

# Comment to: Disease aetiology-based design of multifunctional microemulsion eye drops for moderate or severe dry eye: a randomized, quadruple-masked and active-controlled clinical trial



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## HIGHLIGHTS

Sacha inchi microemulsion (SIME) proved safe and efficacious in improving the stability of the tear film, reducing hyperosmolarity, structural damage and inflammation of the ocular surface.

## ABSTRACT

Sacha inchi (*Plukenetia volubilis*) is an oil plant native to tropical rainforests in South America. The seeds of the plant are a potential source of macro- and microelements,  $\alpha$ -linolenic acid and phytochemicals.

A single-centre, prospective, masked clinical study was designed to investigate the efficacy and safety of multi-ingredient sachu inchi microemulsion (SIME) eye drops in the treatment of patients with dry disease.

Sachu inchi microemulsion (SIME) proved safe and efficacious in re-establishing the physiological protective tear film function and restoring the homeostasis of the ocular surface.

**Key words:** sachu inchi (*Plukenetia volubilis*), multi-ingredient sachu inchi microemulsion (SIME), dry eye disease

## INTRODUCTION

The surface of the eye, which consists of the tear film, cornea, conjunctiva, eyelids and glands, is a natural protective barrier against the harmful factors of the external environment. The condition of the eye surface depends on maintaining its specific homeostasis, i.e., the balance between external factors and the protective factors responsible for keeping the eye surface intact. Continuous external factors, such as temperature change, humidity decrease, wind, air pollution, do not affect the condition of the surface of the eye immediately; however, their repeated and long-lasting effects may have negative effects and contribute to the development of dry eye syndrome.

According to the current definition, dry eye syndrome (DES) is described as a multifactorial disease of the eye surface characterized by the loss of tear film homeostasis accompanied by ocular symptoms. In its etiology the following factors play an important role: instability and hyperosmolarity of the tear film, inflammation, and structural damage the surface of the eye and neurosensory abnormalities [1].

It is worth noting that currently DES is treated as a complex disease entity that cannot be described based on a single process, a physical or subjective symptom. This fact was highlighted for the first time in 2007 by the Tear Film & Ocular Surface Society (TFOS) expert group [2]. An important issue in the treatment of DES is to restore ocular surface homeostasis by acting on all pathophysiological components of the disease and breaking the vicious cycle of DES.

## EPIDEMIOLOGY

Dry eye syndrome is a common health problem. Results of epidemiological studies based on subjective symptoms of patients define the incidence of DES between 5% to 50%, while the incidence of the disease, based on the symptoms, is even 75%. In international, multicenter, cross-sectional epidemiological studies, the incidence of DES has been estimated at 5–30% in the population over 50 years of age [3–5].

The confirmed risk factors for DES include age, female gender, Meibomian gland dysfunction, use of contact lenses, work at a computer monitor screen, as well as environmental factors such as pollution, low air humidity and commonly taken medications, e.g., hormone replacement therapy, antihistamines, antidepressants, and anxiolytics [3, 6, 7].

Due to the observed increase in the elderly population (aging of the population), it is to be expected that the number of patients with DES in ophthalmic practice will increase. It should be emphasized that DES is becoming a significant social and economic problem as it contributes to the reduction of work efficiency.

In view of the above, the introduction of an effective treatment for DES and the establishment of a uniform management regimen for the disease is an extremely important aspect of modern research.

## COMMENTARY

The presented work by Laihia et al. entitled: *Disease aetiology-based design of multifunctional microemulsion eye drops for moderate or severe dry eye: a randomized, quadruple-masked and active-controlled clinical trial* aimed at assessing safety, tolerance and effectiveness of the new ophthalmic preparation [8].

The tested medical device was the hypotonic sachal inchi microemulsion (SIME) (manufacturer: Finnsusp, Lieto, Finland). These are eye drops containing 0.1% sachal inchi seed oil (*Plukenetia volubilis*), polysorbate 80, sorbitan monooleate, 0.2% high molecular weight hyaluronic acid (HA) (1.0–1.5 MDa) and 2% trehalose dihydrate and glycerol in buffer (trometamol/citrate).

The study group consisted of outpatients who had previously been diagnosed with DES. The inclusion and exclusion criteria for a clinical trial have been strictly and reasonably defined.

Inclusion criteria for the study included: adults aged 18–80; (1) Ocular Surface Disease Index (OSDI) value  $\geq 20$  s and tear film break up time (TBUT)  $<10$  s or (2) OSDI value  $\geq 20$  s and abnormal ocular surface (corneal and conjunctiva) according to the Oxford scale; body weight  $\geq 45$  kg; a constant regimen of topical and / or systemic medications used for a minimum of 4 weeks prior to study procedures, and the ability to refrain from using other treatments during the study, as well as the ability and willingness to self-use eye drops.

The exclusion criteria were as follows: being after eye surgery, trauma or laser refractive error correction in less than 3 months; corneal and/or conjunctival infection; Sjögren's syndrome; use of contact lenses during the examination and for a period of less than a week; symptoms of ocular allergy; known allergy to the ingredients of eye drops; current or planned pregnancy or breastfeeding during the study.

The inclusion and exclusion criteria were in line with the current TFOS methodological guidelines [9–11].

The undoubted advantages of the presented study are its prospective, randomized nature and quadruple blinding (at the participant, caregiver, researcher, and results evaluator levels). Both the test drops and the control drops containing a 0.2% HA solution with an average molecular weight (0.7–0.9 MDa) in an isotonic phosphate-buffered sodium chloride solution (manufactured by Finnsusp) were clear, colorless, odorless, and preservative-free, with stable, sterile solutions with a neutral pH. In addition, the test and control drops were housed in similar looking 10 ml multi-dose

translucent containers, allowing the contents to be completely masked for participants, healthcare professionals, data collectors and statisticians.

It is worth emphasizing that medicinal drops containing a single active ingredient were used as a control preparation, unlike in most studies of this type to date, where the control preparation was usually a placebo consisting of a sodium chloride solution or a base used in ophthalmic drops [12–14]. However, in recent randomized clinical trials, moisturizing drops with active ingredients are also selected as the control solution [15–18]. The authors of the publication justify the selection of HA drops as a control preparation with ethical reasons that do not allow patients to be left without appropriate treatment during the study.

The study was divided into three stages, and the transition to the subsequent stage was possible only in the absence of significant adverse effects induced using the test substances. The first stage, involving three patients, was designed to assess the safety of the medical device. It consisted of four times, at two-hour intervals, the use of drops administered to patients by a nurse at a research center. The absence of significant side effects allowed the study to proceed to the second, 10-day stage, which included the study of nine patients.

During its course, patients self-applied the study or control drops 3 times a day. The final, third stage, which served to evaluate not only safety and tolerability but also efficacy of treatment, lasted 30 days and initially included 26 patients each in the study and control groups. After this period, 24 patients in the study group met all the conditions for adherence to the protocol, while in the control group 25 patients met the conditions. At this stage, patients also self-applied the study or control drops 3 times a day.

The ophthalmological tests performed at the inclusion and at the end of the study were selected to test the efficacy of the medical device in relation to the subjective symptoms of patients, as well as the impact on the main pathophysiological components of the disease, such as: tear film instability, hyperosmolarity, inflammation and ocular surface damage. The conducted research included:

**1. Completing a questionnaire and determining the Ocular Surface Disorder Index (OSDI).** The survey created by the Outcomes Research Group at Allergan (Irvine, California) consists of 12 questions, divided into three thematic blocks concerning the symptoms of eye irritation, the impact of symptoms on the development of visual impairment, and the impact of environmental factors leading to the development of DES symptoms that occurred in the patient in the past week.

A score above 13 indicates DES. The OSDI is a reproducible, non-invasive tool that enables the observation of changes over time. Based on numerous studies, the sensitivity and specificity of OSDI in the diagnosis of DES have been estimated at 60% and 83%, respectively [19].

**2. Testing the stability of the tear film.** The study included the analysis of the fluorescein tear film break up time (FTBUT), determination of blinking frequency and the ocular protection index (OPI). The latter was introduced into clinical practice in 2008 and is calculated based on the  $OPI = TBUT/IBI$  formula, where IBI (interblink interval) means the interval between consecutive blinks [20].

Abnormal TBUT result, indicative of DES, is less than 10 seconds. If OPI is  $< 1.0$ , the patient has an abnormal surface of the eye, which puts them at risk of developing physical and subjective symptoms of DES, while if OPI is  $\geq 1.0$ , the patient's ocular surface is properly protected by the tear film.

**3. Examining tear film osmolarity.** It is one of the three basic criteria for the diagnosis of DES, in addition to TBUT and eye surface staining. Increased tear film osmolarity ( $\geq 308$  mOsm/l) in one eye or a difference in osmolarity between the eyes of  $> 8$  mOsm/l indicates DES [11].

**4. Examining inflammation severity.** To assess the inflammation severity of the ocular surface, the authors adopted a simplified analysis of eyelid and conjunctival redness according to the Institute for Eye Research (IER grade) scale introduced by the Australian Ocular Research Institute in 2007. It is a five-grade scale, with successive grades determined relative to reference color photographs and denoting: 0 – no redness, 1 – minimal redness, 2 – slight redness, 3 – moderate redness, 4 – significant redness.

**5. Examining ocular surface damage.** The analysis of ocular surface staining using a slit lamp with photographic documentation in the six-point Oxford scale (grades 0–5) was used in relation to the reference images representing the subsequent degrees of the severity of the ocular surface damage [21]. An abnormal ocular surface staining score is standardly graded as:  $> 5$  point defects in the corneal epithelium or  $> 9$  conjunctival defects or eyelid margin epitheliopathy, length  $\geq 2$  mm and width  $\geq 25\%$ . The assessment is performed 1–4 min. after the administration of fluorescein or lissamine green to the conjunctival sac. Fluorescein is used to assess the cornea, lissamine green to assess conjunctival damage.

Based on the research, the authors obtained the following results in relation to the tested DES parameters:

**1. OSDI Ocular Surface Disorder Index.** In the case of patients receiving SIME and HA, after 30 days of treatment, both the mean total OSDI score and individual components (ocular symptoms, visual disturbances and environmental factors) decreased significantly: by 51% for SIME ( $p < 0.0001$ ) and 58% for HA ( $p < 0.0001$ ).

**2. Testing the stability of the tear film.** After 30 days of treatment, TBUT was prolonged by 50% for SIME and by 25% for HA. The OPI index improved by 57% in the case of SIME and by 4% in the control group. The differences for

SIME compared to the baseline were statistically significant (probability index  $p$  was: for TBUT  $p = 0.0055$ ; for OPI  $p = 0.0068$  in the group treated per protocol [PP]).

**3. Examination of the tear film osmolarity.** After 30 days of treatment, in the PP group of patients with baseline osmolarity ( $\geq 308$  mOsm/l) it decreased significantly in both the study and control groups ( $p = 0.015$  for SIME and  $p = 0.001$  for HA).

**4. Examination of the inflammation severity.** In the ITT (intention-to-treat) group analysis, redness of the conjunctiva and eyelids was significantly reduced by 23% ( $p = 0.001$ ) and 29% ( $p = 0.012$ ) in the study group, respectively. Redness reduction in the control group was on average 15% and it was not a statistically significant difference.

**5. Examination of the ocular surface damage.** Corneal staining decreased significantly by 27% in the study group ( $p = 0.014$ ) (PP analysis) and insignificantly in the control group. In the case of the conjunctiva, the PP analysis in the SIME group showed that a significant reduction in staining by 22% was obtained for the nasal part of the conjunctiva ( $p = 0.043$ ). As in the case of the cornea in the control group, the redness reduction effect was smaller and statistically insignificant.

To properly understand the significance of the findings, it is worth recalling the basic fact concerning the pathophysiology of DES, namely that it has a vicious circle nature, so the factors triggering the disease process can be both its cause and consequence [22]. Tear hyperosmolarity is the primary hallmark of the disease. It then causes damage to the ocular surface both directly and by initiating an inflammatory response.

Hyperosmolarity stimulates the cells of the ocular surface epithelium to secrete a number of substances, such as: MAP (mitogen-activated protein) kinases, pro-inflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-10, IL-8, IL-12, IL-13), tumor necrosis factor (TNF- $\alpha$ ) and proteases, e.g. metalloproteinase 9 (MMP9). Inflammatory mediators released in epithelial cells cause a loss of goblet cells and epithelial cells and damage to the glycocalyx of the conjunctival and corneal epithelium. This results in punctate epitheliopathy and tear film instability. Disruption of the tear film intensifies and increases the hyperosmolarity of the tears and thus completes the vicious cycle of events resulting in damage to the ocular surface. This leads to the self-perpetuation of the disease process in a vicious circle mechanism [9].

In their discussion, the authors emphasize that the treatment of DES requires a therapeutic intervention that targets several pathophysiological factors: tear film instability, hyperosmolarity, chronic inflammation, and ocular surface damage. The tested medical device in the form of a microemulsion containing 0.1% sachai inchi seed oil, 0.2% high molecular weight HA (1.0–1.5 MDa), 2% trehalose dihydra-

te, polysorbate 80, sorbitan monooleate, and glycerol fulfills these conditions and demonstrates efficacy in treating the pathophysiological causes of DES. In comparison, drops containing a single active ingredient, a 0.2% HA solution with a medium molecular weight (0.7–0.9 MDa) significantly affected only one etiological component, namely hyperosmolarity.

The key ingredient of the tested microemulsion was sachai inchi oil. It comes from an oil plant native to the tropical Amazon rainforests of South America. Plant seeds are a potential source of macro- and microelements,  $\alpha$ -linolenic acid and phytochemicals. The authors of the article emphasize that the content of  $\gamma$ -tocopherol (a form of vitamin E), which exhibits strong antioxidant properties, may be of importance [23, 24]. Additionally, the form of microemulsion affects the lipid layer of the tear film, and it should be remembered that as much as 70% of cases of DES are related to evaporative dry eye (EDE) [3, 6].

It is also worth mentioning that all research procedures were carried out at least 8 h after the last dose of the SIME medical device, i.e. the effect of improving tear film stability was permanent. It is currently believed that the use of eye drops with a lipid component provides a long-lasting effect of tear film stability [23]. In a randomized clinical trial by Simmons et al. lipid-containing eye drops with polysorbate 80, sorbitan monooleate, and glycerol provided a significant prolongation of TBUT and a reduction in patients' subjective complaints [25].

Another modification of the test preparation, as compared to the control one, was an increase in the molecular weight of HA from 0.7–0.9 MDa to 1.0–1.5 MDa. This fact is also important for the effectiveness of treating DES, which is confirmed by the latest studies using a mouse model of the disease [26].

The last active ingredient of the test product is trehalose. It is a disaccharide composed of two glucose molecules linked by an O-glycosidic bond. It is the main sugar in insect haemolymph and is also found in fungi and yeasts. In vitro studies have unequivocally proven that it protects against desiccation, UVB radiation, oxidative stress and temperature changes [27–29].

As a component of moisturizing drops, it has a significant osmoprotective, bioprotective, anti-inflammatory, apoptosis-inhibiting and autophagous-inducing effect, i.e., a natural process of self-cleaning of cells, which has been confirmed in numerous studies, including randomized, blinded clinical studies [13, 17, 18, 30].

A separate comment should be made on the fact that there was a significant improvement in the subjective symptoms in the OSDI questionnaire, both for the test and control product. In this case, both medical devices presented comparable effectiveness, which proves the claim that regular, systematic treatment by patients with DES guarantees re-

duction of symptoms and improvement of the quality of vision. Obtaining such an effect should not come as a surprise if we take into account that the control drug was HA, i.e. an active substance with proven effectiveness in the treatment of DES [16, 18].

## CONCLUSIONS

It should be undoubtedly concluded that the selected drops composition of the test product provides a therapeutic effect on many levels, restores the protective role of the tear film and effectively breaks the vicious circle mechanism. In

the author's opinion, the most important conclusions that require consolidation are as follows:

1. DES is a multifactorial disease characterized by a loss of ocular surface homeostasis.
2. Treatment of DES should be adequate to the pathophysiological cause of the disease.
3. The effectiveness of treating DES depends directly on the composition of drops used in the treatment.
4. SIME has high efficacy and safety, significantly improving tear film stability, reducing hyperosmolarity as well as structural damage and ocular surface inflammation.
5. Using SIME restores homeostasis of the ocular surface after one month of use.

## CORRESPONDENCE

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