8. Nevertheless, the patient who experienced the relapse of rheumatoid arthritis stopped the treatment after 10 days.

Three patients showed signs of hypersensitivity to F6H8, which was mild to moderate in intensity and was assessed as probably or definitively related to F6H8. All 3 patients stopped the treatment due to this AE and fully recovered thereafter.

Discussion

Concepts of treating DED are complex and often fail either due to the lack of objective or subjective symptom

TABLE 4. SUMMARY OF SCHIRMER I AND TFBUT (CPS, $N=25$)

Parameter	Baseline	Follow-up	Data	P-values
Schirmer I (mm/5 min)	Right eye: 10.5 ± 4.1 Left eye: 10.2 ± 4.2	Right eye: 16.6 ± 9.8 Left eye: 15.9 ± 9.7	Mean $\pm$ SD	OD: $P=0.0040$ OS: $P=0.0013$
TFBUT (s)	Right eye: 6.0 ± 2.5 Left eye: 5.8 ± 2.6	Right eye: 8.8 ± 4.9 Left eye: 9.6 ± 5.9	Mean $\pm$ SD	OD: $P=0.0026$ OS: $P=0.0006$

TFBUT, tear film breakup time.

TABLE 5. SUMMARY OF OSDI (CPS, $N=25$)

Parameter	Baseline	Follow-up	Data	P-values
OSDI	55.0 ± 23.0	34.3 ± 22.4	Mean $\pm$ SD	$P<0.0001$

TABLE 6. SUMMARY OF CORNEAL STAINING (CPS, $N=25$)

Corneal staining	Baseline			Follow-up ^a			
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2	
Right eye (n)	6 (1)	14	4	21	2	1	OS: $P=0.0013$
Left eye (n)	5 (1)	15	4	16	8	0	OD: $P=0.0041$

^aInformation for 1 patient is not provided for follow-up and is shown in brackets at baseline.

improvement or intolerability to tear substitutes. Novel artificial tears are designed to target both (1) underlying pathomechanisms such as hyperevaporation due to meibomian gland dysfunction and (2) decrease side effects such as intolerabilities by diminishing preservatives.

F6H8 (NovaTears) is a novel water-free tear substitute that demonstrates strong spreading properties due to an extremely low surface tension of just 19.65 mNm compared to water with 72 mNm.²³ This leads to smaller drop sizes compared to water. Furthermore, F6H8 has shown to form an occlusive layer preventing evaporation (Runnsjoe, A., *et al.* Realizing Reformulation, a symposium on surface and materials chemistry. Lund, Sweden. Interaction of perfluorohexyloctan with tetradecan and waterthermotropic phase behavior and occluding effects. 2014; poster presentation). All these characteristics are considered to contribute to the mode of action of F6H8 in DED. The vast spreading properties of F6H8 facilitate a rapid distribution across the ocular surface and, thereby, form a layer, which reduces shearing forces of the eyelid during blinking and prevents evaporation of the aqueous phase of the tear film. This tear film stabilizing effect was also observed in pre-clinical models that showed an increase in TFBUT.

This first prospective observational study showed beneficial effects in patients suffering from hyperevaporative DED. Based on the baseline characteristics, the trial population can be classified as moderately affected according to the 2007 International Dry Eye WorkShop (DEWS) criteria.¹ After 5–7 weeks of treatment, tear film stability and Schirmer test increased, while corneal staining and OSDI score decreased significantly. The decrease of the OSDI by a mean of 21 points was particularly remarkable and clearly exceeds the minimal, clinical important difference of 4.5–7.3 points for mild or moderate disease and 7.3–13.4 points for severe disease.²² Furthermore, the observed improvement in OSDI corresponded well to the subjective symptom assessment.

At the same time, BCVA and intraocular pressure did not decrease, which underlines the nonblurring character of the novel compound.

Interestingly, although TFBUT increased significantly, meibomian gland function as examined by expressibility and quality of the meibum did not improve in general. In 7

patients, no meibum could be expressed at the end of the trial. Subgroup analysis of these patients shows an average increase of TFBUT from 7.1 (right eyes)/6.9 (left eyes) to 8.9/8.3 (right eyes/left eyes), respectively. None of the patients in this subgroup showed any corneal staining at follow-up, whereas all of them showed corneal staining at the baseline (9 eyes with Grade 1, 4 eyes with Grade 2). Schirmer I test decreased in 5/14 eyes, but increased in 9/14 eyes, and OSDI decreased in 6 out of 7 patients. Overall, although demonstrating a lack of meibomian gland expression, the majority of this subgroup demonstrated an improvement of objective symptoms and signs.

In total, 18/28 patients were satisfied or very satisfied with F6H8, 20/29 patients described a pleasant or very pleasant sensation after the first application, and 21/29 patients would continue the treatment if possible. Subjective sensation after the first application was velvety or neutral and only few patients described an oily sensation. 25/29 patients described no or only little impairment of vision immediately after first administration; however, none of the 4 patients that reported an affect on their vision reported a duration of longer than a few minutes.

The reported 5 AEs were considered mild to moderate. The relationship to F6H8 was considered unrelated or unlikely related in 2 cases, probably related in 2 further cases, and 1 patient reported an AE that was clinically characterized as definitely related to F6H8. In the latter 3 cases, mild to moderate local hypersensitivity was reported by the patients that resolved immediately after discontinuation of the substance. Four of the 5 patients that experienced an AE stopped using NovaTears due to the AE. All AEs disappeared at the final visit.

The study has several limitations. Due to the observational character of the study, the efficacy parameters were compared with the baseline measurements, but not to the control group, and data were only collected at 2 time points (baseline and follow-up visit). Variations in endpoints and population make a cross-study comparison difficult in this indication. Follow-up studies will focus on treating patients with more severe forms of DED over longer periods.

Overall, F6H8 (NovaTears) seems to be safe and effective in treating mild to moderate hyperevaporative DED as demonstrated by this prospective observational study. In particular, improvement of Schirmer's test, TFBUT, corneal

TABLE 7. SUMMARY SYMPTOM ASSESSMENT (CPS, $N=25$)

Symptom	Baseline (n)	Follow-up (n)
Red eyes	22	9
Itching	18	7
Clotted eyes	9	1
Headache	2	1
Stringy mucous	2	0

Multiple symptom selection per patient possible.

TABLE 8. SUMMARY OF MEIBUM SECRETION ANALYSIS (CPS, $N=25$)

Description of meibum	Baseline (n)	Follow-up (n)
Clear	18	17
Whitish	5	1
Thick	1	0
None	1	7

TABLE 9. OUTCOME OF THE USABILITY AND TREATMENT SATISFACTION QUESTIONNAIRE (FAS, $N=29$)

(1) How easy was the administration of NovaTears®?	
Very easy	16
Easy	9
Neutral	2
Sometimes difficult	2
(2) How does the patient describe the sensation of NovaTears eye drops after application (1)?	
Velvety	12
Neutral	10
Oily	7
(3) How does the patient describe the sensation of NovaTears eye drops after application (2)?	
Very pleasant	5
Pleasant	15
Neutral	4
Unpleasant	5
(4) Was the patient's vision affected immediately after administration of NovaTears eye drops?	
Not at all	14
A little	11
Somewhat	1
Strongly	3
(5) How fast did NovaTears eye drops relieve dry eye symptoms of the patient?	
Very fast	9
Fast	8
Slow	6
Very slow	2
Not at all	4
(6) How satisfied was the patient with NovaTears treatment? ^a	
Extremely satisfied	8
Satisfied	10
Neutral	2
Dissatisfied	7
Extremely dissatisfied	1
(7) How likely is it that the patient will continue using NovaTears?	
Very likely	17
Likely	4
Unlikely	6
Extremely unlikely	2

^aInformation for 1 patient missing.

TABLE 10. ADVERSE EVENTS

Adverse event no.	Adverse event	Severity	Action taken	Relation to Nova Tears
1	Relapse of rheumatoid arthritis	Moderate	Treatment stopped	Unlikely
2	Seasonal allergy	Mild	Dose not changed	Not related
3	Hypersensitivity	Moderate	Treatment stopped	Probably
4	Hypersensitivity	Moderate	Treatment stopped	Definite
5	Drug hypersensitivity	Mild	Treatment stopped	Probably

staining, and subjective symptoms shows beneficial effects and implicates a broad application opportunity.

In addition, SFAs may be used in combination with anti-inflammatory drugs such as cyclosporine A, which can be formulated much easier due to the lipophilic character of SFAs.²⁴ By this, beneficial effects regarding tear film stability and the ocular surface integrity may be combined with anti-inflammatory T cell-inhibiting properties.

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Author Disclosure Statement

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References

1. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul. Surf.* 5:75–92, 2007.
2. Behrens, A., Doyle, J.J., Stern, L., Chuck, R.S., McDonnell, P.J., Azar, D.T., Dua, H.S., Hom, M., Karpecki, P.M., Laibson, P.R., Lemp, M.A., Meisler, D.M., Del Castillo, J.M., O'Brien, T.P., Pflugfelder, S.C., Rolando, M., Schein, O.D., Seitz, B., Tseng, S.C., van Setten, G., Wilson, S.E., and Yiu, S.C. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. *Cornea.* 25:900–907, 2006.
3. Baudouin, C. A new approach for better comprehension of diseases of the ocular surface. *J. Fr. Ophthalmol.* 30:239–246, 2007.
4. Nelson, J.D., Shimazaki, J., Benitez-del-Castillo, J.M., Craig, J.P., McCulley, J.P., Den, S., and Foulks, G.N. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. *Invest. Ophthalmol. Vis. Sci.* 52:1930–1937, 2011.
5. Bron, A.J., and Tiffany, J.M. The meibomian glands and tear film lipids. Structure, function, and control. *Adv. Exp. Med. Biol.* 438:281–295, 1998.
6. McCulley, J.P., and Shine, W.E. Meibomian gland and tear film lipids: structure, function and control. *Adv. Exp. Med. Biol.* 506:373–378, 2002.
7. Brignole-Baudouin, F., Baudouin, C., Aragona, P., Rolando, M., Labetoulle, M., Pisella, P.J., Barabino, S., Siou-Mermet, R., and Creuzot-Garcher, C. A multicentre, double-masked, randomized, controlled trial assessing the effect of oral supplementation of omega-3 and omega-6 fatty acids on a conjunctival inflammatory marker in dry eye patients. *Acta Ophthalmol.* 89:e591–e597, 2011.
8. Li, Z., Choi, J.H., Oh, H.J., Park, S.H., Lee, J.B., and Yoon, K.C. Effects of eye drops containing a mixture of omega-3 essential fatty acids and hyaluronic acid on the ocular surface in desiccating stress-induced murine dry eye. *Curr. Eye Res.* 39:871–878, 2014.
9. Liu, A., and Ji, J. Omega-3 essential fatty acids therapy for dry eye syndrome: a meta-analysis of randomized controlled studies. *Med. Sci. Monit.* 20:1583–1589, 2014.
10. Carvounis, P.E., Cartwright, N.E.K., Bron, A., and Tiffany, J. Recovery of meibomian oil after lid margin cleansing,

- studied by meibometry in normal individuals. *Invest. Ophthalmol. Vis. Sci.* 45:U122, 2004.
11. Korb, D.R., and Blackie, C.A. Debridement-scaling: a new procedure that increases Meibomian gland function and reduces dry eye symptoms. *Cornea*. 32:1554–1557, 2013.
 12. Lane, S.S., DuBiner, H.B., Epstein, R.J., Ernest, P.H., Greiner, J.V., Hardten, D.R., Holland, E.J., Lemp, M.A., McDonald, J.E., 2nd, Silbert, D.I., Blackie, C.A., Stevens, C.A., and Bedi, R. A new system, the LipiFlow, for the treatment of meibomian gland dysfunction. *Cornea*. 31:396–404, 2012.
 13. Kaercher, T., Thelen, U., Brief, G., Morgan-Warren, R.J., and Leaback, R. A prospective, multicenter, noninterventional study of Optive Plus(R) in the treatment of patients with dry eye: the prolipid study. *Clin. Ophthalmol.* 8:1147–1155, 2014.
 14. Versura, P., Profazio, V., Giannaccare, G., Fresina, M., and Campos, E.C. Discomfort symptoms reduction and ocular surface parameters recovery with Artelac Rebalance treatment in mild-moderate dry eye. *Eur. J. Ophthalmol.* 23:488–495, 2013.
 15. Sindt, C.W., and Foulks, G.N. Efficacy of an artificial tear emulsion in patients with dry eye associated with meibomian gland dysfunction. *Clin. Ophthalmol.* 7:1713–1722, 2013.
 16. Dausch, D., Lee, S., Dausch, S., Kim, J.C., Schwert, G., and Michelson, W. Comparative study of treatment of the dry eye syndrome due to disturbances of the tear film lipid layer with lipid-containing tear substitutes. *Klin. Monbl. Augenheilkd.* 223:974–983, 2006.
 17. Wilson, W.S., Duncan, A.J., and Jay, J.L. Effect of benzalkonium chloride on the stability of the precorneal tear film in rabbit and man. *Br. J. Ophthalmol.* 59:667–669, 1975.
 18. Messmer, E.M. Preservatives in ophthalmology. *Ophthalmologe*. 109:1064–1070, 2012.
 19. Meinert, H., and Roy, T. Semifluorinated alkanes—a new class of compounds with outstanding properties for use in ophthalmology. *Eur. J. Ophthalmol.* 10:189–197, 2000.
 20. Bron, A.J., Evans, V.E., and Smith, J.A. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea*. 22:640–650, 2003.
 21. Schiffman, R.M., Christianson, M.D., Jacobsen, G., Hirsch, J.D., and Reis, B.L. Reliability and validity of the Ocular Surface Disease Index. *Arch. Ophthalmol.* 118:615–621, 2000.
 22. Miller, K.L., Walt, J.G., Mink, D.R., Satram-Hoang, S., Wilson, S.E., Perry, H.D., Asbell, P.A., and Pflugfelder, S.C. Minimal clinically important difference for the ocular surface disease index. *Arch. Ophthalmol.* 128:94–101, 2010.
 23. Kim, Y.K., Gunther, B., and Meinert, H. A new, heavier-than-water silicone oil: a solution of perfluorohexyloctane in polydimethylsiloxane. *Eur. J. Ophthalmol.* 15:627–637, 2005.
 24. Dutescu, R.M., Panfil, C., Merkel, O.M., and Schrage, N. Semifluorinated alkanes as a liquid drug carrier system for topical ocular drug delivery. *Eur. J. Pharm. Biopharm.* 88:123–128, 2014.

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