WHITE PAPER

Considerations for clinical trials of dry eye syndrome in a crowded landscape

A KEY QUESTION

How do you design Dry Eye Syndrome studies that are both scientifically rigorous and operationally feasible, with the challenges of complexity, high placebo response rates, subjective symptoms, environmental variability and a competitive landscape?

KEYWORDS Dry Eye Syndrome (DES), Practical Experience, Ophthalmology Clinical Trials, Patient Selection, Diagnostics, Patient Compliance

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1 Executive summary

We are excited to build the future of therapies in Dry Eye Syndrome (DES) together with you. We know your goal is to develop innovative solutions in a collaborative spirit with a commitment to results and putting patients first. Our team is best placed to collaborate with you to both plan and manage the challenges to be faced. We have knowledge, data and operational experience in the DES space.

A recent primary search using Citeline revealed growing interest in DES research through diverse mechanisms of action with balanced pipeline development across Phase I, II and III, and geographical concentration in U.S. and China.

One of Fortrea's recent successful DES trials was shared in this document. Facing several challenges, we completed it successfully ahead of schedule by standardizing diagnostic criteria, improving patient selection, minimizing placebo effect and enhancing patient compliance. This story is a great example of how we can handle tough situations and keep pushing forward with ophthalmology trials.

In this whitepaper all the practical details from Fortrea's hand-on experience was shared without reservation in section five on how to handle the issue of large differences in repeated Schirmer Tear Test (STT) results, prohibited medication in washout period, sequence of ophthalmic tests, considerations for using a placebo as the control group, STS strip length, corneal epithelial defects issue in enrollment, waiting for more than two minutes in corneal fluorescein staining, the use of other concomitant artificial tears and its potential impact and stratification factor used in randomization and statistics analysis.

Discover how Fortrea can support your DES trials and help you progress toward your clinical development goals.

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INTRODUCTION

Increasing unmet medical needs and recent advances in treatment

Dry eye syndrome (DES) is becoming a significant concern with unmet medical needs. With the aging global population and increasing screen time and changes of other lifestyle of modern era, the rising prevalence of DES are with complex etiology issues.[2,4,7] DES not only affects ocular health but also significantly impacts daily activities.[4]

Current treatments include over-the-counter artificial tears and a few prescription medications that target inflammation mainly.[4,6] However, these treatments often don't address all the symptoms of dry eye disease, aside from inflammation.[9] Another unmet medical need is it usually takes weeks or months for patients to experience improvement is a challenge with some prescribed therapeutics or dry eye disease.[4,8]

To better manage and potentially cure DES, new more effective therapies and advanced drug delivery systems are actively being worked on.[3,8]

FDA-approved medicines to treat DES include cyclosporine formulations (RESTASIS® [cyclosporine 0.05% ophthalmic emulsion], VEVYE® [cyclosporine 0.1% ophthalmic solution] and CEQUA™ [cyclosporine 0.09% ophthalmic solution]), XIIDRA® (lifitegrast), a leukocyte function-associated antigen-1 (LFA-1)/intracellular adhesion molecule-1(ICAM-1) inhibitor, EYSUVIS™ (loteprednol etabonate ophthalmic suspension 0.25%), a corticosteroid and MIEBO™ (perfluorohexyloctane ophthalmic solution), a semifluorinated alkane, TYRVAYA™ (varenicline solution nasal spray), a cholinergic agonist.[16]

FDA-approved medical devices to treat DES related to meibomian glands dysfunction (MGD) include Lumenis OptiLight™ (intense pulsed light [IPL] device), TearCare® system, TearScience™ LipiFlow™ thermal pulsation system and Punctal plugs.[16]

Crowded competitive landscape

A primary search with cutoff at March 4, 2025 was conducted using **Trials | Citeline Trialtrove** and the key words used were (Disease is Ophthalmology: Dry Eye Syndrome) AND [(Trial Phase is I) OR (Trial Phase is I/II) OR (Trial Phase is II) OR (Trial Phase is II/III) OR (Trial Phase is III) OR (Trial Phase is III/IV)] AND [(Trial Status is Planned) OR (Trial Status is Ongoing) OR (Trial Status is Ongoing)] AND (Sponsor/Collaborator Type is Industry). Total of 80 trials were identified.

Key Insights from the Data

- **Growing interest in DES research:**

  The number of clinical trials for Dry Eye Syndrome (DES) is on the rise. We saw seven trials in 2022, 14 in 2023 and a jump to 28 in 2024. This surge clearly shows that DES research is heating up and becoming a major focus in ophthalmology.

- **Balanced pipeline development:**

  What's interesting is that the number of trials across Phase I, II and III is pretty similar. This balance indicates that there's a strong push in both the early and late stages of DES pipeline development which means the strong momentum in development of new therapy in DES.

- **Geographical concentration:**

  Most of these DES trials are happening in Asia and North America, especially in the U.S. and China. These regions are leading the charge in this area of research.

- **Trial protocol design:**

  When it comes to designing these trials, the primary endpoints are all about symptoms or clinical response. To measure efficacy, they commonly use things like ocular surface staining, Visual Analog Scale (VAS), Schirmer's test and the Ocular Surface Disease Index (OSDI).

- **Diverse mechanisms of action:**

  The mechanisms of action (MOA) for these DES trials are highly diverse such as Inflammation Pathways, Hormone Therapy, IL-1 Receptor Antagonist, Neurological and Endocrine Regulation, Immune Responses and T Cell-Driven Inflammation, etc. This diversity suggests that researchers are exploring a wide range of approaches to tackle DES.

Table 1: Number of trials each year

Start date (years)	Number of trials
2025 Q1	7
2024	28
2023	14
2022	7
2021	2
2020	1

Table 2: Number of trials across phases

Trial phase	Number of trials
I	17
I/II	4
II	25
II/III	2
III	31
III/IV	1

Table 3: DES trials distribution in different regions

Trial regions	Number of trials
Asia	35
North America	23
(N/A)	15
Australia/Oceania	4
Europe	2
Western Europe	2
Eastern Europe	1
South America	1

Table 4: DES trials distribution in different countries

Countries	Number of trials
China	23
United States	22
South Korea	7
Australia	4
Japan	2
Canada	1
Columbia	1
France	1
India	1
Indonesia	1
Mexico	1
Netherlands	1
Poland	1
Spain	1
Taiwan, China	1

Table 5: DES trials protocol design—primary endpoint

Primary endpoint	Number of trials
Safety and Tolerability	16
Ocular surface staining	15
Visual Analog Scale	8
Schirmer's test	7
Ocular Surface Disease Index	6
Adverse Events	5
Treatment Emergent Adverse Events	5
Eye Dryness Score	4
BCVA	3
Tear film break up time	3
Visual acuity	3
EULAR Sjogren's Syndrome Disease Activity Index	2
Fundus examination	2
Intraocular pressure	2
National Eye Institute Grading System	2
Slit lamp exam	2
Accumulation index	1
Area under the curve score	1
Cardiac Telemetry	1
Cmax	1

Table 6: DES trials protocol design—primary endpoint Group

Primary endpoint group	Number of trials
Efficacy > Clinical Response	19
Efficacy > Symptom Assessment (Patient Reported Outcomes)	16
Safety/Toxicity > Safety And Tolerability	16
Efficacy > Symptom Assessment	10
Efficacy > Patient Assessment Instruments	9
Safety/Toxicity > Adverse Drug Reactions	8
Efficacy > Imaging	2
Efficacy > Disease Progression	1
Pharmacokinetics/ Pharmacodynamics > Pharmacokinetics/ Pharmacodynamics	1
Safety/Toxicity > Cardiac Measures/Events	1
Safety/Toxicity > Serious Adverse Events	1

Table 7: Primary tested drug in DES trials

Primary tested drug	Number of trials
reproxalap	3
ILYX-002	2
PL-9643	2
SJP-0132	2
TUL-12101	2
VVN-001	2
diquafosol sodium, Taejoon Pharm	2
imatinib, Avixgen	2
lacritin, TearSolutions	2
selenium disulphide, Azura Ophthalmics	2
simpinicline	2
tanfanercept	2
17ß-oestradiol-3-phosphate, Redwood	1
AG-80308	1
BRM-421	1
CAM-101	1
CF-04	1
CT-2000	1
Cationorm	1
Cyclisis PF	1

Table 8: MOA of primary tested drug in DES trials

Primary tested drug: Mechanism of action	Number of trials
Unidentified pharmacological activity such as placebo, M-136101, ILYX-002, FID123360, FID123359, FID123361, FID121843 cevimeline, SQ-22031, rh-lubricin, CF-04, perfluorohexyloctane, PRO-190, PRO-240, selenium disulphide, Glicolub Ultra, KH-732,SLG-100, MR-148, Pluripotent Stem Cell-derived Mesenchymal Stem Cell Exosome, PH-007, EXP-TC, selenium disulphide, lacritin, Cationorm and 17ß-oestradiol-3-phosphate	25
Immunosuppressant	6
T cell inhibitor	6
Aldehyde binder	5
Immune checkpoint stimulant	5
Lymphocyte function-associated molecule inhibitor	5
Calcineurin inhibitor	3
Purinoreceptor P2Y2 agonist	3
Cyclophilin A inhibitor	2
Discoidin domain receptor tyrosine kinase 1 inhibitor	2
Glycosaminoglycan stimulant	2
Hyaluronic acid stimulant	2
Glycosaminoglycan stimulant	2
Melanocortin MC-1 receptor agonist	2
Melanocortin MC-5 receptor agonist	2
Nicotinic receptor agonist	2
TRPM8 agonist	2
Tumour necrosis factor receptor antagonist	2
Vanilloid receptor 1 antagonist	2
Alpha2beta1 integrin antagonist	1
Alpha5beta1 integrin antagonist	1

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Recent success story from Fortrea

We collaborated with a fast-growing biotech company in China to help them move their ophthalmology program forward. This story demonstrates our ophthalmology skills, how we work super well with local sites and investigators and our ability to be flexible and quick in regional operations.

Implementing clinical trials for dry eye syndrome (DES) presents several challenges: [11,12,14]

- **Variability in symptoms and severity:** DES symptoms can vary widely among patients, making it difficult to standardize inclusion criteria and outcome measures
- **Placebo effect:** The vehicle (placebo) used in trials often shows some beneficial effects, complicating the assessment of the actual treatment's efficacy
- **Patient compliance:** Ensuring consistent use of treatments and adherence to trial protocols can be challenging, especially in long-term studies
- **Diagnostic criteria:** There is a lack of consensus on diagnostic criteria and grading systems for DES, which can lead to inconsistencies in trial results
- **Environmental factors:** External factors like humidity, temperature and screen time can influence DES symptoms, adding variability to trial outcomes

Fortrea has strategies to address the challenges in implementing clinical trials for dry eye syndrome (DES):

- **Standardizing diagnostic criteria:** Efforts are made to develop and adopt standardized diagnostic criteria and grading systems to ensure consistency across trials
- **Improved patient selection:** Advanced pre-screening protocols and detailed patient characterizations assist in selecting the right participants, reduce variability and help improve trial outcomes
- **Minimizing placebo effect:** Researchers design trials with robust control groups and use objective measures to help minimize the impact of the placebo effect
- **Enhanced patient compliance:** Utilizing decentralized and virtual tools, such as telemedicine and mobile health apps, supports patient adherence to treatment protocols

To sum it up, our ability to be quick on our feet, and our total dedication to giving our collaborators the best experience is key to their success in ophthalmology. Working hand-in-hand, Fortrea and our collaborator in the APAC region didn't let any hurdles slow us down. We made fast changes, cut through the timeline and got the job done ahead of schedule successfully. This story is a great example of how we can handle tough situations and keep pushing forward with ophthalmology trials.

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Considerations for the design of a DES trial

When designing a clinical trial for dry eye syndrome, the following considerations should be taken into account:[12,13]

The vehicle response issue

Ensuring a convincing placebo

To keep the trial unbiased, it's essential to use a placebo that's virtually indistinguishable from the active treatment. Typically, the vehicle of active formulation serves as the comparator. This helps maintain blinding, ensuring neither participants nor researchers know who's receiving the real treatment. It's also important to consider how the comparator might influence the signs and symptoms of DES.

Key considerations from DEWS II report (2017)

Masking the start of treatment

- One effective strategy is to implement a "run-in" period of one-two weeks, where all participants receive the control (vehicle) before randomization. This helps identify and exclude patients who respond to the vehicle alone, enriching the study population with non-responders. It is crucial to set up appropriate duration of the run-in period and inclusion and exclusion criteria

Withdrawal trial design

- Starting with the active medication, following by randomizing patients to either the vehicle or the trial drug group, the concern of the above design is the long-lasting effects of the active therapy following discontinuation are often unclear. It is crucial to set up an appropriate "time-to-baseline" period based on the Mechanism of Action

Double masking to minimize bias

Implementing double masking to keep all participants, clinical staff and laboratory personnel unaware of the treatment assignment ensures that the trial results are as accurate and unbiased as possible.

Inclusion criteria

Setting clear enrollment criteria

To ensure the representative study population and the results can be generalized properly, it's crucial to clearly set up specific criteria for diagnosing and assessing the severity of DES, including symptoms and signs.

Our recent dry eye syndrome trial

In our recently completed trial mentioned in section three, we enrolled patients with moderate to severe DES. Specifically, patients had to have an Eye Dryness Score (EDS) of 40 or higher, together with consistent signs of DES on slit lamp examination, with a corneal fluorescein staining (CFS) score and Schirmer test results.

Taking account of the duration of symptoms, only patients who had experienced symptoms for at least six months were included; which ensured the patient population had chronic, rather than temporary, dry eye conditions.

All these designs are to ensure the study population represents the broader patient group affected by moderate to severe dry eye.

Managing other dry eye treatments during the trial

Considering the mode of action

For the management of other concomitant DES therapies during the trial, carefully considering the mechanism of action (MOA) of the medication ensures that the primary treatment's effects can be accurately assessed without undue interference from other therapies.

Our recent dry eye syndrome trial

In our recently completed trial mentioned in section three, allowing participants to continue their current therapies, such as artificial tears reflects real-world clinical practice, where patients often use a combination of treatments to manage their symptoms, and also simulate the conditions under which the investigational medication would be used in everyday clinical settings, to ensure the results are relevant to the practical management of DES in clinical practice.

Identifying relevant and measurable endpoints

Identifying relevant and measurable endpoints is crucial to be both clinically meaningful and statistically measurable.[5,12]

Common endpoints in dry eye trials

- **Improvements in tear production:** Schirmer test is often used to quantify the volume of tears
- **Reduction in ocular surface damage:** Corneal fluorescein staining (CFS) is often used to assess whether the treatment is helping to protect and heal the eye's surface
- **Relief of symptoms:** Symptoms such as dryness and discomfort which often significantly impact the patient's quality of life are often measured using patient-reported outcomes (PROs), such as visual analog scales (VAS) or questionnaires like the Ocular Surface Disease Index (OSDI)

Combining objective and subjective measures

- **Objective measures:** By collecting quantifiable and providing hard data Schirmer test for tear production and tear break-up time (TBUT) for assessing tear film stability will give a clear, unbiased view of the physiological changes
- **Subjective measures:** By collecting the patient's experience through PROs like the VAS for dryness and discomfort, and the OSDI for overall ocular surface health, provide insights into how the treatment is affecting the patient's daily life

Adaptive trial designs

With the challenges associated with DES such as high placebo response rates and the need for robust, reliable outcomes, adaptive trial designs can be highly beneficial in DES trials. Interim results are important to optimize the trial parameters and improve the chances of success.[15,18]

As regulatory agencies may have specific requirements and concerns regarding adaptive designs, clear communication and justification of the design choices are essential. Adaptive designs require sophisticated statistical methods to handle interim analyses and potential changes in the trial protocol. Some adaptive designs, such as crossover trials, may require more frequent visits and longer participation from patients.

Statistical study design methodologies stratification factors

Dry Eye Syndrome study design methodologies varied with objective and subjective assessments to define stratification cutoff.

In our recent successful DES trial mentioned in section three, we used specific stratification factors to ensure a balanced and representative study population. It also helps in minimizing variability and enhancing the statistical power of the trial. By using both objective and subjective measures stratification factors (baseline EDS <60 versus ≥60, and baseline STS ≤5 versus >5) and by baseline inferior CFS subgroup (<1.5 versus ≥1.5) were used, we can comprehensively assess the efficacy of the treatment, ensuring that the results are clinically meaningful and generalizable.

Minimizing data variability

Ensuring consistency in data collection and minimizing variability across all study sites is crucial for reliable results. This can be achieved through standardized protocols, training of clinical staff, use of standardized supplies, well-described exam procedures and the use of advanced technologies for data capture and analysis.[5,12]

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Medical guidance in implementation—fresh hands-on experience from our recent successful DES trial

Challenges	We did
The issue of large differences in repeated STS test results	• **Fixed Test Personnel:** Ensure that the same group of personnel conduct the tests to reduce operational differences • **Standardized Operating Procedures:** Develop detailed operating procedures to ensure consistency in each test • **Specified Testing Time:** Conduct tests within the same time frame to avoid differences in tear secretion caused by circadian rhythms • **Appropriate Testing Environment:** Control the temperature and humidity of the testing environment to prevent external factors from affecting tear secretion
Prohibited medication in washout period	Review all the concomitant medications in medical history
Sequence of ophthalmic tests	• Sequence should be clearly defined in protocol usually with BCVA the first, IOP the last • Post-treatment BCVA would wait around 10 minutes after all other ophthalmic tests
Considerations for using a placebo as the control group in this study	**Short study duration:** The entire trial research period is relatively short. Given the disease characteristics of the dry eye subject population, the health risk impact of delaying potentially effective treatment on subjects is minimal. **Permissible concomitant treatments for placebo group:** Subjects in the placebo group are allowed to receive symptomatic treatments other than the prohibited drugs, such as artificial tears. **In terms of scientific basis** **Direct comparison with placebo:** By comparing the study drug directly with the placebo, absolute efficacy and safety data of the study drug can be obtained. Therefore, the trial results are more reliable, which can provide a solid basis for guiding future clinical medication and meeting the requirements for drug registration. **Previous clinical trial data (internal data):** Based on the completed clinical trial data, the proportion of patients in the placebo group with an increase in Schirmer's test score (STS) of ≥10 mm from baseline was 26%, and the average increase in STS from baseline was 4.9 mm.

Challenges	We did
STS strip length: 35mm should be used instead of 30mm	For patients who may reach the end of the current test strip scale (30 mm) within five minutes, how should the operation be conducted? There is still a blank section beyond the scale's end. Use the steel ruler uniformly distributed by the project team to manually measure the part without marked scales as the test data. Please note that the zero mark on the steel ruler should be aligned with the 30 mm mark on the Schirmer test strip for measurement.
Corneal epithelial defects issue in enrollment	A significant proportion of patients with moderate to severe dry eye have corneal epithelial defects. In our recent successful DES trial, researchers will initially determine whether the corneal epithelial defects are clinically significant and related to DES, but do not require intervention, such cases can be screened. If it requires treatment, which may affect the patient's safety in participating in the clinical trial and the evaluation of the trial, the patient should be excluded.
Waiting for more than 2 minutes in corneal fluorescein staining is necessary for several reasons	**1. Optimal staining time for accurate assessment** The optimal time for assessing corneal fluorescein staining can vary depending on the concentration of fluorescein dye in the tear film. Research indicates that the timing of observation can range from immediate assessment to a gap of one to four minutes from the time of dye instillation.[17] For instance, studies have shown that the median time to reach the maximum corneal fluorescein staining (Gmax) is around 2.6 to 3.8 minutes for different conditions.[1] Waiting for more than two minutes allows the dye to distribute evenly across the ocular surface, providing a more accurate representation of the corneal epithelial integrity. **2. Minimizing false positives and negatives** Waiting for an extended period helps in minimizing false positives and negatives. Due to the initial distribution and dilution of the dye, immediate assessment after dye instillation may not accurately reflect the true state of the corneal epithelium. By waiting for more than two minutes, the dye has sufficient time to interact with the corneal surface, highlighting any areas of epithelial defect or instability more reliably. **3. Consistency and reliability** Waiting for more than two minutes ensures consistency in the assessment process. This standardized waiting period helps in obtaining reliable and reproducible results across different patients and clinical settings. It reduces variability in the staining pattern due to the timing of observation, leading to more consistent diagnoses.

Challenges	We did
	4. Impact of tear film dynamics The tear film dynamics, including tear film break-up time (TBUT), can influence the staining pattern. By waiting for more than two minutes, the tear film has time to stabilize, and any initial disturbances caused by the dye instillation can be minimized. This ensures that the observed staining is more reflective of the underlying corneal condition rather than transient tear film changes. **5. Clinical relevance** Waiting for more than two minutes aligns with clinical guidelines and best practices. This approach is supported by various studies and clinical experiences, which recommend allowing sufficient time for the dye to interact with the corneal surface to provide meaningful diagnostic information.
The use of artificial tears are allowed in our recent DES trial and its potential impact on study data are carefully considered.	It would be impossible to distinguish whether the effectiveness observed is due to artificial tears or the investigational drug. **Considerations:** **1. From a statistical perspective:** The purpose of randomization is to balance confounding factors between the placebo group and the active drug group. Therefore, the use of artificial tears and non-use of artificial tears will achieve balance between groups, having no substantial impact on intergroup comparisons. **2. Experience from completed Phase III Trials in the United States with same protocol (internal data):** Artificial tears were included as a covariate in the analysis, and no significant impact of artificial tears on the trial results was found. If artificial tears were not used prior to the start of the study, it is not recommended to actively provide subjects with artificial tears during the trial. Especially considering that even in the placebo group, tear secretion improved significantly, with benefits exceeding those of artificial tears. To sum up, in clinical trials, the use of artificial tears needs to be carefully considered. Although from a statistical standpoint and based on prior study experiences, their impact on study outcomes appears to be limited, it is still essential to minimize confounding factors during trial design and execution to ensure the accuracy and reliability of the study results.
Stratification factors were used in randomization and statistical analysis	• Pre-treatment (baseline) anesthetized Schirmer's score (≤5, >5) measured at the screening visit • Pre-treatment (baseline) EDS (<60, ≥60) measured at the screening visit

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Future directions in dry eye syndrome research and clinical trials

Ongoing research: New therapeutic targets and personalized medicine

Gene therapy: Exploring gene therapy as a potential treatment for DES is an exciting frontier. By targeting the root causes of DES at the genetic level, gene therapy could offer long-term solutions for patients who do not respond well to current treatments.[7]

Fecal replacement treatment: Though unconventional but opening new avenues for treating DES by addressing systemic etiology factors.[7]

Technological integration: AI and machine learning

From patient recruitment to data analysis, AI and machine learning can help streamline trial processes by addressing common challenges such as rising costs and slow recruitment, to support and enhance the precision of clinical trials.[10]

With the capability to analyze vast amounts of data to identify patterns and predict outcomes, AI algorithms can make the trial process more efficient. By selecting the most suitable candidates for trials, machine learning can help improve the overall success rate and help reduce costs.[10]

Collaborations

By sharing data and insights, pooling resources and knowledge, all collaborative efforts within research institutions, pharmaceutical companies and patient advocacy groups can provide additional resources and insights, leading to more comprehensive and impactful trial outcomes, supporting the development of new treatments and therapies.

Patient-centric approaches

By minimizing the burden of participation and providing clear, transparent communication, we can make the trial process more accessible and less daunting for patients, leading to enhanced engagement and adherence.

Using decentralized trial models and telemedicine allowing for remote monitoring and data collection reduced the need for frequent in-person visits and made it easier for patients to participate in trials.[10,19]

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