25 July 2024
EMA/439518/2024
EMA/439518/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vevizye

International non-proprietary name: ciclosporin

Procedure No. EMEA/H/C/006250/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AS	Active Substance
ASM	Active Substance Manufacturer
BDL	Below the limit of detection
BET	Bacterial endotoxin test
BI	Biological indicator
cCFS	central corneal fluorescein staining (cCFS)
CEP	Certificate of suitability
CFS	Corneal Fluorescence stain
CHMP	Committee for Human Medicinal Products
CKC	Cetalkonium chloride
CT	Clinical Trial
CTD	Common technical document
CoA	Certificate of Analysis
CRS	Chemical Reference Standard
CQA	Critical quality attribute
COSY	Correlation Spectroscopy
DAD	Diode-array detection
DED	Dry Eye Disease
EDQM	European Directorate for the Quality of Medicines
EI	Elemental impurities
EMA	European Medicines Agency
EP	European Pharmacopoeia
EO	Ethylene Oxide
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FID	Flame-ion detector
FT-IR	Fourier Transformation Infrared Spectroscopy
FP	finished product
FPS	Finished Product Specifications
GC	gas chromatography
GMP	Good Manufacturing Practice
HCl	Hydrochloric Acid
HMBC	Heteronuclear Multiple Bond Correlation Spectroscopy
HPLC	High performance liquid chromatography
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
IPC	In-process control test
ICH	International conference on harmonisation

IPC	In process control
IR	Infra-red
KF	Karl Fischer
IPA	Isopropyl alcohol
LDPE	low-density polyethylene
LoD	Loss on Drying
LOD	Limit of detection
LOQ	Limit of Quantitation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation holder
MCT	Triglycerides, medium-chain
NLT	Not less than
nm	nanometre
NMT	Not more than
NVR	Non-volatile residue
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
ppm	parts per million
Psi	pressure per square inch
PV	Process Validation
QC	Quality control
QOS	Quality Overall Summary
QP	Qualified Person
QTPP	quality target product profile
RA	Risk Assessment
RH	Relative Humidity
RRF	Relative response factor
RRT	Relative retention time
RS	Residual solvents
PVDF	Polyvinylidene fluoride
Rt	Retention time
RT	Room temperature
SAL	Sterility assurance level
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TAMC	Total aerobic microbial count
tCFS	total corneal fluorescein staining
TTC	Threshold of toxicological concern

TYMC	Total yeast microbial count
UV	Ultraviolet
US	United states
USP	United States Pharmacopoeia
VAS	visual analogue scale
WFI	Water for injections
WS	Working standard

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novaliq GmbH submitted on 28 July 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Vevizye, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2022.

The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on interest of patients.

The applicant applied for the following indication:

Treatment of dry eye disease in adult patients, which has not improved despite treatment with tear substitutes.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

In accordance with Regulation (EC) No 1901/2006, the application included an EMA Decision P/0140/2023 on the granting of a product-specific waiver, on the ground of lack of significant therapeutic benefit in all paediatric subsets.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: Jana Klimasová

The application was received by the EMA on	28 July 2023
The procedure started on	17 August 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	14 November 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	07 May 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	30 May 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 July 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vevizye on	25 July 2024

2. Scientific discussion

2.1. Disease or condition

Dry eye disease (DED), also known as keratoconjunctivitis sicca, is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (international Dry Eye Workshop - DEWS, Craig et al., 2017).

2.2. Epidemiology and risk factors, screening tools/prevention

Epidemiologically, DED is a common ocular surface disorder, with an estimated prevalence in Europe ranging from 10% to 30% (Malet et al 2014; Vehof et al 2014; Viso et al 2009), higher in females and elderly population.

2.3. Aetiology and pathogenesis

DED is a complex, immune-mediated inflammatory disease of the lacrimal gland and ocular surface, where several pathological processes lead to ocular surface damage (Messmer et al., 2023).

Aetiology of DED is multifactorial, and the primary cause may vary. However, all forms of DED enter a common self-reinforcing inflammatory circle (the 'vicious circle') (Craig et al., 2017) affecting the lacrimal function unit, the complex apparatus comprising the lacrimal glands, ocular surfaces, eyelids, and connecting sensory and motor nerves, which regulates the major components of the tear film.

Inflammation of the lacrimal function unit leads to hyperosmolarity of tears, cellular damage and loss of epithelial and goblet cells, finally leading to tear film instability and inflammation (Periman et al., 2020). The loss of goblet cells results in disturbed mucin production and loss of immunoregulation, which in turn results in epithelial damage and further increase of inflammatory cytokines. Hence, a self-reinforcing inflammatory cycle is pivotal in the development and self-perpetuation of the disease, leading to progressive ocular surface damage and related clinical signs and symptoms.

2.4. Clinical presentation, diagnosis and stage/prognosis

Clinically, DED is characterized by a persistently unstable and/or deficient tear film causing discomfort and/or visual impairment, accompanied by variable degrees of ocular surface epitheliopathy, inflammation, and neurosensory abnormalities (Tsubota et al 2020).

The disease is characterized by ocular discomfort signs (e.g., redness, reduction in tear production, mucus discharge, fast tear break-up time) and symptoms (e.g., burning, irritation) of increasing frequency, although there is usually poor correlation between signs and symptoms. If untreated or undertreated, DED progressively damages the ocular surface, with possible major ocular complications such as infections or ulcers, and potentially irreversible impairments of visual functions (Rouen et al 2018).

A compromised ocular surface secondary to DED may affect refractive measurements prior keratorefractive and phacorefractive surgeries and adversely impact expected visual outcomes after surgeries (Starr et al 2019; Goto et al 2002; Koh 2016; Stapleton et al 2017; Donaldson et al 2022). Therefore, it is recommended to treat the corneal surface damage prior to ocular procedures (Starr et al 2019; Craig et al 2017; AAO Dry Eye Syndrome Preferred Practice Pattern 2018; Steinert et al).

DED has been associated with a substantial impact on vision, quality of life (Buchholz et al 2006; Leonardi et al 2021; Morthen et al 2021), and work productivity, and carries a significant physical and psychological burden (Messmer et al., 2023, Morthen et al 2021).

2.5. Management

Goal of DED management is to restore the homeostasis of the ocular surface (Messmer et al., 2023), which can be achieved by breaking the vicious circle of inflammation. The therapeutic approach is typically multistaged. Environmental factors that increase tear evaporation and may decrease tear

production should be minimized. Tear supplementation with artificial tears / lubricants is usually the first choice of treatment for mild to moderate cases of DED (Craig et al 2017).

Tear substitutes are a replacement of the natural tear film, and may provide a beneficial effect on ocular surface by decreasing friction and reduce tear hyperosmolarity, however they do not address the underlying inflammatory pathophysiology. If the first line approach provides insufficient control of the disease, anti-inflammatory agents should be initiated. Pharmacological treatments recommended by the International Dry Eye Workshop (DEWS) of the Tear Film and Ocular Surface Society and multiple treatment guidelines include ciclosporin and corticosteroids (Jones et al 2017, German Leitlinie BVA und DOG, 2019; Guias espanolas Ojo Seco).

Topical corticosteroids are effective in reducing inflammation in DED, but can be used only for short-term treatments due to due to potential adverse events (AEs), including ocular hypertension, cataracts and opportunistic infections.

Topical ocular ciclosporin can be employed as a second line therapy in DED (when lubricating eye drops, lid hygiene measures, and modification of environmental factors are insufficient) for a more extended period of time (Messmer et al. 2023, Leitlinie von BVA und DOG Trockenes Auge, 2019). Ikervis is the only topical ocular ciclosporin product approved in the EU for the treatment of DED (EMA/CHMP/473489/2014). Ikervis is indicated for treatment of severe keratitis in adult patients with DED, which has not improved despite treatment with tear substitutes. DED with severe keratitis represent a subset of the moderate to severe DED patients who may benefit from second line therapies based on international guidelines (Messmer et al. 2023). About 10-15% of patients treated with Ikervis discontinue the treatment due to intolerance to the product (Ikervis EMA EPAR 2015; Deshmukh et al 2022). To mitigate local intolerance and overcome late onset of effect, Ikervis is frequently initiated together with topical corticosteroids, which are tapered off over 4-8 weeks (bridging approach).

Therefore, there is an unmet medical need for topical anti-inflammatory treatments particularly for moderate DED patients not responding to first line therapies such as artificial tears. For patients with moderate and severe DED, there is need for treatments with improved tolerability that would reduce concurrent treatment with corticosteroids.

2.6. About the product

Pharmacotherapeutic group: Ophthalmologicals, other ophthalmologicals, ATC code: S01XA18.

Vevizye (development name: CyclASol) is an ophthalmic sterile solution without preservatives containing 0.1% weight per volume (w/v) ciclosporin (also named cyclosporine A, CsA, cyclosporine or cyclosporin). As ciclosporin is virtually insoluble in water, in Vevizye it is solubilized in a vehicle containing the novel excipient semifluorinated alkane perfluorobutylpentane and ethanol.

Ciclosporin is an anti-inflammatory and selective immunomodulatory substance with a well-characterized pharmacological profile. Primary pharmacodynamic activity of ciclosporin is inhibition of the phosphatase activity of calcineurin, which inhibits lymphokine production and release, including interleukin 2 (IL-2). In addition, ciclosporin reversibly inhibits immunocompetent lymphocytes, particularly T-lymphocytes, in the G0- and G1-phase of the cell cycle.

Systemically, ciclosporin acts as an immunosuppressant, which prolongs the survival of allogenic transplants by suppressing the cell-mediated immune reaction after transplantation, during contact sensitization, graft-versus-host reaction, and T-cell dependent antibody formation.

On the ocular surface, ciclosporin displays a dual and partly opposing mechanism of action on conjunctival and T cells (Pflugfelder and de Paiva, 2017). In the conjunctiva, ciclosporin blocks opening

of the mitochondrial permeability transition pore (MPTP), thereby inhibiting cytochrome C-mediated activation of caspases in the mitochondria (Gao et al., 2013). Inhibition of caspases blocks apoptosis of inflamed conjunctival cells, thereby restoring goblet cell density (Periman et al., 2020). In activated T-cells on the ocular surface, ciclosporin opens MPTP, resulting in the activation of apoptosis. Additionally, ciclosporin blocks NFκB translocation and the mitogen-activated protein kinase pathway, inhibiting the transcription and secretion of inflammatory cytokines and subsequent T cell recruitment.

Excipient perfluorobutylpentane is physically, chemically, and physiologically inert. The low surface and interface tension of perfluorobutylpentane facilitate dissemination of the applied eye drop on the conjunctiva, and the local bioavailability of ciclosporin. Due to these physical properties, Vevizye eye drops are of small volume, approximately 10 µl/drop. One drop of Vevizye 0.1% eye drops solution contains 0.01 mg of ciclosporin.

2.7. The development programme/compliance with guidance/scientific advice

The clinical development programme of Vevizye comprises 6 clinical studies: one study in healthy volunteers, and five studies in the target population of DED including two pivotal studies. All studies are completed, a tabulated summary is provided in section 3.3 of this document. Prior to the initiation of the two pivotal studies, the clinical program was discussed with EU national authorities (BfArM, MPA, and AGES) in various scientific advice meetings (relevant discussions summarized in table 1), as well as with the US FDA.

Table 1: Regulatory interactions with EU national authorities

Agency	Date	Discussion item
BfArM	16. Mar 2011	Discussion and agreement that the proposed data package supports the first clinical study with Vevizye.
	10 Apr 2012	
AGES	25 Jun 2015	Discussion and agreement that the preclinical data package supports the Phase 2 study, and discussion of the clinical development strategy (endpoints, study duration, approval requirements in EU).
MPA	2 Jul 2015	
AGES	1 Jun 2017	Discussion and agreement on the Phase 3 study design (dose selection, endpoints, statistical approach, PK data sufficient). While AGES had no objections with a 1-month study duration for a pivotal study, MPA raised the concern that this duration might not be regarded as pivotal. To address this concern, the CYS-003 study design was modified to a 3-month study.
MPA	28 Jun 2017	

2.8. Quality aspects

2.8.1. Introduction

The finished product is presented as eye drops containing 1mg/ml of ciclosporin as active substance, also referred to in this report as 0.1% eye drops.

Other ingredients are: perfluorobutylpentane and ethanol, anhydrous.

The product is available in a multiple-dose, translucent polypropylene bottle with a translucent polyethylene tip and a white polyethylene cap with tamper-evident ring.

2.8.2. Active Substance

2.8.2.1. General information

The chemical name (IUPAC) of ciclosporin is (3*S*,6*S*,9*S*,12*R*,15*S*,18*S*,21*S*,24*S*,30*S*,33*S*)-30-ethyl-33-[(1*R*,2*R*,4*E*)-1-hydroxy-2-methylhex-4-en-1-yl]-1,4,7,10,12,15,19,25,28-nonamethyl-6,9,18,24-tetrakis(2-methylpropyl)-3,21-bis(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2,5,8,11,14,17,20,23,26,29,32-undecone, corresponding to the molecular formula $C_{62}H_{111}N_{11}O_{12}$. It has a relative molecular mass of 1203 g/mol and the following structure (*Figure 1*):

Figure 1: active substance structure

The chemical structure of ciclosporin was elucidated by a combination of FT-IR and UV spectroscopy, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry and elemental analysis by the active substance manufacturer.

The active substance (AS) is a white or almost white, slightly hygroscopic powder. It is practically insoluble in water and insoluble in pH range 1.2 to 6.8. It is freely soluble in anhydrous ethanol and slightly soluble in saturated hydrocarbons and very soluble in methanol, ethanol, acetone, and diethyl ether.

Ciclosporin is a well-known active substance, and it is monographed in the European Pharmacopoeia (monograph number 0994). As there is a monograph of ciclosporin in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for ciclosporin which has been provided within the current Marketing Authorisation Application.

Different solid state forms have been identified and the most thermodynamically stable has been used throughout development.

Ciclosporin A is a molecule which possesses several chiral carbon atoms. Control of stereoisomers has been assessed in the CEP. The correct enantiomer is controlled by specific optical rotation in the AS specification.

2.8.2.2. Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The details of the container closure are stated on the provided CEP.

2.8.2.3. Specification

The active substance specification includes tests for: appearance (visual), solubility (visual), identity (IR, HPLC), appearance of solution (Ph. Eur.), specific optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), related substances (Ph. Eur.), assay (Ph. Eur.), residual solvents (GC), and microbiological quality (Ph. Eur.).

The control for impurities is in accordance with the requirements of both the CEP and the general monograph on Substances for pharmaceutical use (2034). A request was made to include a test for microbiological quality in line with 5.1.4 non-sterile pharmaceutical substances. The microbiological quality test has been added to the specification and thus, this issue is resolved.

The control tests comply with the specifications and test methods of the Ph. Eur. monograph. An additional residual solvent from the manufacturing process is specified and adequately controlled. The analytical method has been adequately validated and described according to ICH Q2.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for three commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

2.8.2.4. Stability

Information on the stability program, including results of forced degradation, stress studies, photostability and the re-test period were assessed by EDQM. The retest period for ciclosporin AS is defined in the CEP.

2.8.3. Finished Medicinal Product

2.8.3.1. Description of the product and pharmaceutical development

The finished product (FP) Vevizye 0.1 % eye drops (Ciclosporin Eye Drops) is an ophthalmic sterile solution, which does not contain preservatives. One bottle contains 2 mL of a clear, colourless solution containing 2 mg ciclosporin. A single strength is proposed.

Development work started with the acknowledgement that ciclosporin is practically insoluble in water. Due to the lipophilic character of ciclosporin, ciclosporin solutions in aqueous media are difficult to achieve without solution enhancers, emulsifiers, or further additives.

Therefore, an alternative non-aqueous solvent was required and a non-aqueous, lipophilic ophthalmic solution was developed using the novel excipient perfluorobutylpentane as a solvent for the AS. Perfluorobutylpentane was identified as a suitable solvent in the initial solubility study. Further development data demonstrated the feasibility of a 1.0 mg/mL ciclosporin solution.

Perfluorobutylpentane belongs to the chemical class of semi fluorinated alkanes and consists of a perfluorinated hydrocarbon and a non-fluorinated alkane chain. Due to the chemical nature and the absence of any functional group within the molecule the novel excipient does not show any chemical reactivity which could interact with the AS.

Perfluorobutylpentane itself is practically insoluble in water, and water is practically insoluble in perfluorobutylpentane and, therefore, the two liquids do not mix. As perfluorobutylpentane has a higher density (1.295 g/mL) than water, mixtures of the two will separate into two layers with the

perfluorobutylpentane layer on the bottom. Because perfluorobutylpentane does not mix or contain water, it exhibits no pH, osmolality, or water activity, and therefore does not support microbial growth.

The function of each component and a reference to their quality standard has been provided.

The applicant has justified the use of the novel excipient perfluorobutylpentane as it is chemically inert, due to the absence of functional groups. In addition, it is physiologically inert, whilst providing favourable physical properties including low surface tension which allows rapid spread and penetration of the drug in the eye, and a refractive index prevents blurring of vision. The acceptability of this excipient in terms of safety at the proposed concentration has been sufficiently discussed in the dossier (refer to the non-clinical part of this report).

Once perfluorobutylpentane was identified as a suitable solvent, the applicant has presented a quality target product profile (QTPP) and a list of critical quality attributes (CQAs) for the FP in line with ICH Q8.

The focus of development was to identify a formulation with ciclosporin in a sterile, preservative-free solution, in a container closure system suitable for storage and administration of the FP to the eye.

Manufacturing Process Development

The manufacturing process is a non-standard method as it involves sterilisation by filtration and filling using aseptic processing. Nevertheless, the process is not complex and involves the compounding of the AS with the excipients to provide the bulk drug solution which is then sterile filtered into a sterile hold vessel and aseptically filled into the final container closure system. Therefore, the process development data provided is concise.

The container closure system is a translucent 5-mL polypropylene bottle fitted with a low-density polyethylene dropper and high-density polyethylene screw cap and allows controlled dosing to the eye. The materials of the bottle and dropper are not compatible with terminal sterilisation by heat or gamma radiation and therefore, the product is manufactured by sterile filtration followed by aseptic filling. This is considered acceptable.

The multidose container contains 2000 µl (2 ml) including an overfill to ensure that, the maximum daily dose of 2 drops per eye (40 µl/ 0.04 mg), can be dispensed over a 4-week period. The EMA Q&A on multidose container is not applicable in this instance as the usage period is not greater than 4 weeks. The applicant has demonstrated that the FP does not allow microbial growth and meets the Ph. Eur. antimicrobial effectiveness test requirements without the need for added preservative. The integrity of the proposed container closure system has been successfully evaluated through microbial ingress testing.

No data has been presented demonstrating compatibility with other eye medications. Section 6.2 of the SmPC therefore states "In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products."

The suitability of the container closure system in terms of functionality, usability, performance, safety, and compatibility with the contents was discussed. The design and execution of extractable and leachable studies were explained. Several leachable impurities were identified and limits are set at toxicologically justified levels in the finished product specification.

Sterilisation of the packaging is carried out with ethylene oxide (EO) due to intolerance to terminal sterilisation. In this regard, the CHMP raised a MO because in line with EMA/CHMP/CVMP/QWP/850374/2015 Guideline on sterilisation, the applicant had not provided a discussion regarding potential residual known genotoxic impurities. An evaluation of the risk from these impurities carried out in accordance with the requirements of ICH M7 "Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk" was missing from the compatibility discussion for container closure system.

In their response the applicant presented an evaluation of those genotoxic impurities and assessed the contamination of the FP from exposure to EO. Data showed that residual EO and ethylene chlorohydrin (ECH) levels are sufficiently low and adequately controlled by the validated sterilisation process with neither being present above 30% of the acceptable intake in the validation batches. The established routine control for residual EO and ECH is in line with the ICH M7 limit and the proposed control strategy and control limit for residual EO and ECH is acceptable based on the data presented and the MO was resolved.

Novel excipient - Perfluorobutylpentane

General information

The chemical name (IUPAC) of perfluorobutylpentane is 1,1,1,2,2,3,3,4,4-nonafluorononane corresponding to the molecular formula $C_9H_{11}F_9$. It has a relative molecular mass of 290.17 g/mol. and the following structure:

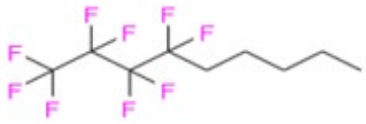


Figure 2. **chemical structure of perfluorobutylpentane**

Perfluorobutylpentane appears as a clear, colourless, practically odourless liquid, practically immiscible with water and miscible with many organic solvents such as ethanol, methanol, 2-propanol, acetone, chloroform, methylene chloride, ethyl acetate.

The chemical structure of perfluorobutylpentane has been elucidated by MS, ^{1}H-NMR, ^{13}C-NMR, UV-VIS, IR and elemental analysis.

Manufacture, characterisation and process controls

Perfluorobutylpentane is manufactured under ISO 9001 standards. The applicant has included both an abbreviated narrative and flow-chart followed by a detailed narrative description of the manufacturing process.

All the material used in the synthesis are stated and a control specification has been provided.

The in-process controls are described and are considered adequate to control all steps of the manufacturing process of this excipient, including the critical steps listed in the dossier.

The packaging material was described and is acceptable.

Specification

The specification of perfluorobutylpentane is presented and includes tests for: description (visual),visible particles (Ph. Eur.), identification (GC, refractive index (Ph. Eur., IR), assay (GC-FID), impurities (GC-FID), residue on evaporation (in-house), density (Ph. Eur.) and microbiological quality (Ph. Eur.).

The control strategy, specification, analytical methods, validation, and justification for specification has been developed and presented.

The applicant has presented a discussion covering, actual and potential impurities.

Toxicological assessment of perfluorobutylpentane has been performed in line with ICH M7. A number of impurities with structure alerts and some potential mutagenic impurities were identified. In relation to the control strategy for the identified impurities the CHMP raised a MO asking the applicant to provide batch data to demonstrate purge capability of the process. In their response the applicant provided further scientific justification, concluding that they would be purged by the process. Based on the presented argumentation, the CHMP considers option 4 control justified, the control strategy for impurities adequate and thus the MO is considered resolved.

Overall, the proposed specification is considered acceptable. The analytical methods were sufficiently described, including the reference standards used. Non-Compendial methods were adequately validated.

Stability

Stability studies under long term (25 °C / 60% RH) and under intermediate conditions (30 °C/ 65% RH) for 36 moths and for 6 months under accelerated conditions (40 °C / 75% RH) on four batches of various batch size.

Data for all test parameters at all time-points and storage conditions are well within the specified limits. Trends could not be observed.

Stress testing and photostability studies were also performed. The excipient is stable under all conditions.

Although no retest period is applicable to excipients, the excipient has been shown to be sufficient stable. It can be confirmed that the stability of perfluorobutylpentane supports the discussions and conclusion presented in the dossier.

2.8.3.2. Manufacture of the product and process controls

The manufacturing process comprises several steps including compounding of AS with excipients, followed by sterile filtration and aseptic filling. The process is considered to be a non-standard manufacturing process due to the aseptic filling.

The information provided for process description, in-process controls (IPCs) and batch formula are acceptable. Critical manufacturing steps have been identified and are controlled by suitable IPCs.The bulk hold and processing times for the sterilised product have been justified by data demonstrating that sterility is maintained.

Major steps of the manufacturing process have been validated by a number of studies. In response to a MO raised in this regard satisfactory process validation results have been provided for three consecutive commercial scale batches; the MO was thus resolved. In addition, validation data for the filters has been provided and is acceptable. A discussion on media fill simulations and validation has been provided as well. Satisfactory data on the validation of the sterilisation of packaging components by ethylene oxide gas was provided. Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.8.3.3. Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), container description and appearance (visual), visible particles (Ph. Eur.), filling volume (weighing), weight loss (weighing), identification of ciclosporin (HPLC), assay (HPLC), impurities (HPLC), leachable impurities (HPLC) and sterility (Ph. Eur.).

The proposed release and shelf-life specifications, and related analytical tests are generally acceptable and in line with ICH Q6. The specified parameters monitored via IPCs, at release and at shelf-life are generally in compliance with the Ph. Eur. monograph for "eyedrops" and ICH Q6A. Justifications for inclusion of test parameters and limits were provided and are acceptable.

As the formulation does not contain water, no tests for pH or osmolarity are included. Regarding the assay, the proposed limit at release is acceptable and the shelf-life limit is justified.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed as requested (MO) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004 Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for three commercial scale batches was provided, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.8.3.4. Stability of the product

Stability data from 3 batches of finished product stored for up to 24 months under long term conditions (25 °C / 60% RH), for up to 24 months under intermediate conditions (30 °C/ 65% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, visible particles, particulate matter, closure integrity and weight loss, ciclosporin assay, impurities and sterility. The analytical procedures used are stability indicating. Overall, the results remain within the specification limits. However, some variability was observed in the results reported for the 3 pilot stability batches at various timepoints. The source of this variability was sufficiently discussed and was justified. Based on this the proposed assay limit at shelf-life was also justified. The applicant included storage instructions in the SmPC (section 6.4) to minimise the observed variability. The statistical analysis presented supports the applicant's claim that the variability observed is within a controlled range for this formulation and dosage form and based on the current method of manufacturing and controls, proposed no further investigation which was considered acceptable.

Supportive stability data for three months under long term conditions and intermediate conditions from the three commercial scale process validation batches have been also provided. Data from these three

batches revealed a new leachable impurity, which led to updating the FP specifications including a test and limit for it. The CHMP recommended in this regard the applicant to submit updated method validation data via a post approval measure (PAM) as a Recommendation.

Photostability study in line with ICH Q1B was performed on the three pilot stability batches. The results showed no change in colour, or any other physical deterioration. Comparison of the assay and purity results for test and dark control samples did not show any significant differences. However, two specified unknown impurities were found slightly higher in the exposed sample versus the control sample and additional unknown, unspecified impurities were also observed. There was also a slight increase in total impurities in the test sample versus the control sample. Overall, the results suggest that ciclosporin eye drops solution does not undergo significant photochemical degradation.

An in-use stability study was performed on the three pilot scale stability batches. After 4 weeks of simulated use and storage at 25 °C / 60% RH, all results comply with the specification limits thus supporting the SmPC shelf-life recommendations in section 6.3.

Based on available stability data, the proposed shelf-life of 2 years with the storage conditions "Do not store above 25 °C" and "Do not freeze or refrigerate" as stated in the SmPC (section 6.3 and 6.4) is acceptable. Vevizye can be used 4 weeks after first opening of the bottle. The bottle should be kept tightly closed when not in use.

2.8.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.8.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A novel excipient is used in the finished product for which sufficient information about its manufacture and control the has been provided.

During the procedure, four Major Objections were raised in relation to the risk assessment on the evaluation of genotoxic impurities, to the sterilisation method of the containers of the finished product, the process validation of the manufacturing process of the finished product, the risk assessment for nitrosamine impurities, and the control of mutagenic impurities in the novel excipient. All MOs were satisfactorily resolved by provision of additional data and justifications.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to updating the validation report of an analytical method. This point was put forward and agreed as a recommendation for future quality development

2.8.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.8.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

- The applicant should provide the method validation report for the newly identified leachable impurity by 11/03/2025. If changes in the test procedure or specification limits are warranted, the appropriate post approval variation should be submitted.

2.9. Non-clinical aspects

2.9.1. Introduction

Vevizye, ciclosporin eye drops, solution 1 mg/mL (development name: CyclASol) is a clear ophthalmic solution of ciclosporin. Vevizye has been developed by Novaliq GmbH for the topical treatment of Dry Eye Disease (DED) in adult patients, which has not improved despite treatment with tear substitutes. Vevizye contains 0.1% (w/v) ciclosporin solubilized in the novel water-free liquid excipient perfluorobutylpentaneas the vehicle with ethanol.

DED (keratoconjunctivitis sicca (KCS)) is characterized by tear film instability, hyperosmolarity and inflammation of the ocular surface appearing independently or consequently of certain eye diseases (e.g., glaucoma and cataracts), ocular inflammations, ocular surgeries and contact lens wear. Thus, DED is an inflammatory-driven disease affecting the lacrimal gland, conjunctiva, and cornea (Periman et al 2020). Reverberating vicious cycles (initiation, amplification recruitment, damage, and re-initiation) develop governed by hyperosmolarity and desiccating stress, along with loss of immunoregulatory controls. Tear hyperosmolarity causes damage to the surface epithelium, beginning with an increase in the mitogen-activated protein kinase (MAPK) and nuclear factor kappa B on the ocular surface (Stern et al 2013). The activation of MAPK triggers the secretion of inflammatory mediators, which facilitate activation of resident dendritic cells and T-cell recruitment to the ocular surface (Stern et al 2013). Recruited T cells release other inflammatory mediators, which compromises the lacrimal functional unit further, elevates the tear hyperosmolarity, which further accentuates cellular damage and loss of epithelial and goblet cells. These processes are leading to a progressive cycle of tear film instability and inflammation.

Ciclosporin is a well-known and potent immunosuppressant cyclic (11 amino acid containing) polypeptide with enormous scientific literature and with a great experience in the clinical practice. Basically,

ciclosporin is a calcineurin inhibitor and at the cellular level, it inhibits the formation and release of cytokines including interleukin 2 (IL-2). Ciclosporin blocks the lymphocytes in the G0 or G1 phase of the cell cycle and inhibits the antigen-mediated release of lymphokines by activated T cells. Ciclosporin bound to cyclophilin inhibits the activity of the serine/threonine phosphatase calcineurin, which normally dephosphorylates NFAT (nuclear factor of activated T cells) after antigen binding to the T-cell receptor (Donnenfeld and Pflugfelder 2009). Dephosphorylated NFAT is transported to the nucleus, where it initiates transcription of T-cell cytokines, notably IL-2 and IFN-gamma (Sall et al 2000). Ciclosporin blocks opening of the mitochondrial permeability transition pore (MPTP) thereby inhibiting activation of caspases in the mitochondria, which blocks apoptosis of inflamed conjunctival cells and restores goblet cell density. Ciclosporin does not affect haematopoiesis and the function of macrophages (Shevach 1985; Hirao et al 1993) and its action is reversible and restricted to the lymphocytes. In addition, ciclosporin has an antiapoptotic and protective action on human conjunctival epithelial cells, unlike corticosteroids (Jones et al 2017, Gao et al 2013).

Application of ciclosporin to the ocular surface accompanies with anti-inflammatory and immunomodulatory action involving the lachrymal glands opening the way to the increased secretion of tear and allow the more proper tear film development on the surface of the eye.

The proposed mode of actions of ciclosporin is summarized in the Figure 3.

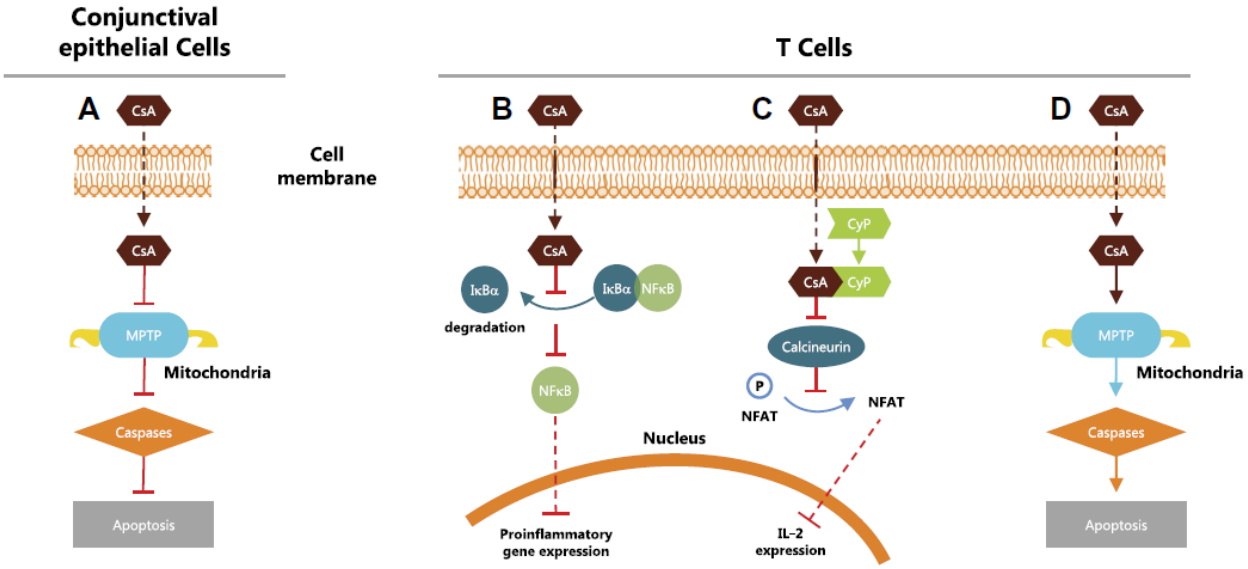


Figure 3. Mode of action of ciclosporin:

(A) Inhibits intrinsic mitochondrial pathway and caspase activation with an antiapoptotic and protective action on human conjunctival epithelial cells.

(B) Inhibits nuclear factor κB (NFκB) activation and the subsequent release of proinflammatory cytokines through modulating proteasome activity.

(C) Binds with cyclophilin to form a calcineurin complex and inhibits dephosphorylation of nuclear factor of activated T cells and the subsequent release of interleukin 2.

(D) Induces T cell apoptosis by regulating Fas/Fas ligand expression, caspase activation, and mitochondrial permeability transition pore (MPTP) opening.

Abbreviations: CsA, ciclosporin A; CyP, cyclophilin; Iκßα, nuclear factor of κ light polypeptide gene enhancer in ß-cell inhibitor, alpha; IL-2, interleukin 2; MPTP, mitochondrial permeability transition pore; NFAT, nuclear factor of activated T cells; NFkB, nuclear factor of kB; P, phosphorylated.

(Jerkins et al 2020)

2.9.2. Pharmacology

Primary pharmacodynamic studies

The Applicant performed animal experiments to investigate the pharmacodynamic properties of Vevizye (ciclosporin with the excipient perfluorobutylpentane) according to the Article 8(3) of Directive 2001/83/EC. Altogether three series of experiments were performed in mice administered the test substance in topical administration to the eye surface as an eye drop.

One of the presented series of results is based on a peer reviewed journal publication (Gehlsen et al 2017), the remaining two experimental series are internal scientific reports from University of Cologne, Department of Ophthalmology and from Ora Inc. USA.

Secondary pharmacodynamic studies

N/A

Safety pharmacology programme

Three GLP compliant toxicological studies of the excipient perfluorobutylpentane were submitted by the Applicant.

The safety profile of ciclosporin is well known in the scientific literature.

The cardiovascular system targeted study (20-3-0106-12) was performed in New Zealand White rabbits as a part of 28 Day Toxicity Study with perfluorobutylpentane after repeated administration into the conjunctival sac.

No evidence of an effect of the repeated administration of perfluorobutylpentane into the conjunctival sac of rabbits over a treatment period of 28 days at daily doses of 1x, 2x and 3x 200 µL/eye (corresponding to 513, 1026 and 1538 mg/animal/day, respectively) on mortality, general and local clinical signs, body weight development, feed consumption and conversion, on parameters of laboratory investigations (i.e. haematology, clinical chemistry and urinalysis) as well as on macroscopic necropsy and histopathological findings was found.

To summarize the results of the present study, a "no observable adverse effect level" (NOAEL) at a daily dose 3x 200 µL/eye (corresponding to 1538 mg/animal/day) could be identified for perfluorobutylpentane in rabbits after repeated administration into the conjunctival sac for 28 days.

CNS safety pharmacology studies were performed in rats in a 28-day repeated dose toxicity of perfluorobutylpentane after 28 day of oral gavage (p.o.) application including a four-week recovery period. Additional safety pharmacology investigations of the respiratory tract were included. Rats in the study were treated either with a 0.9% NaCl solution (control) or 500, 1000 or 2000 mg/kg perfluorobutylpentane orally once daily for 28 days based on the twice weekly determined body weight. The rats in groups 5 and 6 (recovery) were kept for additional 28 days without treatment. The test substance perfluorobutylpentane was used undiluted, and therefore small amounts of the liquid

substance had to be administered orally. The use of higher dose levels reduced the probability of technical problems during substance administration and therefore 2000 mg/kg were selected as high dose. The evaluation conducted on the potential effects of the novel excipient perfluorobutylpentane on the central nervous system (CNS) involved a GLP-compliant 4-week toxicity study in rats. Various assessments, including locomotor activity and a Functional Observational Battery (FOB), were carried out. The totality of the data, including repeat-dose toxicity studies, indicates no consistent adverse effects of perfluorobutylpentane on the CNS, further supporting its safety profile.

2.9.3. Pharmacokinetics

Methods of analysis

Three different validated bioanalytical methods (all are based either on liquid chromatography-mass spectrometry (LC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) were used for quantification of ciclosporin in rabbit whole blood. Two of these methods were also validated for quantification of ciclosporin in some ocular tissues (one was GLP compliant the other is not).

Due to the physicochemical characteristics of F4H5 (apolar, not dissolving in water, volatile) the bioanalytical method development was not straightforward. Three bioanalytical methods, all based on gas chromatography-mass spectrometry (GC-MS), were validated for the quantification of perfluorobutylpentane in rabbit or rat whole blood. The first two methods were not always strictly in compliance with the acceptance criteria suggested by EMA's "Guideline on bioanalytical method validation" (one of those methods were applied in four GLP compliant repeated dose toxicity studies in rabbits and rats). The third method was further optimized and was validated according to regulatory guidelines; however, it was only used in one of five Additionally, in two studies (in rats and rabbits) ^{14}C-labelled perfluorobutylpentane was used to determine the absorption, distribution, and excretion of perfluorobutylpentane by liquid scintillation counting.

Pharmacokinetics of ciclosporin

Only absorption and local tissue distribution after topical ocular administration was studied by the applicant. According to the full mixed application the applicant relies on published data about ciclosporin's systemic distribution, metabolism, and excretion. Three in vivo studies were performed in rabbits. From these single or repeated dose studies it can be concluded that systemic exposure of ciclosporin after topical ocular dosing of Vevizye is negligible, resulting in a C_{max} of approx. 0.6 ng/ml following a 6-month treatment with a high dose formulation (Vevizye 0.15%). The local tissue distribution data suggest that compared to aqueous products of ciclosporin (Ikervis® and Restasis®) perfluorobutylpentane results in a faster increase in ciclosporin tissue concentration in some eye tissues (cornea, lacrimal gland, retina), while after prolonged treatment the difference is maintained for the cornea only and was less pronounced for the conjunctiva.

Pharmacokinetics of perfluorobutylpentane

Due to its physicochemical properties intravenous injection of perfluorobutylpentane was not possible, and s.c. and i.p. administration resulted in local granulomatous inflammation and depot formation with lower systemic exposure than oral administration, so apart from the topical ocular route, oral route of administration was selected to assess systemic exposure of perfluorobutylpentane with acceptable tolerability.

Systemic exposure of perfluorobutylpentane was investigated as part of the repeated dose toxicity studies after oral administration in rats (1-month, and 6-month toxicity studies), and after topical ocular administration in rabbits (1-month and 6-month toxicity studies), as well as in a single dose topical ocular PK study. In addition, absorption was assessed in two ADME studies using radiolabelled 14C-perfluorobutylpentane after oral administration in rats and after topical ocular administration in rabbits.

After oral administration of perfluorobutylpentanemaximum blood concentrations (C_{max}) did not increase with repeated administration up to 6 months, and systemic exposure (AUC levels) generally did not increase proportionally with dose. Saturation of absorption was suggested because of missing dose linearity of exposure parameters and decreasing C_{max} values with increasing doses. However, some discrepancies could be identified between studies applying different methods for concentration measurements. As the applicant has shown, these discrepancies were primarily due to methodological differences between the studies (differences in dosing interval) perhaps amplified by the effect of slow elimination of perfluorobutylpentane.

Similarly, in the performed topical ocular administration studies the systemic exposure for perfluorobutylpentane was not dose-proportional in either sex for single dose and repeated dosing, with a wide variability of peak perfluorobutylpentane concentrations (C_{max} range: 8.49-1178 ng/ml) and modest increases in AUC across the 45-1538 mg/day dose range indicating limited but non-zero absorption.

The systemic distribution of perfluorobutylpentane was assessed after a single or multiple oral administrations of radiolabelled 14C-perfluorobutylpentane. The highest levels of perfluorobutylpentane-related radioactivity were found in gastrointestinal tract contents. The maximum percentage recoveries in tissues (not including the gastrointestinal tract contents) were <0.6% of the administered dose at 24 hours post-dose, indicating little but not zero association or accumulation of perfluorobutylpentane with tissues. The tissue:plasma concentrations ratios were mostly greater than one, indicating a greater association of substance-related radioactivity with tissues than with plasma. The almost insolubility in water and adherence to lipophilic structures were probably also responsible for the observed higher blood:plasma concentration ratios which seemed to be time dependent and hence was more pronounced after multiple dosing. At 168-hr post-dose, substantially higher levels of substance-related radioactivity relative to plasma were observed in ovaries and reproductive fat in females (tissue:plasma ratios of 10.4 and 14.1), while 3.5-4.5-fold higher radioactivity contents relative to plasma were measured in prostate and testes in males (tissue:plasma ratios of 4.36 and 3.62). High levels of substance-related radioactivity were also seen in adrenals and pituitary gland in males (tissue:plasma ratios of 19.9 and 13.8).

Metabolism of perfluorobutylpentane was evaluated in an in vitro study which demonstrated that perfluorobutylpentane is not metabolized by liver microsomes of rats, rabbits or humans.

2.9.4. Toxicology

Single dose toxicity

No single dose toxicity studies have been conducted with Vevizye by the Applicant.

Repeat dose toxicity

The Applicant conducted a 1- and 6-month repeat-dose ocular toxicity studies for examination of the safety of Vevizye ophthalmic solution. Ciclosporin is a well-known active ingredient of several drug products indicated for systemic use, so systemic toxicity of ciclosporin is well characterized.

The repeat-dose ocular toxicity studies were carried out according to the requirements of the relevant guideline (Guideline on non-clinical local tolerance testing of medicinal products, EMA/CHMP/SWP/2145/2000 Rev. 1, Corr.1, 2015).

The test articles used in the repeat-dose ocular toxicity studies correspond to the final formulation of Vevizye, their quality is supported by the submitted CoAs. The tests were carried out on New Zealand White rabbits, which is a suitable species for evaluation of biocompatibility, safety and toxicity of topical ocular formulations.

The purpose of the pivotal 6-month ocular study was to evaluate the local ocular and systemic toxicity of Vevizye ophthalmic solution in rabbits after repeated ocular administration over a period of 3 (interim) and 6 months.

Vevizye ophthalmic solution was administered at two different concentrations (0.05% and 0.15%) topically into the conjunctival sac of both eyes of test animals which correspond to the intended route for therapeutic use in humans. The vehicle used in this study was the vehicle to Vevizye, the vehicle contains Perfluorobutylpentane / Ethanol. In parallel test groups the vehicle or the control (physiological saline) or a comparator (Restasis) were administered via the same route.

According to the ophthalmologic and histopathological examinations no signs of test item-related local toxicity were revealed. No signs of test item-related systemic toxicity were recorded in the investigated clinical parameters and in organ weights. The histopathology findings in the lungs and liver were considered not to be related to treatment with vehicle and test item.

The results of the 6-month ocular study show that final formulation of Vevizye is safe and well tolerated by the rabbit eye after repeated locally exposure. Based on the findings in this study, the highest dose, 0.15% Vevizye was proved to be the no observed adverse effect level (NOAEL).

Systemic toxicity of ciclosporin

No systemic toxicity studies of ciclosporin were conducted by the Applicant. Published data were submitted on repeat-dose toxicity (oral and IV), genotoxicity, carcinogenicity, reproductive and developmental toxicity studies for ciclosporin. Systemic exposure of ciclosporin in human studies as well as in repeat-dose ocular toxicity study in rabbits was negligible, so the well-known systemic toxic effects are not considered to be relevant for ocular use of ciclosporin.

Tolerance

The local ocular tolerance of Vevizye has been examined in the 1-month and 6-month topical ocular toxicity studies in rabbits. According to the studies' results the final formulation of the drug product did not cause any local intolerance in rabbit eye.

Other toxicity studies

Vevizye ophthalmic solution contains 0.1% (w/v) ciclosporin solubilized in the novel water-free liquid excipient perfluorobutylpentane as the vehicle with ethanol. Comprehensive toxicology studies were carried out with the novel excipient, perfluorobutylpentane.

In the 6-month oral toxicity study in rats, the novel excipient, perfluorobutylpentane did not cause any systemic toxic effect. The findings were minimal and limited to changes in plasma and urinary electrolytes and increased kidney and liver weight at all doses. There were not any histopathological changes in

kidney or liver, so the findings were not considered adverse. The NOAEL was established at the highest dose tested, 1000 mg/kg/day.

In the 1- and 6-month ocular toxicity study in rabbits, the novel excipient, perfluorobutylpentane did not cause any systemic and local toxic effect. The repeated administration of perfluorobutylpentane in rabbits over 1 month or 6 months at daily doses of 513, 1026 and 1538 mg/animal/day did not have any effect on mortality, clinical signs, body weight development, food consumption, ophthalmic examination, ECG, and parameters of laboratory investigations (i.e. haematology, clinical chemistry and urinalysis) as well as on macroscopic necropsy, organ weights and histopathological findings.

The potential genotoxicity of perfluorobutylpentane was evaluated in a standard test battery including a reverse mutation test in bacteria (Ames test), a chromosomal aberration test in human lymphocytes, and a micronucleus test in mice according to the requirement of ICH S2 (R1) guideline. The negative study results demonstrated that perfluorobutylpentane does not have any mutagenic or genotoxic effect.

An adequate reproductive risk assessment was submitted for the new excipient, perfluorobutylpentane in the response documentation on Day 120.

The Applicant justified that perfluorobutylpentane has a different toxicity profile, which translates in a robust safety profile, compared to PFAS with known toxicity. The non-clinical pharmacokinetic data did not show that reproductive organs are the specific target of compound retention or toxicity. In the chronic toxicology studies (oral or topical ocular administration) the new excipient, perfluorobutylpentane, did not cause any systemic or local adverse effect. There were no signs of toxicity in the reproductive organs and in tissues related to steroid synthesis.

The embryo-fetal development toxicity studies of the structural surrogate compound, perfluorohexyloctane did not show embryo-fetal toxicity. In the reproductive toxicity studies the tested oral doses (1000 mg/kg/day in the rabbit, 2000 mg/kg/day in rat) provide more than 1000-fold safety margins compared to the human topical ocular dosing (0.87 mg/kg/day).

The clinical safety database of the drug product under review as well as the available safety data of the structural similar compound (perfluorohexyloctane) did not reveal any risk for long-term-use.

Based on the mentioned facts the risk for reproductive toxicity of the new excipient is considered very low and dedicated studies are not considered necessary.

An adequate carcinogenic risk assessment was submitted for the new excipient, perfluorobutylpentane .

The carcinogenic potential of perfluorobutylpentane is considered very low because the genotoxicity studies did not reveal any genotoxic potential of perfluorobutylpentane. The route of administration is topical ocular which is associated with negligible systemic exposure according to the human and animal pharmacokinetic studies. In these studies there was no notable accumulation in any tissues or organs. In the chronic toxicity studies in rats and rabbits the perfluorobutylpentane did not cause any proliferative or preneoplastic lesions. In these studies high safety margins for perfluorobutylpentane can be calculated.

PFAS with known toxicity can act as ligands for the peroxisome proliferator-activated receptors (PPARs), these nuclear receptors are transcription factors with many biological effects. The new excipient, perfluorobutylpentane is not expected to induce epigenetic alterations in genome and to bind to PPARs because of its different physicochemical properties. The structurally similar compound, perfluorohexyloctane did not also show any induction of PPARs in an in-vitro-test conducted by the Applicant. Therefore, the chemical structure of perfluorobutylpentane without functional groups and heteroatoms does not suggest any structure reactivity relationship indicative for carcinogenic risk.

The structurally related product (perfluorohexyloctane) of the SFAS class has been marketed as medical device since 2015 and no evidence of carcinogenic risk has been shown.

Based on the mentioned facts, the new excipient, perfluorobutylpentane is not associated with a carcinogenic risk, so a dedicated study is not required.

Local tolerance of perfluorobutylpentane in the eye was examined in the 1- and 6-month repeat-dose toxicity studies in rabbits with topical ocular administration of the compound. No significant ocular irritation or toxicity was seen with topical ocular doses of ≤ 1538 mg/day (200 µL/eye administered 3 times a day for up to 6 months).

In 2 *in vitro* cytotoxicity studies, potential cytotoxic effects of perfluorobutylpentane were analyzed. Under the conditions prevailing in these studies, no leachable substances were released in cytotoxic concentrations from the test item.

In a non-GLP study, tear film changes after multiple daily topical ocular instillations of perfluorobutylpentane were investigated in NZW rabbits. In conclusion, 30 µL/eye perfluorobutylpentane (38 mg/eye) administered by topical ocular administration 4 times daily (152 mg/day) for 7 days to rabbits was well tolerated and had no effects on TBUT or tear secretion.

Ecotoxicity/environmental risk assessment

Table 2

Substance (INN/Invented Name): Cyclosporin A			
CAS-number (if available): 59856-13-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	ECHA, 2017		Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2,92	not B
	BCF		not B
Persistence	DT50 or ready biodegradability		not P
Toxicity	NOEC or CMR		not T
PBT-statement:	The compound is not considered as PBT.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.00044	µg/L	< 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)

Ciclosporin PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, ciclosporin is not expected to pose a risk to the environment.

Concerning the perfluorobutylpentane excipient from environmental risk assessment:

Perfluorobutylpentane belongs to PFAS compounds which are of a particular environmental concern due to their persistence in the environment. In accordance with Article 8(3) of Directive 2001/83/EC the

environmental impact should be assessed on a case-by-case basis like in the case of perfluorobutylpentane in the present application.

The conclusion of the submitted ERA is that the excipient perfluorobutylpentane has the potential to be persistent. Applicant has added adequate risk mitigation measure in section 6.6 of the SmPC according to the relevant guideline.

2.9.5. Discussion on non-clinical aspects

Pharmacodynamic aspects

Ciclosporin is a well-known and potent immunosuppressant cyclic (11 amino acid containing) polypeptide. Ciclosporin is a calcineurin inhibitor and at the cellular level, it inhibits the formation and release of cytokines including interleukin 2 (IL-2). Ciclosporin blocks the lymphocytes in the G0 or G1 phase of the cell cycle and inhibits the antigen-mediated release of lymphokines by activated T cells. Cyclosporine bound to cyclophilin inhibits the activity of the serine/threonine phosphatase calcineurin, which normally dephosphorylates NFAT (nuclear factor of activated T cells) after antigen binding to the T-cell receptor. Dephosphorylated NFAT is transported to the nucleus, where it initiates transcription of T-cell cytokines, notably IL-2 and IFN-gamma. Ciclosporin blocks opening of the mitochondrial permeability transition pore (MPTP) thereby inhibiting activation of caspases in the mitochondria, which blocks apoptosis of inflamed conjunctival cells and restores goblet cell density. Ciclosporin does not affect haematopoiesis and the function of macrophages, and its action is reversible and restricted to the lymphocytes. In addition, ciclosporin has an antiapoptotic and protective action on human conjunctival epithelial cells, unlike corticosteroids. In activated T cells on the ocular surface, ciclosporin opens MPTP, resulting in the activation of apoptosis.

The salient results of the presented studies demonstrate that dry-eye disease (DED) (scopolamine administration combined with low humidity induced corneal damages) can be improved with the study drug Vevizye (0.05%, 0.1% and in one experiment 0.2%), but it did not show concentration-dependent responses. It is stated in the study reports and easy to deduct from the presented data and figures that even the used excipient perfluorobutylpentane had a significant effect using the experimental protocols presented in the performed studies.

In the three submitted study reports the same method was used with slight modification described here in brief: The Experimental dry eye (EDE) was induced in 10–12-week-old female C57BL/6 mice. Mice were placed in a controlled environment chamber (humidity 30 ± 5%, constant airflow, temperature 25 ± 1 °C) for 14 days. Scopolamine was administered (0.1 mg/day) by subcutaneous implanted osmotic pumps (Alzet, model #1002). Pumps were explanted after 2 weeks (day 14). After 14 days of desiccating stress, animals were transferred to normal controlled housing conditions (humidity 45–55%, no airflow, temperature 24 ± 2 °C) for another 3 weeks. Topical therapy (5 µl/eye, 3 times daily) was applied from day 11 (late therapy/therapeutic) or from day 4 (early therapy/prophylactic) of experimental dry eye. Mice were distributed in four groups: (1) Vevizye in different concentrations (0.05%, 0.1%, 0.2%), (2) carrier perfluorobutylpentane with ethanol, in some experiments (3) Restasis (Allergan Inc., Irvine, CA, USA) was used as a reference and (4) unpreserved Dexamethasone (Monodex 1 mg/ml, TheaPharma, Berlin, Germany) in one experiment. The control group was left untreated and received no eye drops but was housed under the same desiccating stress and standard housing conditions as the other therapy groups. The used methods are adequate to investigate the effect of the product in EDE but does not model exactly the human DED because the human disease is a long-lasting and continuous one and, in these experiments, the exsiccating influences (scopolamine and the low humidity environment) were ceased, thus the experimental setup does not strictly conform to the requirements of translational medicine.

Secondary pharmacodynamic experiments were not performed.

The safety profile of ciclosporin is well known in the literature and no study was submitted into this direction, which is acceptable. The novel excipient (perfluorobutylpentane) was under the scope in two reports. The central nervous system (CNS) and the respiratory system (RS) safety were assessed in rats after systemic administration of perfluorobutylpentane and the cardiovascular system safety was examined on rabbits after topical administration of perfluorobutylpentane to the surface of the eye as an eye-drop. The presented experimental results show no serious safety concerns.

Pharmacokinetic aspects

The applicant developed three liquid chromatography-mass spectrometry (LC-MS) based methods for ciclosporin concentration measurements which were validated according to the guidelines for quantification of ciclosporin in rabbit whole blood and ocular tissues. Although not all validation studies claimed strict GLP compliance, they were adhered to GLP requirements and were in line with EMA's Guideline on bioanalytical method validation. Using these methods for characterization of the systemic absorption and local tissue distribution ciclosporin after topical ocular administration of Vevizye, the applicant showed that systemic exposure of ciclosporin after topical ocular dosing is negligible, and, compared to aqueous products of ciclosporin, the local eye tissue penetration of ciclosporin is similar or even faster. The applicant relies on published data about ciclosporin's systemic distribution, metabolism, and excretion which is acceptable considering that the application is a full mixed application.

Because of the physicochemical properties (apolar, immiscible with water and volatile) of the novel excipient perfluorobutylpentane, the bioanalytical method development proved to be somewhat difficult. Three bioanalytical methods, all based on gas chromatography-mass spectrometry (GC-MS), were validated for the quantification of perfluorobutylpentane in rabbit or rat whole blood, but only one was fully validated according to regulatory guidelines. Although generally the accuracy and precision of these methods were in the predetermined range in the validation studies, the large variability of the individual measurements at least partly might be due to its physicochemical properties and the methodology (e.g., sample handling). Potential issues related to long-term stability of perfluorobutylpentane in animal matrix and sensitivity of the methods were clarified by the applicant.

The performed studies after oral and topical ocular administration of perfluorobutylpentane did not show extended absorption and distribution but some discrepancies could be identified between studies applying different methods for concentration measurements (GC-MS based versus liquid scintillation based). Systemic exposure for perfluorobutylpentane was not dose-proportional and signs of saturation of absorption were noted. Peak perfluorobutylpentane concentrations showed wide variability of exposure (C_{max} range: 8.49-1178 ng/ml) across the 45-1538 mg/day dose range indicating limited but non-zero absorption. The studies with radiolabelled perfluorobutylpentane confirmed the not-extensive systemic exposure but it was noted that despite the declining tissue concentrations, low level of radioactivity was detectable even at 168 hours post-dose in tissues.

Toxicology aspects

The Applicant conducted only repeat-dose ocular toxicity studies for examination of the safety of Vevizye ophthalmic solution. **Ciclosporin** is a well-known ingredient of several drug products indicated for systemic use in the prevention of graft rejection in solid organ transplantation, in the treatment of autoimmune diseases, so its systemic toxicity is well characterized.

The Applicant carried out 1- and 6-month ocular toxicity studies of Vevizye in New Zealand White rabbits and comprehensive toxicity studies of the novel excipient perfluorobutylpentane. For the systemic toxicity of ciclosporin, published data were submitted.

No adverse ocular or systemic effects with low ciclosporin systemic exposure were observed in the 1-month topical ocular toxicity study with 0,05% Vevizye (perfluorobutylpentane /ethanol) BID (50 µg/eye/day) and in the 6-months topical ocular toxicity study with 0.15% Vevizye (perfluorobutylpentane /ethanol) 3 times daily (TID) (180 µg/eye/day), respectively, in rabbits. The ocular dose safety margin for ciclosporin at the NOAEL in these studies was 2.5- and 9-times higher, respectively, than the daily human ocular dose of 0.1% Vevizye BID (20 µg/eye/day). Systemic exposure of ciclosporin was below the lower limit of quantification (0.1 ng/mL) in studies with healthy volunteers and dry eye patients, therefore, a safety margin (SM) based on PK could not be calculated.

Published data were submitted on repeat-dose toxicity (oral and IV), genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies for ciclosporin. Systemic exposure of ciclosporin in human studies as well as in repeat-dose ocular toxicity study in rabbits was negligible, so the well-known systemic toxic effects are not considered to be relevant for ocular use of ciclosporin.

Vevizye ophthalmic solution contains 0.1% (w/v) ciclosporin solubilized in the novel water-free liquid excipient **perfluorobutylpentane** as the vehicle with ethanol. Comprehensive toxicology studies were carried out with the novel excipient, perfluorobutylpentane.

In the 6-month **oral** toxicity studies with perfluorobutylpentane in rats, the novel excipient did not cause any systemic toxic effect. The findings were minimal and limited to changes in plasma and urinary electrolytes and increased kidney and liver weight at all doses. There were no histopathological changes in kidney or liver, so the findings were not considered adverse. The NOAEL was established at the highest dose tested, 1000 mg/kg/day.

In the 1- and 6-month **ocular** toxicity studies in rabbits, the novel excipient, perfluorobutylpentane did not cause any systemic and local toxic effect. The repeated administration of perfluorobutylpentane in rabbits over 6 months at daily doses of 513, 1026 and 1538 mg/animal/day did not have any effect on mortality, clinical signs, body weight development, food consumption, ophthalmic examination, ECG, and parameters of laboratory investigations (i.e. haematology, clinical chemistry and urinalysis) as well as on macroscopic necropsy, organ weights and histopathological findings. In connection with the similar systemic exposure of the treated groups in the 1- and 6-month study the Applicant argues that the flat systemic exposure across dose groups may reflect volume limitations of a topical ocular dose. Based on the Applicant’s response on Day 120 it is acceptable that nasolacrimal drainage followed by swallowing as well as oral intake of the test compound via grooming are considered particularly relevant after topical ocular application of higher application volumes.

Because the volume limitations after ocular treatment it is agreed that high doses and repeated administration were used in the topical ocular toxicity studies. The high doses were clearly supratherapeutic and allowed high local periocular concentrations. According to the toxicokinetic parameters of perfluorobutylpentane in the 1-month and 6-month topical ocular toxicity studies the NOAEL values determined by the Applicant (1538 mg/day perfluorobutylpentane) is acceptable.

The safety margin values for perfluorobutylpentane were calculated on the bases of PK data, the Applicant took into account the highest Cmax (13.7 ng/ml) obtained in clinical studies. In the case of 6-month ocular toxicity study in rabbits with the Vevizye vehicle only 1-fold SM can be calculated. That is acceptable because the treatment-related topical or systemic toxic effects were not observed. In the case of 6-month ocular toxicity study in rabbits with perfluorobutylpentane more than 10-fold SM can be calculated that justifies the systemic safety of perfluorobutylpentane.

The potential genotoxicity of perfluorobutylpentane was evaluated in a standard test battery including a reverse mutation test in bacteria (Ames test), a chromosomal aberration test in human lymphocytes, and a micronucleus test in mice according to the requirement of ICH S2 (R1) guideline. The negative study results demonstrated that perfluorobutylpentane does not have any mutagenic or genotoxic effect.

Adequate reproductive and carcinogenic risk assessments were submitted for the new excipient, perfluorobutylpentane.

The Applicant justified that perfluorobutylpentane has a different toxicity profile, which translates in a robust safety profile, compared to PFAS with known toxicity. The non-clinical pharmacokinetic data did not show that reproductive organs are the specific target of compound retention or toxicity. In the chronic toxicology studies (oral or topical ocular administration) the new excipient, perfluorobutylpentane, did not caused any systemic or local adverse effect. There were not any signs of toxicity in the reproductive organs and in tissues related to steroid synthesis.

The embryo-fetal development toxicity studies of the structural surrogate compound, perfluorohexyloctane did not show embryo-fetal toxicity. In the reproductive toxicity studies the tested oral doses (1000 mg/kg/day in the rabbit, 2000 mg/kg/day in rat) provide more than 1000-fold safety margins compared to the human topical ocular dosing (0.87 mg/kg/day).

The carcinogenic potential of perfluorobutylpentane is considered very low because the genotoxicity studies did not reveal any genotoxic potential of perfluorobutylpentane. The route of administration is topical ocular which is associated with negligible systemic exposure according to the human and animal pharmacokinetic studies. In these studies there was no notable accumulation in any tissues or organs. In the chronic toxicity studies in rats and rabbits the perfluorobutylpentane did not cause any proliferative or preneoplastic lesions. In these studies high safety margins for perfluorobutylpentane can also be calculated.

The structurally related product (perfluorohexyloctane) of the SFAS class has been marketed as medical device since 2015 and no evidence of reproductive and carcinogenic risk has been shown.

Based on the mentioned facts, the new excipient, perfluorobutylpentane is not associated with reproductive and carcinogenic risk, so dedicated reproductive and carcinogenic studies are not required.

According to the results of the repeat-dose ocular toxicity studies neither the final formulation of the drug product nor the new excipient (perfluorobutylpentane) caused any local intolerance in rabbit eye. Based on tear film evaluation test in rabbits the F4H5 was well tolerated and had no effects on tear film break-up time or tear secretion.

Based on lack of ocular or systemic effects with Vevizye vehicle (perfluorobutylpentane /ethanol) in the 6-month ocular toxicity study in rabbits and an associated ocular dose safety margin of ethanol that is 6-times higher than the daily human ocular dose, ethanol is qualified up to the used concentration for topical ophthalmic administration in humans.

Ciclosporin PEC surfacewater value is below the action limit of 0.01 µg/L and ciclosporin is not a PBT substance as log Kow does not exceed 4.5. Therefore, ciclosporin is not expected to pose a risk to the environment. The Applicant sufficiently justified the lack of a detailed ERA for the new excipient, perfluorobutylpentane.

PFAS compounds are of a particular environmental concern due to their persistence in the environment. Perfluorobutylpentane is a relatively frequently used PFAS compound. The environmental impact of the present excipient (perfluorobutylpentane) is necessary to address according to the Article 8(3) of Directive 2001/83/EC on a case-by-case basis.

The Applicant submitted an ERA for the novel excipient perfluorobutylpentane, based on weight-of-evidence determination. According to the available information, excipient perfluorobutylpentane has the potential to be persistent. Applicant has added adequate risk mitigation measure in section 6.6 of the SmPC.

2.9.6. Conclusion on non-clinical aspects

Pharmacology

In conclusion, the pharmacodynamic properties of ciclosporin are well known in the literature and the submitted non-clincal studies prove the effectiveness of ciclosporin in experimental dry eye. The safety of the new excipient (perfluorobutylpentane) was properly demonstrated by the Applicant.

Pharmacokinetics

The performed pharmacokinetic studies proved the local tissue distribution and negligible systemic exposure to ciclosporin after topical ocular administration of Vevizye. However, some questions and discrepancies were identified with respect to the pharmacokinetic studies of the excipient perfluorobutylpentane, for which the systemic exposure seemed to be limited but not insignificant. The applicant reassuringly clarified the raised issues.

Toxicology

In conclusion, the established well-known toxicological profile of ciclosporin in the literature, the results of ocular toxicity studies of Vevizye, and a range of repeat-dose ocular and oral toxicity studies, genotoxicity studies and other toxicity studies of perfluorobutylpentane, support the safety profile of Vevizye ophthalmic solution. Adequate reproductive and carcinogenic risk assessments were submitted for the new excipient, perfluorobutylpentane. It was justified that perfluorobutylpentane is not associated with reproductive and carcinogenic risk, so dedicated reproductive and carcinogenic studies are not required.

Adequate ERA was submitted for the novel excipient perfluorobutylpentane. According to the available information, excipient perfluorobutylpentane has the potential to be persistent and, so risk mitigation measure was added to the 6.6 section of the SmPC.

2.10. Clinical aspects

2.10.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The clinical development program of Vevizye comprises six clinical studies, summarized in Table 3 Pivotal studies are indicated in bold type. All studies are completed.

One study was conducted in healthy volunteers and five studies in the target population of DED. All Novaliq's studies were conducted in the US, with exception of the study on healthy volunteers (CYS-001), which was carried out in Germany. An additional study (SHR8028-301) was conducted in patients with DED by Novaliq's partner Jiangsu Hengrui Pharmaceutical Co. in China.

Two studies are considered as pivotal in this application, i.e., studies CYS-003 and CYS-004, and three are supportive, i.e. study CYS-002, study CYS-005, and study SHR8028-301 (Table 3).

Table 3: Overview of the clinical development program

Study ID **Phase** **Relevance**	**Objectives**	**Design** **Main inclusion criteria**	**Population**	**Study drug** **Dose regimen** **Duration of treatment**	**Primary endpoint(s)**
CYS-001 Phase 1 *Supportive*	Safety and tolerability, PK	Single-center, randomized, double-masked, vehicle-controlled, 2-period, 2-way cross-over	N 18 Healthy subjects 18-45 years All treated with Vevizye	Vevizye 0.05% or vehicle <u>Dosing regimen A:</u> Day 1: single drop OD (one eye), Day 2 and 3: single drop OU BID <u>Dosing regimen B</u>: Days 9, 10, and 11: Two drops OU BID 11 days per period, wash-out of 5 days between A and B	Safety
CYS-002 Phase 2 *Supportive*	Efficacy, safety and tolerability, PK	Multicenter, randomized, double-masked, vehicle-controlled, with open-label comparator arm. Subjects with DED, tCFS ≥6 (NEI), dryness score ≥ 40, total lissamine green conjunctival score ≥2 (Oxford), Schirmer's tear test score ≥2 to ≤8 mm.	N 207 Vevizye 0.05%: 51 Vevizye 0.1%: 51 Vehicle: 52 Restasis: 53	Vevizye 0.05%, Vevizye 0.1%, vehicle, or Restasis Single drop OU, BID for 112 days	CFB in tCFS Day 113 CFB in dryness score Day 113
CYS-003 **Phase 2b/3** ***Pivotal***	**Efficacy, safety and tolerability**	**Multicenter, randomized, double-masked, vehicle-controlled.** **Subjects with DED, tCFS ≥10 (NEI), OSDI score ≥20, total lissamine green conjunctival score ≥2 (Oxford), Schirmer's tear test score ≥1 to ≤10 mm.**	**N 328** **Vevizye 0.1%: 162** **Vehicle: 166**	**Vevizye 0.1% or vehicle** **Single drop OU, BID for 84 days**	**CFB in tCFS Day 29** **CFB in total OSDI Day 29**
CYS-004 **Phase 3** ***Pivotal***	**Efficacy, safety and tolerability**	**Multicenter, randomized, double-masked, vehicle-controlled.** **Subjects with DED, tCFS ≥10 (NEI), dryness score ≥ 50, total lissamine green conjunctival score of ≥2 (Oxford), Schirmer's tear test score ≥1 to ≤10 mm.**	**N 834** **Vevizye 0.1%: 423** **Vehicle: 411**	**Vevizye 0.1% or vehicle** **Single drop OU, BID for 29 days**	**CFB in tCFS Day 29** **CFB in dryness score Day 29**
CYS-005 (open-label extension to CYS-004) Phase 3 *Supportive*	Safety, tolerability and efficacy during long-term use	Multicenter, open-label, single arm extension study to CYS-004. Subjects with DED, tCFS ≥10 (NEI), dryness score ≥ 50, total lissamine green conjunctival score of ≥2 (Oxford), Schirmer's tear test score ≥1 mm to ≤10 mm.	N 200* (all Vevizye 0.1%)	Vevizye 0.1% Single drop OU, BID for up to 12 months	Safety
SHR8028-301**	Efficacy, safety and tolerability	Stage I: multi-center, randomized, double-blind,	Stage I: 206 Vevizye 0.1%: 103	Stage I: Vevizye 0.1% or vehicle Single drop OU,	Stage I: CFB in tCFS D29;

Study ID Phase Relevance	Objectives	Design Main inclusion criteria	Population	Study drug Dose regimen Duration of treatment	Primary endpoint(s)
Phase 3 *Supportive*		parallel-group, vehicle-controlled Stage II: 12-week safety follow-up period without vehicle group set or blinding. Subjects with DED, tCFS ≥10 (NEI), dryness score ≥ 50, total lissamine green conjunctival score of ≥2 (Oxford), Schirmer's tear test score ≥1 to ≤10 mm.	Vehicle: 103 Stage II: 77*** (all Vevizye 0.1%)	BID for 29 days Stage II: Vevizye 0.1% Single drop OU, BID for 12 weeks	CFB in eye dryness score (VAS) D29. Stage II: Safety

2.10.2. Clinical pharmacology

Pharmacokinetics

Pharmacokinetics of ciclosporin and perfluorobutylpentane have been studied in two clinical studies.

Study CYS-001 was a phase 1, two period, double-blind, randomised, placebo-controlled, cross-over study. The study comprised 2 identical dosing / evaluation periods in a cross-over design. In each of the 2 periods, subjects received 2 dosing regimens (A and B) of a 0.05% formulation (i.e. half of the concentration of the commercial formulation which is 0.1%). In dosing regimen A, the subjects were administered saline drops into each eye in the morning of Day 1, a single drop (10 µL) of either Vevizye or the vehicle control into 1 eye in the evening of Day 1 and 1 drop into each eye in the morning and evening of Days 2 and 3; this was followed by a 5-day treatment-free PK sampling period from Days 4-8. After this treatment-free period, subjects received dosing regimen B, comprising administration of 2 drops (each 10 µL) of either Vevizye or vehicle control into each eye in the morning and evening on 3 consecutive days (Days 9-11); this was followed by a wash-out and PK sampling period lasting from Day 12 to Day 20. After completion of Period 1, subjects crossed over to the alternative dosing group in Period 2. Period 2 was performed identically to Period 1. In dosing regimen A, blood samples were taken within 30 minutes after the first dosing on Day 2 and a full set of samples was taken on the third day of each 3-day dosing period (pre-dose and 5, 15, 30, 60 minutes, 4, 8, 12, 24 hours, and 48 and 72 hours post-dose). In dosing regimen B, blood samples were taken within 30 minutes after the first dosing on Day 9; after the last dosing on Day 11, blood samples were taken at 5, 15, 30, 60 minutes 4, 8, 12, 24 hours (Day 12), and 2 (Day 13), 4 (Day 15), 6 (Day 17) and 8 (Day 19) days after the last dosing.

In study CYS-002, 0.1% and 0.05% formulations were compared to vehicle and to the comparator Restasis in subjects with moderate to severe DED. This study consisted of two periods: a 14-day run-in period with lubricant eye drops (Systane Balance, Alcon) in both eyes BID and a 112-day treatment period. In the treatment period, subjects were dosed with one drop (10 µL) in each eye BID for 4 months (112 days). PK blood samples were collected on day 1 (pre-dose and 0.5, 1, 2, and 4 hours after instillation) and on day 113 (pre-dose).

Bioanalytical methods

The plasma concentration of ciclosporin was determined by a LC/MS method. The concentration of perfluorobutylpentane was determined by a GC/MS method. Bioanalytical and validation reports of ciclosporin and perfluorobutylpentane determination are included. Certificates of analysis and chromatograms were submitted.

Absorption

Blood concentrations of ciclosporin and the novel excipient perfluorobutylpentane have been measured in two clinical studies, CYS-001 and CYS-002, after administration of 1 or 2 drops/eye BID of the 0.05% ciclosporin solution and 1 drop/eye BID of the 0.1% ciclosporin solution. Perfluorobutylpentane is used to improve the solubility of ciclosporin. Ciclosporin is practically insoluble in water. Study CYS-001 is a phase 1 study, performed in healthy volunteers. Study CYS-002 is a phase 2 study, performed in subjects with a history of dry eye disease (DED). Ciclosporin concentrations in whole blood were all below the LLOQ (0.100 ng/mL). Concentrations of perfluorobutylpentane in whole blood were also mostly below the LLOQ (1.7 ng/mL). Samples with concentrations perfluorobutylpentane above the LLOQ were collected mostly within half an hour after administration, but also occasionally at other time points. The highest concentration perfluorobutylpentane found was 13.7 ng/mL (collected pre-dose on day 113).

Distribution

Not applicable because ciclosporin does not become systemically available.

Elimination

Not applicable because ciclosporin does not become systemically available.

Dose proportionality and time dependencies

Not applicable because ciclosporin does not become systemically available.

Special populations

Ciclosporin does not become systemically available. The pharmacokinetics in renally or hepatically impaired patients is therefore not applicable and neither is the effect of body weight. Studies CYS-001 and CYS-002 in which ciclosporin was found to be not systemically available, contained both male and female subjects and Caucasian and African American subjects. Vevizye is not indicated in children.

Pharmacokinetic interaction studies

Not applicable because ciclosporin does not become systemically available.

Pharmacokinetics using human biomaterials

Not applicable because ciclosporin does not become systemically available.

Pharmacodynamics

Mechanism of action

Cyclosporine is a well-known and widely-used immunosuppressant and anti-inflammatory agent, with a well-characterized pharmacodynamic profile, both systemic and following topical ocular administration. The mechanism by which ciclosporin exerts its therapeutic effect in DED is hypothesised to be related to the suppression of the underpinning inflammatory process.

Primary and Secondary pharmacology

No new primary or secondary pharmacology studies were conducted by the Applicant, instead reference is made to the known pharmacology profile of ciclosporin following both local and systemic exposure.

Moreover, as local administration results in low systemic exposure, the risk of systemic (adverse) effects is considered negligible, and no drug interaction studies were performed by the Applicant.

2.10.3. Discussion on clinical pharmacology

Ciclosporin was found to be not systemically available (LLOQ = 0.100 ng/mL) after administration of 1 or 2 drops/eye BID of the 0.05% ciclosporin solution and 1 drop/eye BID of the 0.1% ciclosporin solution. This was reflected adequately in section 5.2 of the SmPC. In animal studies, higher ocular tissue concentrations of ciclosporin were found after administration of Vevizye compared to aqueous products, while after prolonged treatment the difference is not maintained for all eye tissues, indicating an effect of perfluorobutylpentane on local concentrations which may be only temporary.

The plasma concentration of ciclosporin was determined by a LC/MS method. Concentration of perfluorobutylpentane was determined by a GC/MS method. Bioanalytical and validation reports of ciclosporin and perfluorobutylpentane determination are included. Certificates of analysis and chromatograms were submitted.

The validation of the method for cyclosporine is acceptable. Incurred sample reanalysis was not performed as there were no observable concentrations of cyclosporine.

Blood concentrations of perfluorobutylpentane were either below LLOQ (1.7 ng/mL) or low (highest concentration found was 13.7 ng/mL). Observed maximal concentrations of perfluorobutylpentane in animal studies after ocular administration were up to approximately 80 times higher. For perfluorobutylpentane, no incurred sample reanalysis (ISR) has been done, mainly because the method used only allows for one analysis from one blood sample aliquot.

The plasma concentration of perfluorobutylpentane was determined only in patients receiving the vehicle treatment. No interaction between cyclosporin and perfluorobutylpentane is expected, neither from the absorption point of view, nor from analytical interference point of view. The number of samples where perfluorobutylpentane was above of LLOQ was small and did not significantly differ between Vevizye group and vehicle group, as shown in study CYS-002. This is therefore acceptable.

Perfluorobutylpentane plasma levels were detected also in the Restasis group and pre-dose samples. A measurable concentration in a pre-dose sample prior to the start of treatment was found only on one occasion (2.4 ng/mL). This is not considered an issue. Measurable concentrations in Restasis samples were found more often, i.e., 6 times. This is attributed by the applicant to unusually low internal standard responses. Although chance occurrences of low IS values are not expected to occur only in the analyses

of Restasis samples, the conclusion that the systemic availability of perfluorobutylpentane is low, is not expected to be changed because of this issue.

The discussion provided by the Applicant on the therapeutic effect of ciclosporin in DED is sufficient to support the proposed text in section 5.1 of the SmPC.

Ciclosporin has a well-known pharmacodynamic interactions profile and very low systemic exposure following administration of Vevizye, hence drug interaction studies are not considered necessary. A discussion on interactions of Vevizye with other topical or systemic products at the level of the ocular surface was provided. With respect to corticosteroids, it is agreed that a warning in section 4.4 is not warranted as the risk is theoretical with no clinical data available. However, the potential additive immunosuppressive effect when using cyclosporin and corticosteroids was included in SmPC section 4.5. With respect to glaucoma medications, including a specific drug-drug interaction between cyclosporine and glaucoma medications to the SmPC section 4.4 or 4.5 is not warranted. However, the available clinical data on concomitant use is limited and due to contrasting effects on ocular comfort, patients should be frequently monitored. A warning alerting prescribers is included in SmPC section 4.4.

2.10.4. Conclusions on clinical pharmacology

In general, the pharmacokinetics of ciclosporin and perfluorobutylpentane have been sufficiently characterised, in healthy subjects and in subjects with a history of dry eye disease.

The Applicant did not conduct any pharmacodynamic studies. Considering the low systemic exposure and the well-known active substance, the literature discussion provided on the primary and secondary discussion is acceptable. Discussion on interaction of the product with local and systemic therapies used in the treatment of DED was provided, and the SmPC was updated accordingly.

2.10.5. Clinical efficacy

Vevizye 0.1% is proposed for the treatment of dry eye disease in adult patients, which has not improved despite treatment with tear substitutes. The proposed posology o is one drop (corresponding to 0.01 mg ciclosporin) to be applied to each eye twice daily. Two pivotal studies are considered as pivotal for the sought indication and posology, i.e. study CYS-003 and CYS-004. Dose selection was based on Study CYS-002.

Dose-response study

Study CYS-002 was a Phase 2, multi-center, randomized, double-masked, placebo(vehicle)-controlled clinical study that included a total of 207 adult subjects with a reported history of DED in both eyes for ≥6 months and use of eye drops for dry eye symptoms within 30 days.

Subjects were eligible if, both at screening and after a 14-day run-in period with lubricant eye drops OU BID, they rated their eye dryness based on a visual analogue scale (VAS) ≥ 40, and had at least one eye (the same eye) with a total corneal fluoresceine staining score (tCFS) ≥ 6 (National Eye Institute - NEI- scale), total conjunctival lissamine green score of ≥ 2 (Oxford scale), and unanesthetized Schirmer's tear test score between ≥ 2 and ≤ 8 mm.

Subjects were randomized in a 1:1:1:1 ratio to Vevizye 0.05% (n=51), Vevizye 0.1% (n=51), vehicle (n=52), or Restasis (n=53, open label arm) and treated OU BID for 112-days. The same excipients of Vevizye, i.e. perfluorobutylpentane and ethanol, in the same quantitative amounts, were utilized as vehicle in the placebo arm.

Predefined primary efficacy endpoints aimed to demonstrate efficacy of Vevizye on both signs and symptoms of DED. Specifically, change from baseline (CFB) in total corneal fluorescein staining (tCFS, NEI scale) to Day 113 (Visit 5) was the primary sign endpoint, whereas CFB in dryness severity (VAS scale) at Visit 5 was the primary symptom endpoint.

All 207 randomized subjects were treated with study drug, thus representing the FAS population and the safety population of study CYS-002. The PP and PK population comprised 192 subjects and 55 subjects, respectively. Main demographic and baseline characteristics of the FAS population per treatment group are provided in below table.

Table 4: Demographic and baseline clinical characteristics by treatment groups – CYS-002 - FAS

	Vevizye 0.05% (N=51)	**Vevizye 0.1% (N=51)**	**Restasis (N=53)**	**Vehicle (N=52)**
Age (years)				
Mean (SD)	64.3 (10.72)	61.1 (12.29)	62.8 (11.90)	61.3 (10.45)
Median	64.0	61.0	62.0	62.0
Min, Max	33, 85	30, 86	27, 94	26, 82
< 65 years	26 (51.0%)	32 (62.7%)	35 (66.0%)	31 (59.6%)
≥ 65 years	25 (49.0%)	19 (37.3%)	18 (34.0%)	21 (40.4%)
Sex				
Male	13 (25.5%)	15 (29.4%)	13 (24.5%)	13 (25.0%)
Female	38 (74.5%)	36 (70.6%)	40 (75.5%)	39 (75.0%)
Ethnicity				
Hispanic or Latino	1 (2.0%)	3 (5.9%)	2 (3.8%)	2 (3.8%)
Not Hispanic or Latino	50 (98.0%)	48 (94.1%)	51 (96.2%)	50 (96.2%)
tCFS (NEI)				
Mean (SD)	8.78 (2.138)	8.75 (1.885)	8.83 (1.889)	8.71 (2.145)
Median	9.00	9.00	9.00	9.00
Min, Max	6.0, 14.0	6.0, 13.0	6.0, 14.0	6.0, 14.0
Two-Sided 95% CI	(8.18, 9.39)	(8.21, 9.28)	(8.31, 9.35)	(8.11, 9.31)
Dryness (VAS)				
Mean (SD)	72.78 (19.545)	71.18 (16.170)	68.51 (18.800)	68.52 (21.383)
Median	80.00	71.00	70.00	70.50
Min, Max	20.0, 100.0	35.0, 100.0	30.0, 100.0	10.0, 100.0
Two-Sided 95% CI	(67.29, 78.28)	(66.63, 75.72)	(63.33, 73.69)	(62.57, 74.47)

Vevizye groups showed statistically significant improvements in tCFS from baseline to Visit 5. The improvements in both the Vevizye 0.05% group and the Vevizye 0.1% group were not different compared to vehicle. Similarly, both Vevizye groups showed statistically significant improvements in severity of dryness from baseline to Visit 5, which were not statistically different compared to vehicle (Table 11). Analysis on the PP population yielded consistent results.

Table 5: Primary efficacy analysis – CYS-002 - FAS

		Vevizye 0.05% (N=51)	**Vevizye 0.1% (N=51)**	**Vehicle (N=52)**
tCFS (NEI)				
Baseline	Mean (SD)	8.78 (2.138)	8.75 (1.885)	8.71 (2.145)
Visit 5	Mean (SD)	6.46 (2.727)	6.64 (2.538)	7.10 (3.157)
Change from baseline	Mean (SD)	-2.38 (2.156)	-2.10 (2.252)	-1.69 (2.619)
	P-value (paired t-test vs baseline)	<0.0001	<0.0001	<0.0001
	LS mean difference (95% CI)	-0.68 (-1.57, 0.21)	-0.42 (-1.32, 0.47)	-
	P-value (ANCOVA Vevizye -vehicle)	0.1334	0.3505	-
Severity of Dryness (VAS)				
Baseline	Mean (SD)	64.18 (15.058)	64.51 (14.251)	64.63 (15.449)
Visit 5	Mean (SD)	52.66 (23.328)	54.76 (27.452)	51.15 (26.585)
Change from baseline	Mean (SD)	-11.00 (19.362)	-9.30 (27.832)	-13.85 (25.301)
	P-value (paired t-test vs baseline)	0.0002	0.0222	0.0004
	LS mean difference (95% CI)	2.45	4.27	-
	P-value (ANCOVA Vevizye -vehicle)	0.6166	0.3829	-

Abbreviations: CI = confidence interval; ANCOVA = analysis of covariance; VAS = visual analog scale

In the CYS-002 Modelling and Simulation analysis, there was a borderline significant drug effect on total corneal fluorescein staining (tCFS), but no significant difference between the 0.05% and 0.1% formulations. There was a significant drug effect on ocular surface disease index (OSDI), but no significant difference between the 0.05% and 0.1% formulations. There was no significant drug effect on severity of dryness (VAS).

The subgroup analysis from this Phase 2 study indicated that subjects with tCFS ≥ 10 (NEI scale) at baseline responded best after treatment with Vevizye in terms of ocular surface staining outcomes as well as symptom outcomes.

The statistical analysis on the total population, and the modelling and simulation analysis did not identify a clear dose-response for sign or symptoms between the two Vevizye groups. The Vevizye 0.1%, however, showed some trends over Vevizye 0.05% in symptoms in all subjects and in the target population for the subsequent studies (subjects having tCFS ≥10 at baseline) and was therefore selected as dose for the confirmatory program.

Treatment-emergent adverse events were reported for 65 of the 207 randomized subjects (31.4%). Thirty-three subjects (15.9%) reported 47 ocular TEAEs during the study period, similarly distributed across treatment groups. Most frequently reported ocular TEAE (11 subjects, 5.3%) was visual acuity reduction. Three subjects (1.4%) withdrew from study treatment due to an ocular TEAE and also 3 treatment-emergent serious adverse events (SAEs) were reported. All SAEs were non-ocular, considered not-related to study treatment, and recovered by the end of the study.

Main studies

Data from two multicenter RCT trials with similar study design are considered as pivotal to support efficacy of Vevizye, i.e. Phase 2b/3 study CYS-003, and Phase 3 study CYS-004. Due to similarities in their study methodologies, the two pivotal studies will be reported jointly, relevant differences are highlighted.

CYS-003 (ESSENCE-1) and CYS-004 (ESSENCE-2)

Methods

Studies CYS-003 and CYS-004 were two multicenter, randomized, double-masked and vehicle-controlled studies with partially overlapping eligibility criteria.

Study Participants

Inclusion criteria

Study CYS-003 included adult subjects (≥18 years old), with a reported history of DED in both eyes for at least 6 months, and who used over-the-counter or prescription eye drops or lubricating gels for dry eye symptoms within 30 days before Visit 0 (screening).

In addition, subjects were eligible if, both at screening (Visit 0), and at baseline (Visit 1) after a 14-day run-in period with artificial tears, they had an OSDI score ≥20, and at least one eye satisfying the following DED signs scores: tCFS ≥10 (NEI scale), total lissamine green conjunctival score ≥2 (Oxford scale), and unanesthetized Schirmer's tear test score between ≥1 and ≤10 mm.

Study CYS-004 had identical inclusion criteria with regard to DED signs (tCFS, total lissamine green conjunctival score and unanesthetized Schirmer's tear test score), but a different criterion with regard to symptoms, namely a VAS dryness score ≥50 (instead of OSDI score ≥20) at screening and baseline.

Exclusion criteria

Main exclusion criteria in both studies were: abnormal lid anatomy (incomplete eyelid closure, entropion, ectropion) or blinking; ocular or periocular malignancy; corneal epithelial defect, or in more than 2 of the 5 corneal regions >50% confluent corneal staining; history of herpetic keratitis; ocular allergies; ongoing ocular or systemic infection; contact lenses; intraocular or ocular laser surgery within the previous 6 months; use of any eye drops within 2 hours before visit 0 and before visit 1; any topical anti-glaucoma medication within 3 months prior to Visit 0; any topical ocular or facial steroids within one month prior to Visit 0; systemic steroids or immunomodulating agents on a no stable regimen; any oral

medication known to cause ocular drying (e.g., antihistamines, antidepressants, etc.) on a no stable regimen; woman who was pregnant, nursing or planning a pregnancy, or of childbearing potential not using an acceptable means of contraception; participation in a previous Vevizye trial.

Treatments

Study treatment

328 subjects in study CYS-004, and 834 subjects in study CYS-004 meeting all trial eligibility criteria were randomized to receive treatment either with Vevizye 0.1% ophthalmic solution (Vevizye) or vehicle ophthalmic solution (Vehicle) in a 1:1 ratio.

Vehicle was composed of the same excipients of Vevizye, i.e. perfluorobutylpentane and ethanol, in the same quantitative amounts as in Vevizye.

The trials were composed of two parts: a run-in period and a treatment period.

During the 14-day run-in period, between screening (Visit 0) and baseline (Visit 1), subjects dosed with artificial tears both eyes (OU) twice daily (BID) morning and evening. The first dose was self-administered at Visit 0 under the supervision of a trained study technician.

Thereafter, eligible subjects dosed the investigational medicinal product (either Vevizye or vehicle), single drop OU BID, morning and evening, for 84 days in CYS-003, and for 29 days in CYS-004. The first dose was self-administered at Visit 1 under the supervision of a trained study technician.

Prior and concomitant therapies

Medications and treatments that were not allowed prior to the trial (listed in the exclusion criteria) were also not allowed during the trials, in particular no other prescription or over-the-counter topical ophthalmic medications including dry eye treatments such as artificial tears were allowed within 2 hours prior to Visit 0 and throughout the course of the trials. No escape medications were required. The use of any concurrent medication was to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

Objectives

Objectives of both pivotal trials were to assess efficacy, safety, and tolerability of Vevizye 0.1% ophthalmic solution in comparison to its vehicle for the treatment of the signs and symptoms of DED.

Outcomes/endpoints

Primary efficacy endpoints

Common primary sign endpoint in study CYS-003 and CYS-004 was:

- Change from baseline (CFB) in total corneal fluorescein staining score (tCFS, NEI) at Day 29.

Primary symptom measure in study CYS-003 was:

- CFB in total Ocular Surface Disease Index (OSDI) score at Day 29.

Primary symptom measure in study CYS-004 was:

- CFB in Dryness Score (VAS) at Day 29.

Secondary efficacy endpoints

In study CYS-**003**, key secondary efficacy measures were:

- tCFS (NEI) and CFB to each measured post-baseline visit (other than Day 29);

- Total OSDI score and CFB to each measured post-baseline visit (other than Day 29);
- Lead/Worst symptom assessment;
- Reading impairment score and CFB to each measured post-baseline visit;
- Unanesthetized Schirmer's tear test responders and CFB to each measured post-baseline visit;
- Central and inferior corneal staining score (NEI) and CFB to each measured post-baseline visit.

Additional secondary efficacy measures were:

- Conjunctival lissamine green staining by region and total (Oxford scale) and changes from baseline to each measured post-baseline visit;
- Proportion of responders in tCFS score (≥3 score improvement on NEI Scale) at Day 29;
- Tear film break-up time (TFBUT) and changes from baseline to each measured post-baseline visit;
- Visual analog scale (VAS) and changes from baseline for severity of dryness.

In study CYS-**004**, key secondary efficacy measures were:

- CFB in total conjunctival lissamine green staining score (Oxford scale) at Day 29;
- Proportion of responders in central corneal fluorescein staining (cCFS) score (≥1 score improvement on NEI scale) at Day 29;
- Proportion of responders in tCFS score (≥3 score improvement on NEI scale) at Day 29;
- CFB in cCFS score (NEI) to Day 29;
- CFB in tCFS score (NEI) at Day 15;
- CFB in blurred vision (VAS) at Day 29;
- cCFS score and CFB at Day 15;

Additional secondary efficacy measures were, among others:

- OSDI total score and CFB at each measured post-baseline visit
- Unanesthetized Schirmer's tear test and CFB to each measured post-baseline visit
- Proportion of responders in unanesthetized Schirmer's tear test (≥ 10 mm increase) at each measured post-baseline visit
- Tear film break-up time (TBUT) and CFB at each measured post-baseline visit.

The predefined primary and secondary efficacy endpoints were suitable to demonstrate efficacy of Vevizye on both signs and symptoms of DED, by assessing both objective and subjective parameters of the disease. Relevant clinical measures of DED were included. According to recent recommendations from the European panel of experts in DED (Messmer et al., 2023), disease severity should be primarily determined based on symptoms severity, corneal and conjunctival staining, low tear production, and short tear film break-up time. Accordingly, the most commonly parameters used in clinical trials on topical ocular ciclosporin to assess effects on signs in DED (including the SANSIKA pivotal study for IKERVIS), are CFS, lissamine green conjunctival staining, Schirmer's test, and TBUT. Therefore, these measures will be considered as the most relevant sign endpoints for Vevizye.

Scheduled study visits for both study CYS-003 and CYS-004 were: Visit 0 (Screening; Day -14 ± 2), Visit 1 (Baseline/Randomization; Day 1), Visit 2 (Day 15 ± 1), Visit 3 (Day 29 ± 2). Additional study visits in study CYS-003 were Visit 4 (Day 57 ± 2), and Visit 5 (Study Exit; Day 85 ± 2).

In both studies, dry eye signs and symptoms were assessed at baseline and at follow-up visits, and primary efficacy endpoints were assessed at Visit 3 (Day 29).

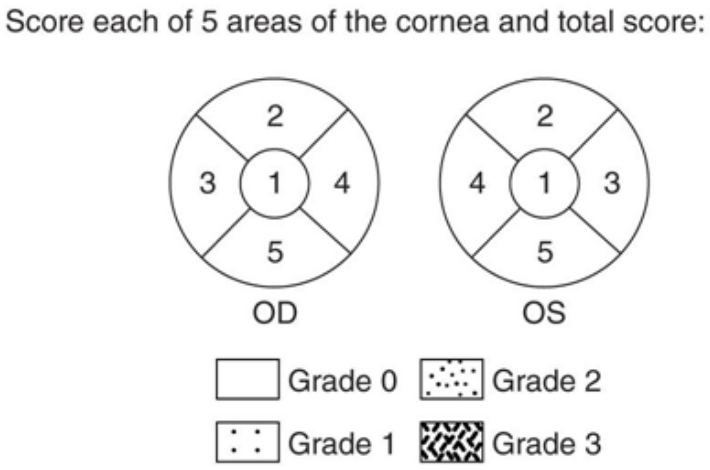
DED ocular surface integrity, and tear production and stability measures

Corneal surface

Corneal surface damage may be assessed by grading corneal staining using fluorescein dye (CSF). The intensity of the stain is increased in areas of cellular degeneration or death, where the damage to cells, cell membranes and cell-to-cell junctions allow for the intracellular spaces to be more highly penetrated by the dye. Corneal fluorescein is often observed as a late finding in DED (Novack et al, DEWS II, Clinical Trial Design, 2017). Staining is first observed inferiorly and then may spread over the corneal surface (Savini et al, 2008). Central staining of the cornea is considered important, because is correlated with visual function (Kaido et al, 2011).

The NEI scale used for assessing fluoresceine corneal staining in the Vevizye pivotal studies relies on a chart that divides the cornea into five corneal zones: central (1), superior (2), temporal (3), nasal (4), and inferior (5). For each zone, the amount of corneal fluorescein staining is graded on a scale of 0 to 3, as depicted in the figure below: 0 = normal or negative slit-lamp findings; 1 = mild or superficial stippling; 2 = moderate or punctate staining, including superficial abrasion of the cornea; and 3 = severe abrasion or corneal erosion, deep corneal abrasion, or recurrent erosion. The total corneal fluorescein staining (tCFS) score is the sum score of the 5 regions (ranging from 0-15, hence from absent to severe corneal damage).

Figure 4



Source: American Academy of Ophthalmology, NEI/ Industry Grading System

The NEI scale is not linear, i.e., a decrease of 1 grade in a region typically corresponds to a 3-fold reduction of punctate staining in the area or more for areas with severe and confluent staining (Amparo et al 2017). A ≥3 score improvement in NEI total corneal staining, and ≥1 score improvement in the central region staining, are considered clinically meaningful.

Conjunctival surface

In chronic DED, disturbance of the lacrimal function unit results in disruption of conjunctival surface integrity which is reflected by lissamine green staining of the conjunctiva. Lissamine green is a vital dye which stains epithelial cells only if the cell membrane is damaged (Wolffsohn et al, DEWS II Diagnostic Methodology, 2017). Typically, the conjunctival staining in DED begins in the nasal area and spreads to the temporal area with progression of the disease (Rolando et al, 2005; Caffery et al, 2010).

In the clinical studies Vevizye, the Oxford scale was used to grade lissamine green staining of 2 conjunctival regions: temporal and nasal. Staining scores for each region ranged from 0 to 5. The total staining score using the Oxford scale was the sum of the temporal and nasal regions and ranged from 0 to 10 (absent to severe conjunctival damage).

Tear production

In DED, the immune-based inflammation of the lacrimal gland can result in insufficient tear production. The Schirmer's Test evaluates tear production, and can be performed with anaesthetic or without. Schirmer test with anaesthetic quantifies the basal tear secretion, whereas the unanaesthetised test measures the basal plus reflex secretions. In the clinical studies for Vevizye, the Schirmer's tear test strip was placed in the lower temporal lid margin of each unanesthetized eye to measure tear production. After 5 minutes, the test strip was removed and the length of the moistened area was recorded in millimeters (mm) for each eye. Lower values indicated less tears produced in the eye. The normal test value for unanaesthetised Schirmer's Test is ≥10mm: an increase of this order of magnitude is considered clinically relevant, and indicates normal tear production.

Tear Film stability

Tear film stability is the most important indicator of tear film stability. In patients with dry eye, the tear film is unstable and breaks up faster. The Tear Film Break-up Time (TBUT) is a standard test for tear-film stability assessment. After application of fluorescein, the TBUT is recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film. TBUT less than 10 sec suggests an abnormal tear film, with values < 5 sec indicative of dry eye.

Sample size

In study CYS-003, 142 intent-to-treat (ITT) subjects (study eyes) per treatment group were needed to yield a 90% power to reject H_{01} in favor of H_{A1} and conclude superiority of Vevizye over vehicle in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 assuming a true difference (Vevizye minus vehicle) of -0.85, a common SD of 2.2, and a two-sided $\alpha = 0.05$. Additionally, 142 ITT subjects per treatment group would yield a 82% power to reject H_{02} in favor of H_{A2} and conclude superiority of Vevizye over vehicle in the mean change from baseline total OSDI score at Day 29 assuming a true difference (Vevizye minus vehicle) of -5.0, a common SD of 14.5, and a two-sided $\alpha = 0.05$. Accounting for subject discontinuations, 316 total enrolled subjects were planned assuming a dropout rate of 10%.

Study CYS-004 was designed to have 90% power to reject both H_{01} and H_{02} assuming independence between the sign and symptom endpoint; positive correlation between these two endpoints increased the overall power. 379 full analysis set (FAS) subjects (study eyes) per treatment group yielded 96.8% power to reject H_{01} in favor of H_{A1} and conclude superiority of Vevizye over vehicle in the mean CFB in tCFS score at Day 29 assuming a true difference (Vevizye minus vehicle) of -0.75, a common standard deviation (SD) of 2.7, and a two-sided alpha = 0.05.

Additionally, 379 FAS subjects per treatment group yielded 93.0% power to reject H_{02} in favor of H_{A2} and conclude superiority of Vevizye over vehicle in the mean CFB in dryness score (VAS) at Day 29, assuming a true difference (Vevizye minus vehicle) of -5.0, a common SD of 20.0, and a two-sided alpha = 0.05.

Therefore, assuming independence between tCFS score and dryness score (VAS), 379 FAS subjects per treatment group yielded 96.8% * 93.0% = 90.0% power to reject both H_{01} and H_{02}. Accounting for subject discontinuations, approximately 834 total subjects (417 per treatment arm) were planned to be enrolled assuming a dropout rate of approximately 10%.

Randomisation and blinding (masking)

In study CYS-003, each subject who met all inclusion criteria and none of the exclusion criteria at Visit 0 and at Visit 1 was assigned a randomization number at the end of Visit 1. The Interactive Web Response System (IWRS) was used to assign all randomization numbers. Randomization and kit numbers were assigned automatically to each subject by strata as the subject was entered into the IWRS. Stratification was determined by site and by Visit 1 total OSDI score (i.e., < 36 or ≥ 36).

In study CYS-004, each subject was assigned a unique subject number in sequential order by the site. If all inclusion and none of the exclusion criteria were met at Visit 0 (Day -14) and Visit 1 (Day 1), each qualifying subject was randomized. Site and dryness score (<75 vs ≥ 75 [VAS]) were used as stratification factors in this trial. The Interactive Response Technology (IRT) was used to account for the stratification factor while assigning the drug kit numbers at Visit 1 (Day 1). Dynamic site allocation was used to stratify by site using Suvoda IRT.

These were double-masked and vehicle-controlled studies. Subjects, investigators, and site staff, sponsor staff, and staff of the CROs were masked to the treatment group assignments during the randomization process and for the duration of the study.

Statistical methods

The primary endpoints were tested in a hierarchical fixed sequence. The **statistical hypotheses** for the primary endpoint of change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 are as follows:

> H_{01}: The difference, between study eyes treated with Vevizye and study eyes treated with vehicle, in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 = 0.
> H_{A1}: The difference, between study eyes treated with Vevizye and study eyes treated with vehicle, in the mean change from baseline corneal fluorescein staining (NEI scale) total score at Day 29 $\neq$ 0, with superiority claimed if the difference is less than 0 (Vevizye minus vehicle).

For study CYS-003, the statistical hypotheses for the primary endpoint of the change from baseline total OSDI score at Day 29 were as follows:

> H_{02}: The difference, between subjects treated with Vevizye and subjects treated with vehicle, in the mean change from baseline total OSDI score at Day 29 = 0.
> H_{A2}: The difference, between subjects treated with Vevizye and subjects treated with vehicle, in the mean change from baseline total OSDI score a t D ay 2 9 $\neq$ 0, with superiority claimed if the difference is less than 0 (Vevizye minus vehicle).

For study CYS-004, the statistical hypotheses for the primary endpoint of the CFB in dryness score (VAS) at Day 29 were as follows:

> H_{02}: The difference, between subjects treated with Vevizye and subjects treated with vehicle, in the mean CFB in dryness score (VAS) at Day 29 = 0.
> H_{A2}: The difference, between subjects treated with Vevizye and subjects treated with vehicle, in the mean CFB in dryness score (VAS) at Day 29 $\neq$ 0, with superiority claimed if the difference was less than 0 (Vevizye minus vehicle).

In study CYS-003, there were no adjustments for secondary endpoints; thus, all secondary endpoints were considered exploratory. In study CYS-004, the following key secondary endpoints could be tested hierarchically: CFB in total conjunctival lissamine green staining score (Oxford scale) at Day 29; proportion of responders in cCFS score ($\geqslant$ 1 score improvement on NEI scale) at Day 29); proportion of

responders in tCFS (⩾ 3 score improvement on NEI scale) at Day 29; and CFB in cCFS score (NEI scale) to Day 29. After that CFB in VAS for blurred vision and at Day 29 and CFB in tCFS (NEI scale) at Day 15 could be tested hierarchically using Hochberg's procedure.

All statistical tests were two-sided with a significance level of 0.05 (α = 0.05). Confidence intervals (CIs) for differences between the Vevizye and vehicle groups were two-sided at 95% confidence.

Safety endpoints were analyzed for both eyes. For efficacy endpoints that were measured separately in each eye, the unit of analysis was the "study eye." Eyes were eligible for analysis if they met all inclusion criteria. In the case that both eyes were eligible for analysis, the "study eye" was the eye with the higher mean corneal fluorescein staining score (NEI scale) at Visit 1. If the mean corneal fluorescein staining score (NEI Scale) was the same OU, then the right eye (OD) was designated as the "study eye."

The following **analysis populations** were considered:

The Full Analysis Set (FAS) included all subjects randomized and having received at least one dose of study drug. The primary analysis was performed on the FAS using observed data only. Subjects in the FAS were analyzed as randomized.

The Per Protocol Set (PPS) included subjects in the FAS who did not have major protocol deviations and who completed the study. Protocol deviations were assessed prior to database lock and unmasking. The PPS was analyzed using observed data only for efficacy variables. Subjects in the PPS were analyzed as treated.

The Safety Set (SAF) included all randomized subjects who received at least one dose of the study drug. The SAF was analyzed for all safety assessments. Subjects in the SAF were analyzed as treated.

The primary comparisons in this study were between Vevizye and vehicle at Day 29. The **primary efficacy analysis** compared the mean changes from baseline in total corneal fluorescein staining (NEI scale) and OSDI scores for study CYS-003 or dryness scale for study CYS-004, which were analyzed separately using an analysis of covariance (ANCOVA) model with terms for baseline value, site, treatment. In study CYS-003, the interaction of treatment by baseline value was added to the model, the interaction term was maintained in the model only if the P-value for the term was < 0.10, which was not the case. In study CYS-004, no interaction term was added.

No interim analyses were planned for this study.

Results

Participant flow

In study CYS-003:

- 727 subjects were screened;
- **328** subjects were randomized;
- 328 subjects comprised the Full Analysis Set (FAS);
- 313 subjects comprised the Per Protocol Set (PPS);
- 328 subjects comprised the Safety Set (SAF).

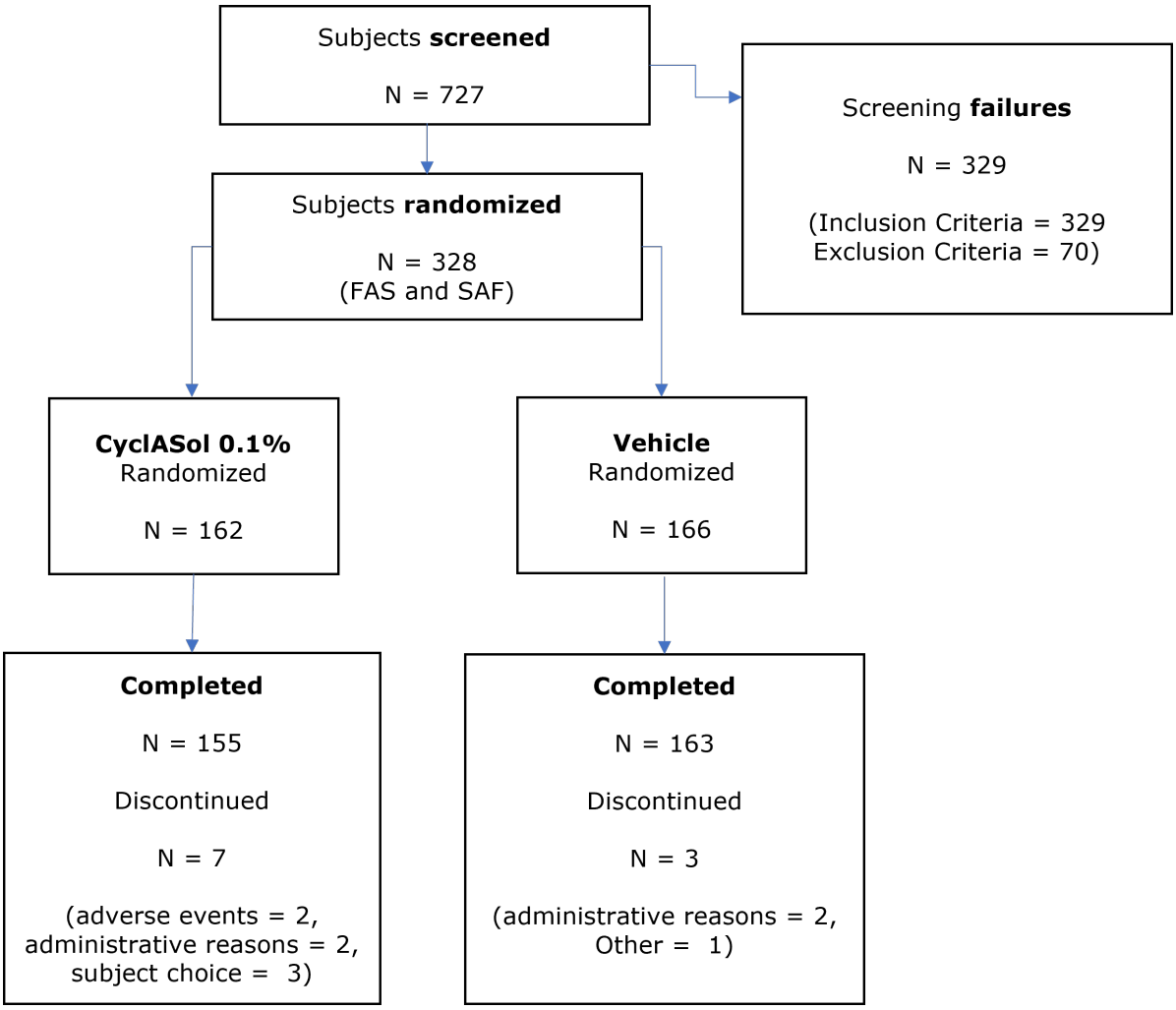


*Figure 5**:** subject disposition in study CYS-003.*

In study CYS-004:

- 1,879 subjects were screened;
- **834** subjects were randomized with 423 to Vevizye and 411 to vehicle;
- 817 subjects completed the trial;
- 834 subjects comprised the Full Analysis Set (FAS);
- 796 subjects comprised the Per Protocol Set (PPS);
- 834 subjects comprised the Safety Set (SAF).

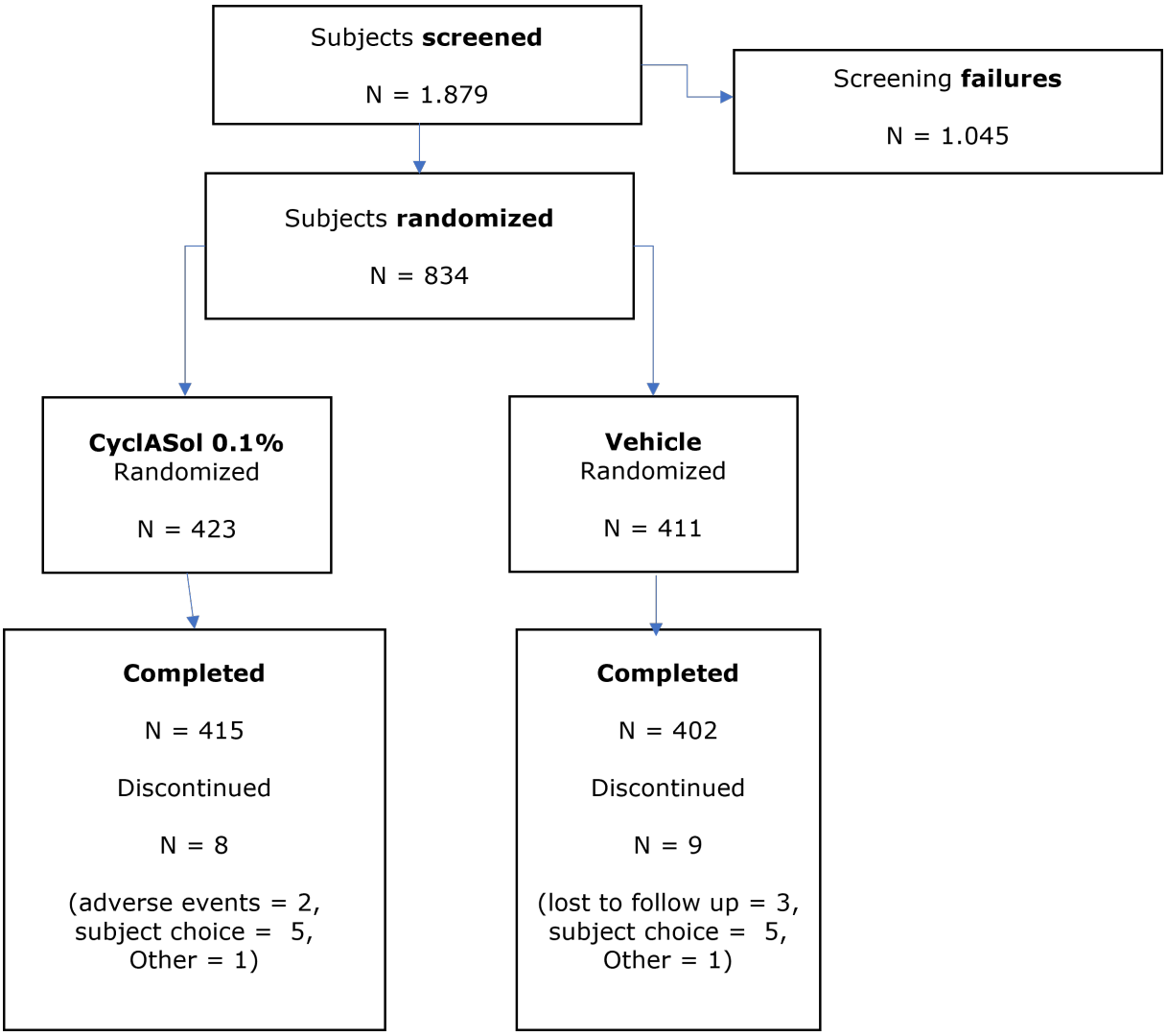


Figure 6 subject disposition in study CYS-004

Recruitment

Study CYS-003
Date first subject visit: 19 Oct 2017; Date last subject visit: 22 May 2018.

Study CYS-004
Date first subject visit: 19 Nov 2020; Date last subject visit: 3 Sept 2021.

Conduct of the study

Protocol amendments

CYS-003

Changes to the original protocol of study CYS-003 (dated 14 Sept 2017) included one major protocol amendment (20 Dec 2017). This amendment made clarifications to the inclusion and exclusion criteria, specifically added the use of lubricating gels as satisfying inclusion criterion of use of ocular lubricants within 30 days before screening, and the use of Lipiflow procedures during the past 180 days prior to

Visit 0 as not allowed under the exclusion criteria. The history of no response to topical ciclosporin was removed from exclusion criterion as there is no clearly defined ciclosporin response.

Collection of demographic data collection pertaining to language and heritage were included. If a subject's native tongue was Japanese, they were asked three further questions regarding their heritage (born in Japan, living in Japan, and parent's heritage).

Additionally, an increase in VA of 0.22 or greater in LogMAR was defined as an AE.

This protocol amendment clarified that total corneal fluorescein staining score (NEI scale) and total OSDI score were not to be considered co-primary endpoints. This clarification was made to better reflect the statistical approach of the study, which did not require both endpoints to be favorable for the study to be considered a success. The amendment also aligned the wording throughout the document and clarified that "study eye" is the term to be used as the unit of analysis for efficacy endpoints. The term "study eye" is the functional equivalent of "worst eye".

CYS-004

Changes to the original protocol of study CYS-004 (dated 27 Aug 2020) included 2 global protocol amendments.

The first amendment (2 Dec 2020) revised the discontinuation of treatment in case of a COVID-19 infection and provided guidance related to COVID-19 related protocol deviations. This amendment also provided clarification on corneal and conjunctival staining methods as well as guidance on what to do in case a prohibited medication became necessary.

The second amendment (15 Mar 2021) revised language to be based upon rate of missing data for an endpoint rather than trial discontinuation and clarified that observed data more than + 7 days out of window was to be considered missing. It amended estimand language to account for out of window data for more than 7 days and removed the distinction between COVID-19 missing data and any other missing data. This amendment added language to elaborate upon permutation test using dichotomous key secondary endpoints and removed Baseline Observation Carried Forward (BOCF) throughout protocol.

Protocol deviations

Protocol deviations were classified as major or minor before database lock and unmasking. Protocol deviations were reported in 145/328 (44.2%) and in 257/834 (30.8%) of the study subjects in study CYS-003 and CYS-004, respectively.

Specifically, in study CYS-003, a total of 227 protocol deviations were reported in 145 (44.2%) subjects: 107 deviations in 68 (42.0%) subjects in the Vevizye 0.1% group and 120 deviations in 77 (46.4%) subjects in the vehicle group.

Five protocol deviations were classified as major protocol deviations, reported in 5 subjects: 3 subjects in the Vevizye 0.1% group and 2 subjects in the vehicle group. No subjects with major protocol deviations were discontinued from the study due to the major protocol deviations.

The identified major protocol deviations were improper protocol procedures at site = Visit <2 hours after subject took morning dose: 3 subjects (1 Vevizye, 2 Vehicle); subject's non-compliance with test article/study drug = Subject had been dosing TID for 18 days prior to Visit 3: 1 subject (Vevizye); subject's use of prohibited concomitant medication = Subject began taking a systemic steroid 3 days prior to Visit 3: 1 subject (Vevizye).

73 of the 222 minor protocol deviations were improper protocol procedures occurring at the sites (e.g., procedures missed, repeated, or not per protocol). 71 minor protocol deviations involved visits out of window (e.g., missed, early, or late). Of the remaining minor protocol deviations, 43 deviations resulted

from a subject's noncompliance with study drug (e.g., occasionally missed dose or dosing diary omission, extra dose, or unreturned study drug), 19 deviations resulted from a subject's failure to follow instructions (e.g., unreturned study drug or diary completion errors), and 16 deviations resulted from a subject's use of prohibited concomitant medication.

In study CYS-004, a total of 372 protocol deviations were reported in 257 subjects (30.8%): 131 (31.0%) subjects in the Vevizye group and 126 (30.7%) subjects in the vehicle group. Of these, 249 subjects (29.9%) reported minor protocol deviations: 128 subjects (30.3%) in the Vevizye group and 121 subjects (29.4%) in the vehicle group, while 21 subjects (2.5%) reported total major protocol deviations: 10 subjects (2.4%) in the Vevizye group and 11 subjects (2.7%) in the vehicle group.

Among all subjects, the key types of protocol deviations included visit out of window (11.3%), improper protocol procedures at site (9.4%), informed consent (6.8%) and subject's non-compliance with test article/study drug (4.0%). The protocol deviations related to the informed consent were all related to re-consenting, which was necessary due to minor updates in the informed consent form. A substantial number of improper procedures was related to reading assessments, which turned out to be challenging to be implemented in a larger trial.

The major protocol deviations were related to study visits out of window (12 events [5 in the Vevizye group and 7 in the vehicle group] and violation of inclusion or exclusion criteria (5 events [2 in the Vevizye group and 3 in the vehicle group]; further major protocol deviations were related to use of prohibited concomitant medication (2 events in vehicle group), study drug assignment (2 events in Vevizye group) and subject's non-compliance (1 event in each group).

Baseline data

Baseline demographic characteristics

Demographic information of studies CYS-003 and CYS-004 is provided in

Table 6.

Table 6: Demographic characteristics – Pivotal studies – Full Analysis Set Population

	CYS-003			CYS-004		
	Vevizye (N=162)	**Vehicle (N=166)**	**All Subjects (N=328)**	**Vevizye (N=423)**	**Vehicle (N=411)**	**All Subjects (N=834)**
Age (Years)						
Mean (SD)	61.5 (13.60)	61.3 (12.66)	61.4 (13.11)	57.6 (15.36)	56.6 (16.30)	57.1 (15.83)
Median	62.0	63.0	62.0	60.0	59.0	60.0
Min, Max	18, 93	19, 89	18, 93	19, 86	18, 93	18, 93
Age Category: n (%)						
< 45 Years	14 (8.6%)	18 (10.8%)	32 (9.8%)	85 (20.1%)	90 (21.9%)	175 (21.0%)
>= 45 and < 65 Years	85 (52.5%)	73 (44.0%)	158 (48.2%)	181 (42.8%)	171 (41.6%)	352 (42.2%)
>= 65 Years	63 (38.9%)	75 (45.2%)	138 (42.1%)	157 (37.1%)	150 (36.5%)	307 (36.8%)
Sex: n (%)						
Male	46 (28.4%)	47 (28.3%)	93 (28.4%)	117 (27.7%)	108 (26.3%)	225 (27.0%)
Female	116 (71.6%)	119 (71.7%)	235 (71.6%)	306 (72.3%)	303 (73.7%)	609 (73.0%)
Ethnicity: n (%)						

Hispanic or Latino	15 (9.3%)	11 (6.6%)	26 (7.9%)	62 (14.7%)	60 (14.6%)	122 (14.6%)
Not Hispanic or Latino	147 (90.7%)	155 (93.4%)	302 (92.1%)	359 (84.9%)	348 (84.7%)	707 (84.8%)
Unknown	0	0	0	1 (0.2%)	0	1 (0.1%)
Not Reported	0	0	0	1 (0.2%)	3 (0.7%)	4 (0.5%)
Race: n (%)						
American Indian or Alaska Native	1 (0.6%)	1 (0.6%)	2 (0.6%)	2 (0.5%)	0	2 (0.2%)
Asian	14 (8.6%)	19 (11.4%)	33 (10.1%)	40 (9.5%)	39 (9.5%)	79 (9.5%)
Black or African American	16 (9.9%)	14 (8.4%)	30 (9.1%)	53 (12.5%)	55 (13.4%)	108 (12.9%)
Native Hawaiian or Other Pacific Islander	1 (0.6%)	1 (0.6%)	2 (0.6%)	1 (0.2%)	0	1 (0.1%)
White	130 (80.2%)	127 (76.5%)	257 (78.4%)	323 (76.4%)	312 (75.9%)	635 (76.1%)
Other	0	1 (0.6%)	1 (0.3%)	1 (0.2%)	1 (0.2%)	2 (0.2%)
Multiple	0	3 (1.8%)	3 (0.9%)	2 (0.5%)	3 (0.7%)	5 (0.6%)
Unknown	0	0	0	0	1 (0.2%)	1 (0.1%)
Not Reported	0	0	0	1 (0.2%)	0	1 (0.1%)
Dry Eye Disease Duration (years)						
Mean (SD)	12.17 (10.595)	12.34 (10.693)	12.26 (10.629)	10.3 (9.55)	10.4 (10.32)	10.4 (9.93)
Median	9.97	10.10	10.10	6.4	6.3	6.4
Min, Max	1.1, 72.8	0.9, 48.1	0.9, 72.8	1, 65	1, 55	1, 65
Dry Eye Disease Duration Category						
< 10 years	81 (50.0%)	80 (48.2%)	161 (49.1%)	261 (61.7%)	256 (62.3%)	517 (62.0%)
>= 10 years	81 (50.0%)	86 (51.8%)	167 (50.9%)	162 (38.3%)	155 (37.7%)	317 (38.0%)

Abbreviations: SD = Standard Deviation. **Notes**: N in the headers represented the total number of subjects in the respective treatment group for the given population. Percentages were based on the total number of subjects in each respective treatment group. Subjects who had selected more than one race were summarized in the Multiple Race group.

Most subjects enrolled in the pivotal studies were female (72-73%), and aged > 45 years. Epidemiologic studies showed that DED is more prevalent in women and elderly population, with prevalence linearly increasing with age (Stapleton et al, DEWS II Epidemiology, 2017). Overall, the demographic characteristics of the pivotal studies populations can be considered representative of the target patient population.

Within studies, demographic characteristics were balanced across treatment arms. Between studies, patients in study CYS-004 were on average 4.3 years younger (CYS-004 Mean age 57.1 y, CYS-003 Mean age 61.4 y), and with a 1.8 years shorter duration of the disease (CYS-004 Mean duration DED 10.4 y, CYS-003 Mean duration DED 12.26 y).

Baseline disease characteristics

In both pivotal studies, inclusion criteria for signs of DED were tCFS ≥10 (NEI scale), total lissamine green conjunctival score ≥2 (Oxford scale), and unanaesthetised Schirmer's tear test score between ≥1 and ≤10 mm. Baseline disease characteristics of the subjects randomized in study CYS-003 and CYS-004 are summarized in Table 7 and Table 8, respectively.

Table 7: Baseline Disease Characteristics – CYS-003 - Full Analyses Set Population

Measurement	Vevizye (N=162)	Vehicle (N=166)
Total Corneal Fluorescein Staining (0 - 15: Higher is Worse)		
Mean (SD)	11.5 (1.26)	11.5 (1.25)
Median	11.0	11.0
Min, Max	10, 15	10, 15
Total OSDI score		
Mean (SD)	46.94 (16.732)	47.13 (16.408)
Median	44.10	47.61
Min, Max	20.0, 93.8	20.5, 90.0
Score < 36 (n [%])	45 (27.8%)	49 (29.5%)
Score ≥ 36 (n [%])	117 (72.2%)	117 (70.5%)
Reading impairment score[1]		
Mean (SD)	2.1 (1.13)	2.1 (1.02)
Median	2.0	2.0
Min, Max	0, 4	0, 4
Unanesthetized Schirmer's Tear Test (mm)		
Mean (SD)	5.3 (2.82)	5.1 (2.64)
Median	5.0	5.0
Min, Max	1, 10	1, 10
Central Corneal Fluorescein Staining		
Mean (SD)	2.0 (0.51)	2.0 (0.52)
Median	2.0	2.0
Min, Max	1, 3	1, 3
Inferior Corneal Fluorescein Staining		
Mean (SD)	2.6 (0.48)	2.6 (0.51)
Median	3.0	3.0
Min, Max	2, 3	1, 3
Total Lissamine Green Conjunctival Staining		
Mean (SD)	4.2 (1.64)	4.4 (1.73)
Median	4.0	4.0
Min, Max	2, 8	2, 8
Best-Corrected Visual Acuity (LogMAR)		
Mean (SD)	0.120 (0.1482)	0.116 (0.1409)
Median	0.100	0.100
Min, Max	-0.24, 0.60	-0.18, 0.54
Intraocular Pressure (mmHg)		
Mean (SD)	15.7 (2.57)	15.4 (2.65)
Median	16.0	15.0

Min, Max	9, 21	10, 26

[1]Assessment relates to both eyes.
Abbreviation: FAS = Full Analysis Set; LogMAR = logarithm of the minimum angle of resolution; MMP-9 = matrix metalloproteinase 9; OSDI = Ocular Surface Disease Index; SD = standard deviation.
Note: N in the headers represents the total number of subjects enrolled in each respective treatment group within the FAS population. Percentages are based on the total number of subjects in each treatment group. Baseline measures are defined as the last non-missing measure prior to the administration of study drug. The study eye from each subject is an eye that meets all of the inclusion criteria and is selected based on the mean corneal fluorescein staining score at Visit 1.

Table 8: Baseline Disease Characteristics – CYS-004 – Full Analyses set Population

Measurement	Vevizye (N=423)	Vehicle (N=411)	All Subjects (N=834)
Primary Endpoints			
Total Corneal Fluorescein Staining (0 - 15: Higher is Worse)			
Mean (SD)	11.5 (1.41)	11.5 (1.36)	11.5 (1.38)
Median	11.0	11.0	11.0
Min, Max	10, 15	8, 15	8, 15
Dryness from VAS (0 - 100: Higher is Worse)			
Mean (SD)	70.4 (12.53)	70.0 (12.59)	70.2 (12.56)
Median	70.0	70.0	70.0
Min, Max	50, 100	50, 100	50, 100
Key Secondary Endpoints			
Total Conjunctival Lissamine Green Staining (0 – 10: Higher is Worse)			
Mean (SD)	3.7 (1.72)	3.8 (1.67)	3.8 (1.70)
Median	3.0	3.0	3.0
Min, Max	2, 10	2, 8	2, 10
Central Corneal Fluorescein Staining (0 – 3: Higher is Worse)			
Mean (SD)	2.1 (0.63)	2.1 (0.63)	2.1 (0.63)
Median	2.0	2.0	2.0
Min, Max	1, 3	1, 3	1, 3
Blurred Vision from VAS (0 – 100: Higher is Worse)			
Mean (SD)	53.4 (26.56)	51.9 (24.97)	52.7 (25.79)
Median	59.0	57.0	59.0
Min, Max	0, 100	0, 100	0, 100
Total Ocular Surface Disease Index (0 -100: Higher is Worse)			
Mean (SD)	47.06 (21.066)	47.15 (19.290)	47.10 (20.198)
Median	47.50	47.50	47.50
Min, Max	0.0, 100.0	0.0, 93.2	0.0, 100.0
Unanesthetized Schirmer's Tear Test (mm)			
Mean (SD)	5.1 (2.96)	4.8 (2.78)	4.9 (2.87)

Median	5.0	4.0	4.0
Min, Max	1, 10	1, 10	1, 10
Tear Film Break-Up Time (seconds)			
Mean (SD)	3.3555 (1.45211)	3.2793 (1.56159)	3.3180 (1.50663)
Median	2.9800	2.8550	2.9125
Min, Max	0.730, 10.200	1.020, 17.205	0.730, 17.205
Visual Acuity (LogMAR)			
Mean (SD)	0.110 (0.1674)	0.113 (0.1641)	0.112 (0.1657)
Median	0.100	0.100	0.100
Min, Max	-0.20, 0.68	-0.30, 0.72	-0.30, 0.72
Intraocular Pressure (mmHg)			
Mean (SD)	15.6 (2.88)	15.5 (2.95)	15.6 (2.91)
Median	16.0	16.0	16.0
Min, Max	8, 23	6, 26	6, 26

Abbreviations: LogMAR = Logarithm of the Minimum Angle of Resolution; mmHg = millimeters of Mercury; NEI = National Eye Institute/Industry; tCFS = Total Corneal Fluorescein Staining; VAS = Visual Analog Scale.

Note: N in the headers represents the total number of subjects in the given treatment for the population being analyzed.

Study eye was the eye with higher mean tCFS score (NEI Scale) at Visit 1 (Day 1) if both eyes were eligible. If the mean tCFS score was equivalent in both eyes, then the right eye was selected as the study eye.

All reported endpoints are for study eye or subject level unless otherwise noted.

Baseline measures were defined as the last non-missing measure prior to the initiation of randomized study treatment, usually at Visit 1 (Day 1).

Study populations of both pivotal studies were characterized by subjects who had a mean tCFS = 11.5, comparable mean unanesthetized Schirmer's tear test score, but differing total lissamine green conjunctival score (CYS-003: Vevizye Mean 4.2, Vehicle Mean 4.4; CYS-004: Vevizye Mean 3.7, Vehicle Mean 3.8). This could be related to the relatively younger age of the patient population investigated in study CYS-004 (CYS-004 Mean age 57.1 y, CYS-003 Mean age 61.4 y), with (consequently) shorter history of the underlying disease (CYS-004 Mean duration DED 10.4 y, CYS-003 Mean duration DED 12.26 y), and possibly less severe conjunctival impairment at baseline in study CYS-004.

Numbers analysed

The FAS population was used for the primary efficacy analyses, for a total of 1.162 patients with DED. Specifically, the FAS population of study CYS-003 was 328 subjects (162 subjects in the Vevizye group and 166 in the vehicle group). The FAS population of study CYS-004 was 834 subjects (423 subjects in the Vevizye group and 411 in the vehicle group).

Sensitivity analyses were performed on the PP population (313 subjects in study CYS-003, 796 subjects in study CYS-004). Both FAS and PP were used for the secondary efficacy analyses. All safety analyses were conducted using the SAF population. The FAS and SAF populations were identical.

Outcomes and estimation

Primary endpoints

Results of the primary endpoints analysis of both pivotal studies, conducted in the full analysis set (FAS) populations, are presented in Table 9

In both studies, the primary and first hierarchically tested endpoint was met: analysis of change from baseline in total corneal fluorescein staining score at day 29 showed a statistically significant difference between the Vevizye and the vehicle group. The between-treatment difference (Vevizye 0.1% - vehicle) in LS mean was -0.8 (95% CI -1.3 to -0.4; p = 0.0002, ANCOVA) in study CYS-003, and -0.4 (95% CI -0.77 to -0.04; p = 0.0278, ANCOVA) in study CYS-004.

Both studies did not meet their second hierarchically tested primary endpoint: there were no differences between treatment groups in either total OSDI score (CYS-003), or Dryness Score VAS (CYS-004), at day 29.

Table 9: Primary analyses – Pivotal studies – FAS populations

	CYS-003		**CYS-004**	
Change from Baseline to Visit 3 (Day 29)	**Vevizye (N=162)**	**Vehicle (N=166)**	**Vevizye (N=423)**	**Vehicle (N=411)**
DED Sign	**tCFS (NEI Scale)**			
N	157	165	409	395
Mean (SD)	-2.9 (2.59)	-2.2 (2.73)	-4.3 (3.15)	-3.9 (3.44)
LS Mean	-3.5	-2.6	-3.96	-3.55
LS Mean Difference (CI), ANCOVA Model, Vevizye – vehicle	**-0.8 (-1.3, -0.4)**		**-0.41 (-0.77, -0.04)**	
p-value	**0.0002**		**0.0278**	
DED Symptoms	**OSDI**		**Dryness Score (VAS)**	
N	157	165	409	395
Mean (SD)	-7.08 (18.650)	-5.37 (15.291)	-12.6 (23.72)	-13.7 (23.41)
LS Mean (SE)	-8.76	-6.81	-12.2 (1.29)	-13.6 (1.31)
LS Mean Difference (CI), ANCOVA Model, Vevizye – vehicle	-1.95 (-5.38, 1.48)		1.4 (-1.8, 4.6)	
p-value	0.2634		0.3842	
Abbreviations: ANCOVA = Analysis of Covariance; CI = Confidence interval; FAS = Full Analysis Set; LS = Least Squares; OSDI = Ocular Surface Disease Index; SD = Standard Deviation				

Secondary Endpoints

In study CYS-003, secondary measures of ocular surface integrity (corneal and conjunctival staining scores) were reduced in the Vevizye 0.1% group compared to the vehicle group. Specifically:

Total and central corneal fluorescein staining scores improved during the course of the study, with significant reductions in the Vevizye 0.1% group compared to vehicle from the first follow-up visit (Day 15). The proportion of responders in tCFS score (≥3 score improvement on NEI Scale) at Day 29 was higher in the Vevizye 0.1% group. Results are presented in *Table 10*,

Table 11 and Table 12.

- Analysis of conjunctival lissamine green staining showed that the Vevizye 0.1% group had statistically larger reductions compared to vehicle group at both visits at which the assessment was performed, i.e. Visit 3 (Day 29) and at Visit 5 (Day 85). See Table 13.
- Analysis of Schirmer's test showed that tears production was reduced and proportion of responders (subjects with improvement in Schirmer's tear test results of ≥10 mm) was higher in the Vevizye 0.1% group compared to the vehicle group at visit 5 (Day 85) (Table 14 and Table 15).

Both treatment groups showed similar increases from baseline in TBUT over the duration of the study, but differences between treatment groups were not significant.

In terms of symptoms, there were improvements from baseline in OSDI total score at other study visits, lead/worst symptom, and reading impairment in both treatment groups, but with no differences between them.

In sum, secondary analyses in study CYS-003 were supportive of efficacy of Vevizye 0.1% compared to vehicle for the treatment of signs of DED. There was no difference between Vevizye and vehicle in improvements in TBUT and in DED symptoms.

Table 10: Total Corneal Fluorescein Staining (Secondary Endpoints) -CYS-003- FAS Population with Available Data

		Vevizye 0.1% (N=162)	**Vehicle (N=166)**
Visit 1 (Day 1, Baseline)	n	162	166
	Mean (SD)	11.5 (1.26)	11.5 (1.25)
Visit 2 (Day 15)	n	160	165
	Mean (SD)	9.4 (2.24)	9.8 (2.33)
	CFB Mean (SD)	-2.1 (2.09)***	-1.7 (2.26)***
	Δ in mean CFB[1]	-0.4*	
	Two-sided 95% CI	(-0.9, 0.1)	
Visit 4 (Day 57)	n	155	164
	Mean (SD)	7.9 (3.07)	8.6 (2.85)
	CFB Mean (SD)	-3.6 (2.95)***	-2.9 (2.79)***
	Δ in mean CFB[1]	-0.6**	
	Two-sided 95% CI	(-1.3, 0.0)	
Visit 5 (Day 85)	n	155	163
	Mean (SD)	7.5 (2.99)	8.0 (3.04)
	CFB Mean (SD)	-4.0 (2.94)***	-4.0 (2.94)***
	Δ in mean CFB[1]	-0.5*	
	Two-sided 95% CI	(-1.2, 0.2)	

*$P \leq 0.05$ (CFB = paired t-test; Δ = ANCOVA)
**$P \leq 0.01$ (CFB = paired t-test; Δ = ANCOVA)
***$P \leq 0.001$ (CFB = paired t-test; Δ = ANCOVA)
[1] Vevizye 0.1% - Vehicle

Abbreviations: ANCOVA = Analysis of Covariance; CFB = change from baseline; CI = confidence interval; FAS = Full Analysis Set; NEI = National Eye Institute; SD = standard deviation.
Note: N in headers represents the total number of subjects enrolled in each respective treatment group within the FAS population. Corneal fluorescein staining (NEI scale) was assessed on a 0 to 3 scale in each of five regions of the cornea. A score of 0 meant no staining and 3 meant severe staining. Total corneal fluorescein staining was the sum of staining scores for all five regions, on a 0 to 15 scale.
ANCOVA model includes site and treatment as fixed factors, and baseline score as a covariate. Mixed effects model is estimated using data from all visits and include site, treatment, visit and the interaction between treatment and visit as fixed effects, and subject as a random effect.

Table 11: Central Corneal Fluorescein Staining -CYS-003- FAS Population with Available Data

		Vevizye 0.1% (N=162)	Vehicle (N=166)
Visit 1 (Day 1, Baseline)	n	162	166
	Mean (SD)	2.0 (0.51)	2.0 (0.52)
Visit 2 (Day 15)	n	160	165
	Mean (SD)	1.7 (0.68)	1.9 (0.73)
	CFB Mean (SD)	-0.3 (0.76)***	-0.2 (0.84)**
	Δ in mean CFB[1]	-0.1*	
	Two-sided 95% CI	(-0.3, 0.0)	
Visit 3 (Day 29)	n	157	165
	Mean (SD)	1.4 (0.75)	1.6 (0.76)
	CFB Mean (SD)	-0.6 (0.87)***	-0.4 (0.86)***
	Δ in mean CFB[1]	-0.2***	
	Two-sided 95% CI	(-0.4, 0.0)	
Visit 4 (Day 57)	n	156	164
	Mean (SD)	1.4 (0.83)	1.6 (0.79)
	CFB Mean (SD)	-0.6 (0.95)***	-0.6 (0.95)***
	Δ in mean CFB[1]	-0.6 (0.95)***	
	Two-sided 95% CI	-0.6 (0.95)***	
Visit 5 (Day 85)	n	155	163
	Mean (SD)	1.3 (0.82)	1.5 (0.75)
	CFB Mean (SD)	-0.8 (0.93)***	-0.6 (0.85)***
	Δ in mean CFB[1]	-0.2**	
	Two-sided 95% CI	(-0.4, 0.0)	

*$P \leq 0.05$ (CFB = paired t-test; Δ = ANCOVA)
**$P \leq 0.01$ (CFB = paired t-test; Δ = ANCOVA)
***$P \leq 0.001$ (CFB = paired t-test; Δ = ANCOVA)
[1] Vevizye 0.1% - Vehicle
Abbreviations: ANCOVA = Analysis of Covariance; CFB = change from baseline; CI = confidence interval; FAS = Full Analysis Set; NEI = National Eye Institute; SD = standard deviation
Note: N in headers represents the total number of subjects enrolled in each respective treatment group within the FAS population. Corneal fluorescein staining (NEI scale) was assessed on a 0 to 3 scale in each of five regions of the cornea. A score of 0 meant no staining and 3 meant severe staining.
ANCOVA model includes site and treatment as fixed factors, and baseline score as a covariate. Mixed effects model is estimated using data from all visits and include site, treatment, visit and the interaction between treatment and visit as fixed effects, and subject as a random effect.

Table 12: Total Conjunctival Lissamine Green Staining -CYS-003- FAS Population with Available Data

		Vevizye 0.1% (N=162)	Vehicle (N=166)
Visit 1 (Day 1, Baseline)	n	162	166
	Mean (SD)	4.2 (1.64)	4.4 (1.73)
Visit 3 (Day 29)	n	157	165
	Mean (SD)	3.3 (1.81)	3.9 (1.93)
	CFB Mean (SD)	-1.0 (1.49)***	-0.5 (1.49)***
	Δ in mean CFB[1]	-0.5***	
	Two-sided 95% CI	(-0.9, -0.2)	
Visit 5 (Day 85)	n	155	163
	Mean (SD)	2.8 (1.62)	3.3 (1.68)
	CFB Mean (SD)	-1.4 (1.58)*** -1.0	-1.0 (1.56)***
	Δ in mean CFB[1]	-0.4**	
	Two-sided 95% CI	(-0.7, 0.0)	

*$P \leq 0.05$ (CFB = paired t-test; Δ = ANCOVA)
**$P \leq 0.01$ (CFB = paired t-test; Δ = ANCOVA)
***$P \leq 0.001$ (CFB = paired t-test; Δ = ANCOVA)
[1] Vevizye 0.1% - Vehicle
Abbreviations: ANCOVA = Analysis of Covariance; CFB = change from baseline; CI = confidence interval; FAS = Full Analysis Set; SD = standard deviation.
Note: N in headers represents the total number of subjects enrolled in each respective treatment group within the FAS population. Conjunctival lissamine green staining (Oxford) is assessed on a 0 – 5 scale for each region. A score of 0 means no staining. ANCOVA model includes site and treatment as fixed factors, and baseline score as a covariate.

Table 13: Total Corneal Fluorescein Staining Responder Analysis –CYS-003- FAS Population with Available Data

		Vevizye 0.1% (N=162)	Vehicle (N=166)
Visit 3 (Day 29)	n	157	165
	Responder	83 (52.9%)	67 (40.6%)
	Difference of Proportions	0.12	
	Two-sided Exact 95% CI	(0.01, 0.23)	
	Fisher's Exact Test, P-value	0.0337	
	Odds Ratio, Vevizye: Vehicle	2.1	
	Two-sided 95% CI	(1.3, 3.4)	
	Difference in log (Odds), P-value	0.0032	

Abbreviations: CI = confidence interval; FAS = Full Analysis Set.

Table 14: Unanesthetized Schirmer's Tear Test -CYS-003- FAS Population with Available Data

		Vevizye 0.1% (N=162)	Vehicle (N=166)
Visit 1 (Day 1, Baseline)	n	162	166
	Mean (SD)	5.3 (2.82)	5.1 (2.64)
Visit 2 (Day 15)	n	160	164
	Mean (SD)	6.5 (6.07)	4.8 (4.23)
	CFB Mean (SD)	1.2 (5.54)**	-0.3 (4.20)
	Δ in mean CFB[1]	1.6**	
	Two-sided 95% CI	0.5, 2.7	
Visit 3 (Day 29)	n	157	165
	Mean (SD)	6.4 (5.25)	5.8 (4.53)
	CFB Mean (SD)	1.2 (4.58)**	0.7 (4.31)*
	Δ in mean CFB[1]	0.5	
	Two-sided 95% CI	-0.5, 1.5	
Visit 4 (Day 57)	n	156	164
	Mean (SD)	5.7 (4.99)	5.2 (4.48)
	CFB Mean (SD)	0.5 (4.93)	0.1 (4.50)
	Δ in mean CFB[1]	0.4	
	Two-sided 95% CI	-0.6, 1.4	
Visit 5 (Day 85)	n	155	163
	Mean (SD)	7.6 (7.24)	6.3 (5.27)
	CFB Mean (SD)	2.3 (6.71)***	1.1 (5.09)**
	Δ in mean CFB[1]	1.2	
	Two-sided 95% CI	-0.1, 2.5	

*P ≤ 0.05 (CFB in mean value = paired t-test; Δ = ANCOVA)
**P ≤ 0.01 (CFB in mean value = paired t-test; Δ = ANCOVA)
***P ≤ 0.001 (CFB in mean value = paired t-test; Δ = ANCOVA)
[1] Vevizye 0.1% - Vehicle
Abbreviations: ANCOVA = Analysis of Covariance; CFB = change from baseline; CI = confidence interval; FAS = Full Analysis Set; SD = standard deviation
Note: N in headers represents the total number of subjects enrolled in each respective treatment group within the FAS population. Unanesthetized Schirmer's Tear Test is measured in mm. ANCOVA model includes site and treatment as fixed factors, and baseline score as a covariate.

Table 15: Proportion of Responders in Unanesthetized Schirmer's Tear Test (≥ 10mm increase) - CYS-003- FAS Population with Available Data

Visit (Study Day), Time Point Statistic	Vevizye (N=162)	Vehicle (N=166)
Visit 3 (Day 29)		
Total Number of Subjects	157	165
Number of Subjects with ≥ 10 mm increase from baseline: n (%)	7 (4.5%)	7 (4.2%)
Logistic Regression		
Predictive Marginal Proportions	4.46%	4.24%
Difference in Predictive Marginal Proportions (CI), Vevizye – vehicle	0.22 % (-4.24%, 4.67%)	
p-value	0.9243	

Visit 5 (Day 85)		
Total Number of Subjects	155	163
Number of Subjects with ≥ 10 mm increase from baseline: n (%)	19 (12.3%)	9 (5.5%)
Logistic Regression		
Predictive Marginal Proportions	12.26%	5.52%
Difference in Predictive Marginal Proportions (CI), Vevizye – vehicle	6.74 % (0.50%, 12.98%)	
p-value	0.0344	

Abbreviations: CI = Confidence Interval;
Lower values indicate less tears produced in the eye. Logistic regression model included treatment group.

Table 16: Tear Film Break-Up Time -CYS-003- FAS Population with Available Data

		Vevizye 0.1% (N=162)	**Vehicle (N=166)**
Visit 1 (Day 1, Baseline)	n	162	166
	Mean (SD)	2.3493 (0.89397)	2.2789 (0.98885)
Visit 3 (Day 29)	n	157	165
	Mean (SD)	2.4928 (1.11258)	2.4331 (1.12478)
	CFB Mean (SD)	0.1387 (0.97652)	0.1592 (0.97917)*
	Δ in mean CFB[1]	-0.0205	
	Two-sided 95% CI	(-0.2350, 0.1940)	
Visit 5 (Day 85)	n	155	163
	Mean (SD)	2.7839 (0.99190)	2.7912 (1.70282)
	CFB Mean (SD)	0.4293 (1.01597)***	0.5117 (1.54147)***
	Δ in mean CFB[1]	-0.0823	
	Two-sided 95% CI	(-0.3719, 0.2073)	

*P ≤ 0.05 (CFB = paired t-test; Δ = ANCOVA)
**P ≤ 0.01 (CFB = paired t-test; Δ = ANCOVA)
***P ≤ 0.001 (CFB = paired t-test; Δ = ANCOVA)
[1] Vevizye 0.1% - Vehicle
Abbreviations: ANCOVA = Analysis of Covariance; CFB = change from baseline; CI = confidence interval; FAS = Full Analysis Set; SD = standard deviation.
Note: N in headers represents the total number of subjects enrolled in each respective treatment group within the FAS population. Tear film break-up time is presented in seconds. ANCOVA model includes site and treatment as fixed factors, and baseline score as a covariate.

In study **CYS-004**, measures of ocular surface integrity (corneal and conjunctival staining scores) were reduced in the Vevizye 0.1% group compared to the vehicle group. Specifically:

- Total corneal fluorescein staining scores improved during the course of the study, with significant reductions in the Vevizye 0.1% group compared to the vehicle group both at the first follow-up visit (Day 15, secondary analysis, see
- *Table* 17), and the second follow-up visit (Day 29, see primary analysis).
- Central corneal fluorescein staining and conjunctival lissamine green staining significantly improved in the Vevizye 0.1% group compared to vehicle at Day 29 (
- *Table* 17).

- The proportion of responders in total corneal fluorescein staining score (≥3 improvement), and in central corneal fluorescein staining score (≥1 improvement) was higher in the Vevizye 0.1% group (*Table 18*).
- Analysis of tears production (Schirmer's test) showed that the proportion of responders (subjects with improvement in Schirmer's tear test results of ≥10 mm) was higher in the Vevizye 0.1% group compared to the vehicle group at Day 29 (*Table 18*).

Both treatment groups showed similar increases from baseline in TBUT over the study, with no differences between the groups (Table 19).

In terms of symptoms, there were improvements from baseline in OSDI total score at day 29 in both treatment groups, with no differences between the two groups. There were no differences between the two groups in blurred vision score as measured by visual analog scale (

Table 17).

In sum, secondary analyses in study CYS-004 were supportive of efficacy of Vevizye compared to vehicle for the treatment of signs of DED. No differences between Vevizye and vehicle in improvements in TBUT and DED symptoms were found.

Table 17: Key Secondary Objective Endpoints for CYS-004 – FAS population

	Vevizye (N=423)	**Vehicle (N=411)**
Total Conjunctival Lissamine Green Staining Change from Baseline to Visit 3 (Day 29)		
N	409	395
Mean (SD)	-1.3 (1.83)	-1.0 (1.74)
Min, Max	-9, 5	-8, 4
LS Mean (SE)	-1.24 (0.078)	-0.91 (0.079)
LS Mean Difference (CI), ANCOVA Model, Vevizye - vehicle	**-0.33 (-0.53, -0.14)**	
p-value	**0.0009**	
Proportion of Responders in Central Corneal Fluorescein Staining Score (≥1 Score Improvement in NEI Scale) at Day 29 Visit 3 (Day 29)		
Total Number of Subjects	409	395
Number of Subjects with ≥ 1 Score Improvement from baseline: n (%)	275 (67.2%)	238 (60.3%)
Number of Subjects with < 1 Score Improvement from baseline: n (%)	134 (32.8%)	157 (39.7%)
Predictive Marginal Proportions	71.22%	63.89%
Difference in Predictive Marginal Proportions (CI)	**7.33% (0.26%, 14.40%)**	
p-value	**0.0421**	
Proportion of Responders in Total Corneal Fluorescein Staining Score (≥3 Score Improvement on NEI Scale) at Day 29 Visit 3 (Day 29)		
Total Number of Subjects	409	395
Number of Subjects with ≥ 3 Score Improvement from baseline: n (%)	293 (71.6%)	236 (59.7%)

Number of Subjects with < 3 Score Improvement from baseline: n (%)	116 (28.4%)	159 (40.3%)
Predictive Marginal Proportions	77.78%	65.16%
Difference in Predictive Marginal Proportions (CI)	**12.62% (5.98%, 19.26%)**	
p-value	**0.0002**	
Central Fluorescein Staining (NEI Scale) Change from Baseline to Visit 3 (Day 29)		
N	409	395
Mean (SD)	-0.9 (0.95)	-0.8 (0.99)
Min, Max	-3, 2	-3, 2
LS Mean (SE)	-0.79 (0.045)	-0.67 (0.046)
LS Mean Difference (CI), ANCOVA Model, Vevizye – vehicle	**-0.12 (-0.23, 0.00)**	
p-value	**0.0410**	
Total Fluorescein Staining Score (NEI Scale) Change from Baseline to Visit 2 (Day 15)		
N	418	403
Mean (SD)	-3.9 (2.91)	-3.3 (3.15)
Min, Max	-12, 4	-14, 3
LS Mean (SE)	-3.53 (0.144)	-2.97 (0.147)
LS Mean Difference (CI), ANCOVA Model, Vevizye – vehicle	**-0.56 (-0.92, -0.20)**	
p-value	**0.0022**	
Blurred Vision Change (VAS) from Baseline to Visit 3 (Day 29)		
N	409	395
Mean (SD)	-7.3 (22.66)	-5.8 (23.21)
Min, Max	-86, 75	-87, 63
Two-Sided 95% CI	(-9.5, -5.1)	(-8.1, -3.5)
LS Mean (SE)	-7.1 (1.19)	-6.1 (1.21)
LS Mean Difference (CI), ANCOVA Model, Vevizye – vehicle	-1.0 (-4.0, 2.0)	
p-value	0.5099	
Abbreviations: ANCOVA = Analysis of Covariance; CI = Confidence Interval; LS = Least Squares; SD = Standard Deviation; SE = Standard Error ANCOVA model included baseline value, site, and treatment group.		

Table 18: Proportion of Responders in Unanesthetized Schirmer's Tear Test (≥ 10mm increase) - CYS-004- FAS Population with Available Data

Visit (Study Day), Time Point Statistic	Vevizye (N=423)	Vehicle (N=411)
Visit 3 (Day 29)		
Total Number of Subjects	409	395

Number of Subjects with ≥ 10 mm increase from baseline: n (%)	44 (10.8%)	27 (6.8%)
Number of Subjects with < 10 mm increase from baseline: n (%)	365 (89.2%)	368 (93.2%)
Logistic Regression		
Predictive Marginal Proportions	10.76%	6.84%
Difference in Predictive Marginal Proportions (CI), Vevizye – vehicle	**3.92% (0.02%, 7.82%)**	
p-value	**0.0487**	
Abbreviations: CI = Confidence Interval; Lower values indicate less tears produced in the eye. Logistic regression model included treatment group.		

Table 19: TBUT total score -CYS-004– FAS population

Change from baseline in TBUT		**Vevizye 0.1% (N=423)**	**Vehicle (N=411)**
Visit 3 (Day 29)	n	409	395
	Mean (SD)	0.5359 (1.68850)	0.5068 (1.59980)
	Two-Sided 95% CI	(0.3718, 0.7001)	(0.3485, 0.6650)
	p-value, Paired t-test	<0.0001	<0.0001
	Vevizye 0.1% - Vehicle ANCOVA Model		
	LS Mean (SE)	0.5263 (0.08195)	0.4397 (0.08383)
	Two-Sided 95% CI	(0.3654, 0.6871)	(0.2752, 0.6043)
	LS Mean Difference (SE)	0.0865 (0.10409)	
	Two-Sided 95% CI	(-0.1178, 0.2909)	
	p-value	0.4060	

ANCOVA = Analysis of Covariance; CI = Confidence Interval; LS = Least Squares

Ancillary analyses

Main subgroup analysis were conducted on the following subgroups:

- Age: 18 to <65 years, ≥65 years;
- Sex: male, female;
- Race: any race with a pooled sample size of at least 20 subjects;
- Baseline dryness score: <75, ≥75 (VAS).

The VAS dryness score was chosen for subgroup analyses based on symptoms as it was used as a stratification factor in the larger pivotal study (CYS-004). The cut point of 75 for baseline dryness VAS was adopted as close to the median of dryness score at baseline in both treatment groups in study CYS-003. Subgroup analyses were conducted on the primary and key secondary endpoints, including:

- CFB in tCFS score (NEI Scale) at Day 29 and Day 15;
- CFB in cCFS at Day 29;
- Proportion of responders in tCFS score (≥ 3 score improvement on NEI Scale) at Day 29;
- Proportion of responders in cCFS score (≥ 1 score improvement on NEI Scale) at Day 29;

- Proportion of responders in Schirmer's test (≥ 10 mm increase from baseline) at Day 85 (CYS-003 only), or at Day 29 (CYS-004 only);
- CFB in lissamine green staining at Day 29;
- CFB in dryness (VAS) at Day 29.

For the Schirmer's test responder endpoints at Day 85 and Day 29, subgroup analyses were conducted using the CYS-003 FAS, and the CYS-004 FAS, respectively. For all other endpoints, subgroup analyses were only conducted using the pooled CYS-003 and CYS-004 data (see Section 3.7). Results of subgroup analyses are summarized in Table 20.

Table 20: Overview of efficacy results by baseline age, sex, race, and dryness score, per efficacy endpoint

Subgroup factor	**Age**		
	Between-treatment difference (Δ)		
Endpoint	**Overall analysis (CYS-003 + CYS-004 pooled, N 1162)**	**Age 18 to <65 years** **n 717**	**Age ≥65 years** **n 445**
CFB in tCFS at Day 29	CYS-003 Δ: -0.84* CYS-004 Δ: -0.41* Pooled Δ: -0.53*	Pooled Δ: -0.54*	Pooled Δ: -0.52*
Responders in tCFS at Day 29	CYS-003 Δ: 20.12%* CYS-004 Δ: 12.62%* Pooled Δ: 15.26%	Pooled Δ: 11.73%*	Pooled Δ: 12.68%*
CFB in tCFS at Day 15	CYS-003 Δ: -0.43* CYS-004 Δ: -0.56* Pooled Δ: -0.52*	Pooled Δ: -0.69*	Pooled Δ: -0.29
Schirmer's test	CYS-003 Δ: 6.74%* CYS-004 Δ: 3.92%*	CYS-003 Δ: 4.68% CYS-004 Δ: 5.89%*	CYS-003 Δ: 9.00%* CYS-004 Δ: 0.55%
CFB in lissamine green staining at Day 29	CYS-003 Δ: -0.56* CYS-004 Δ: -0.33* Pooled Δ: -0.40*	Pooled Δ: -0.40*	Pooled Δ: -0.38*
Responders in cCFS at Day 29	CYS-003 Δ: 27.07%* CYS-004 Δ: 7.33%* Pooled Δ: 12.25*	Pooled Δ: 9.70%*	Pooled Δ: 9.36%
CFB in cCFS at Day 29	CYS-003 Δ: -0.25* CYS-004 Δ: -0.12* Pooled Δ: -0.15*	Pooled Δ: -0.18*	Pooled Δ: -0.13
CFB in dryness at Day 29	CYS-003 Δ: -4.8* CYS-004 Δ: 1.4 Pooled Δ: -0.3	Pooled Δ: 0.6	Pooled Δ: -1.9
Subgroup factor	**Sex**		
	Between-treatment difference (Δ)		
Endpoint	**Overall analysis (CYS-003 + CYS-004 pooled, N 1162)**	**Male** **n 318**	**Female** **n 844**
CFB in tCFS at Day 29	CYS-003 Δ: -0.84* CYS-004 Δ: -0.41* Pooled Δ: -0.53*	Pooled Δ: -0.20	Pooled Δ: -0.63*
Responders in tCFS at Day 29	CYS-003 Δ: 20.12%* CYS-004 Δ: 12.62%* Pooled Δ: 15.26%*	Pooled Δ: 6.61%	Pooled Δ: 14.44%*

CFB in tCFS at Day 15	CYS-003 Δ: -0.43* CYS-004 Δ: -0.56* Pooled Δ: -0.52*	Pooled Δ: -0.33	Pooled Δ: -0.56*
Schirmer's test	CYS-003 Δ: 6.74%* CYS-004 Δ: 3.92%*	CYS-003 Δ: 4.35% CYS-004 Δ: 5.31%	CYS-003 Δ: 7.72%* CYS-004 Δ: 3.35%
CFB in lissamine green staining at Day 29	CYS-003 Δ: -0.56* CYS-004 Δ: -0.33* Pooled Δ: -0.40*	Pooled Δ: -0.51*	Pooled Δ: -0.33*
Responders in cCFS at Day 29	CYS-003 Δ: 27.07%* CYS-004 Δ: 7.33%* Pooled Δ: 12.25%*	Pooled Δ: 5.22%	Pooled Δ: 11.49%*
CFB in cCFS at Day 29	CYS-003 Δ: -0.25* CYS-004 Δ: -0.12* Pooled Δ: -0.15*	Pooled Δ: -0.14	Pooled Δ: -0.17*
CFB in dryness at Day 29	CYS-003 Δ: -4.8* CYS-004 Δ: 1.4 Pooled Δ: -0.3	Pooled Δ: 1.5	Pooled Δ: -0.7

Subgroup factor	**Race**			
	Between-treatment difference (Δ)			
Endpoint	**Overall analysis (CYS-003 + CYS-004 pooled, N 1162)**	**Asian** **n 112**	**Black/ African American** **n 138**	**White** **n 892**
CFB in tCFS at Day 29	CYS-003 Δ: -0.84* CYS-004 Δ: -0.41* Pooled Δ: -0.53*	Pooled Δ: 0.09	Pooled Δ: -0.25	Pooled Δ: -0.62*
Responders in tCFS at Day 29	CYS-003 Δ: 20.12%* CYS-004 Δ: 12.62%* Pooled Δ: 15.26%*	Pooled Δ: 1.17%	Pooled Δ: 12.73%	Pooled Δ: 13.08%*
CFB in tCFS at Day 15	CYS-003 Δ: -0.43* CYS-004 Δ: -0.56* Pooled Δ: -0.52*	Pooled Δ: -0.76	Pooled Δ: -0.03	Pooled Δ: -0.53*
Schirmer's test	CYS-003 Δ: 6.74%* CYS-004 Δ: 3.92%*	CYS-003 Δ: 2.43% CYS-004 Δ: 7.31%	CYS-003 Δ: -3.08% CYS-004 Δ: 11.88%	CYS-003 Δ: 8.03%* CYS-004 Δ: 1.98%
CFB in lissamine green staining at Day 29	CYS-003 Δ: -0.56* CYS-004 Δ: -0.33* Pooled Δ: -0.40*	Pooled Δ: -0.82*	Pooled Δ: -0.16	Pooled Δ: -0.38*
Responders in cCFS at Day 29	CYS-003 Δ: 27.07%* CYS-004 Δ: 7.33%* Pooled Δ: 12.25*	Pooled Δ: 11.68%	Pooled Δ: 5.13%	Pooled Δ: 10.09%*
CFB in cCFS at Day 29	CYS-003 Δ: -0.25* CYS-004 Δ: -0.12* Pooled Δ: -0.15*	Pooled Δ: -0.13	Pooled Δ: -0.09	Pooled Δ: -0.17*
CFB in dryness at Day 29	CYS-003 Δ: -4.8* CYS-004 Δ: 1.4 Pooled Δ: -0.3*	Pooled Δ: 1.1	Pooled Δ: -0.1	Pooled Δ: -0.7

Subgroup factor	**Dryness score**		
	Between-treatment difference (Δ)		
Endpoint	**Overall analysis (CYS-003 + CYS-004 pooled, N 1162)**	**Baseline dryness score <75** **n 698**	**Baseline dryness score ≥75** **n 464**
CFB in tCFS at Day 29	CYS-003 Δ: -0.84* CYS-004 Δ: -0.41* Pooled Δ: -0.53*	Pooled Δ: -0.54*	Pooled Δ: -0.52*
Responders in tCFS at Day 29	CYS-003 Δ: 20.12%* CYS-004 Δ: 12.62%* Pooled Δ: 15.26%*	Pooled Δ: 13.63%*	Pooled Δ: 10.35%*
CFB in tCFS at Day 15	CYS-003 Δ: -0.43* CYS-004 Δ: -0.56*	Pooled Δ: -0.32	Pooled Δ: -0.86*

	Pooled Δ: -0.52*		
Schirmer's test	CYS-003 Δ: 6.74%* CYS-004 Δ: 3.92%*	CYS-003 Δ: 10.37%* CYS-004 Δ: 5.23%*	CYS-003 Δ: 2.96% CYS-004 Δ: 1.69%
CFB in lissamine green staining at Day 29	CYS-003 Δ: -0.56* CYS-004 Δ: -0.33* Pooled Δ: -0.40*	Pooled Δ: -0.39*	Pooled Δ: -0.45*
Responders in cCFS at Day 29	CYS-003 Δ: 27.07%* CYS-004 Δ: 7.33%* Pooled Δ: 12.25%*	Pooled Δ: 10.09%*	Pooled Δ: 9.46%*
CFB in cCFS at Day 29	CYS-003 Δ: -0.25* CYS-004 Δ: -0.12* Pooled Δ: -0.15*	Pooled Δ: -0.18*	Pooled Δ: -0.12
CFB in dryness at Day 29	CYS-003 Δ: -4.8* CYS-004 Δ: 1.4 Pooled Δ: -0.3*	Pooled Δ: 1.0	Pooled Δ: -1.9

CFB=change from baseline, cCFS=central corneal fluorescein staining, tCFS=total corneal fluorescein staining. *statistically significant at $p \leq 0.05$ level.

There was a treatment effect of CyclASol compared to vehicle across all investigated sign efficacy endpoints in both age groups. For a number of parameters the effect size in the age subgroups was comparable to the overall study population and statistical significance was reached.

Males were a proportionally smaller subgroup compared to females. This reflects the typical DED population, and may explain, at least in part, the statistical non-significance in the male subgroup.

CyclASol showed a treatment effect compared to vehicle across all sign efficacy endpoints in three race subgroups. Effect sizes varied in the Asians and Blacks/ African Americans subgroups, which may be related to the relatively smaller size of the samples.

There was a treatment effect compared to vehicle across all sign efficacy endpoints in the two subgroups with higher and lower symptom of dryness as measured by VAS.

Consistently with the individual studies, there was no clear treatment effects of CyclASol for CFB to Day 29 in dryness score in the pooled sample, nor in the subgroups.

Overall, results from the subgroup analyses by age and dryness score may be considered consistent with the results from the overall analysis, supporting efficacy of CyclASol across subgroups, with the caveat that interpretability of subgroup analyses by sex and race may be limited by the smaller size of the males, Asians and Blacks/ African Americans subgroups.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21: Summary of efficacy for trial CYS-003

Title: A Phase 2b/3, multicenter, randomized, double-masked, vehicle controlled clinical study to assess the efficacy and safety of topical CyclASol® (Vevizye) for the treatment of signs and symptoms of Dry Eye Disease	
Study identifier	CYS-003, ESSENCE 1, NCT03292809
Design	Phase 2b/3, multicenter, randomized, double-masked, vehicle controlled clinical study to assess the efficacy and safety of Vevizye for the treatment of signs and symptoms of Dry Eye Disease.

	Main inclusion criteria: ≥18 years of age; both sexes; reported history of DED in both eyes (OU) for ≥ 6 months; use eye drops or lubricating gels for dry eye symptoms within 30 days before Visit 0 (screening). In addition, subjects were eligible if, both at screening (Visit 0), and at baseline (Visit 1) after a 14-day run-in period with artificial tears, they had an OSDI score ≥20, and at least one eye with: tCFS ≥10 (NEI scale), total lissamine green conjunctival score ≥2 (Oxford scale), and unanesthetized Schirmer's tear test score between ≥1 and ≤10 mm. Subjects were randomized to receive treatment with either Vevizye 0.1% or vehicle OU twice daily (BID) in a 1:1 ratio. Two study periods: 14-day run-in followed by 84-day treatment. Scheduled visits: Visit 0 (Screening; Day -14), Visit 1 (Baseline/Randomization; Day 1), Visit 2 (Day 15), Visit 3 (Day 29), Visit 4 (Day 57), and Visit 5 (Study Exit; Day 85). Dry eye signs and symptoms were assessed at baseline and at the 4 follow-up visits. Primary endpoints were assessed at Day 29.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		84 days 14 days not applicable
Hypothesis	Superiority		
Treatments groups	CYC		Vevizye 0.1% 84 days, n = 162
	VEH		Vehicle 84 days, n = 166
Endpoints and definitions (incl. the most relevant secondary and exploratory endpoints)	Primary endpoint	tCFS	Change from baseline (CFB) in total corneal fluorescein staining score (NEI scale) at Day 29
	Primary endpoint	OSDI	CFB in total OSDI score at Day 29
	Secondary endpoint	cCFS	CFB in central corneal staining score (NEI scale) at day 29
	Secondary endpoint	tCFS Resp.	Proportion of Responders in tCFS score (≥3 score improvement on NEI Scale) at Day 29
	Secondary endpoint	LGS	CFB in total conjunctival lissamine green staining score (Oxford scale) at Day 29
	Secondary endpoint	Schirmer (D29; D85)	Proportion of Responders in Unanesthetized Schirmer's Tear Test (≥10mm increase) at Day 29 and 85
	Secondary endpoint	TBUT	CFB in Tear film break-up time at Day 29
Database lock	<date>		

Results and Analysis			
Analysis description	**Primary Analyses**		
Analysis population and time point description	FAS (all subjects randomized and having received at least one dose of study drug) Day 29 (and 85)		
tCFS	Treatment group	CYC	VEH
	Number of subjects	157	165
	Mean (SD)	-2.9 (2.59)	-2.2 (2.73)
	LS Mean	-3.5	-2.6
	LS Mean Difference (CI), ANCOVA Model	-0.8 (-1.3, -0.4)	
	p-value	0.0002	
OSDI	Treatment group	CYC	VEH
	Number of subjects	157	165
	Mean (SD)	-7.08 (18.650)	-5.37 (15.291)
	LS Mean	-8.76	-6.81
	LS Mean Difference (CI), ANCOVA Model, Vevizye - vehicle	-1.95 (-5.38, 1.48)	
	p-value	0.2634	
Analysis description	**Secondary analysis:**		
cCFS	Treatment group	CYC	VEH
	Number of subjects	157	165
	Mean (SD)	-0.6 (0.87)	-0.4 (0.86)
	Δ in mean CFB (CI), ANCOVA Model	-0.2 (-0.4, 0.0)	
	p-value	≤ 0.001	
tCFS Resp.	Treatment group	CYC	VEH
	Number of subjects	157	165
	Number of subjects with ≥3 improvement tCFS score D29; n (%)	83 (52.9%)	67 (40.6%)
	Difference of Proportions	0.12	
	Two-sided Exact 95% CI	(0.01, 0.23)	
	Fisher' s Exact Test, P-value	0.0337	
	Odds Ratio, Vevizye: Vehicle	2.1	
	Two-sided 95% CI	(1.3, 3.4)	
	Difference in log (Odds), P-value	0.0032	
LGS	Treatment group	CYC	VEH
	Number of subjects	157	165
	Mean (SD)	-1.0 (1.49)	-0.5 (1.49)
	Δ in mean CFB (CI), ANCOVA Model	-0.5 (-0.9, -0.2)	
	p-value	≤ 0.001	
Schirmer D29	Treatment group	CYC	VEH
	Number of subjects	157	165
	Number of Subjects with ≥ 10 mm increase from baseline: n (%)	7 (4.5%)	5.8 (4.53)

	Predictive Marginal Proportions	4.46%	0.7 (4.31)
	Difference in Predictive Marginal Proportions (CI), Vevizye - vehicle	0.22 % (-4.24%, 4.67%)	
	p-value	0.9243	
Schirmer D85	Treatment group	CYC	VEH
	Number of subjects	155	163
	Number of Subjects with ≥ 10 mm increase from baseline: n (%)	19 (12.3%)	9 (5.5%)
	Predictive Marginal Proportions	12.26%	5.52%
	Difference in Predictive Marginal Proportions (CI), Vevizye - vehicle	6.74 % (0.50%, 12.98%)	
	p-value	0.0344	
TBUT	Treatment group	CYC	VEH
	Number of subjects	157	165
	Mean (SD)	0.1387 (0.97652)	4.24%
	Δ in mean CFB (CI), ANCOVA Model	-0.0205 (-0.2350, 0.1940)	
	p-value	ns	

Table 22: Summary of efficacy for trial CYS-004

Title: A Phase 3, multi-center, randomized, double-masked, vehicle-controlled clinical trial to assess the efficacy and safety of topical CyclASol® (Vevizye) for the treatment of Dry Eye Disease		
Study identifier	CYS-004, ESSENCE 2, NCT04523129	
Design	Phase 3, multi-center, randomized, double-masked, vehicle-controlled clinical trial to evaluate the efficacy, safety and tolerability of CyclASol 0.1% ophthalmic solution (Vevizye) in subjects with signs and symptoms of DED. Subjects of either sex and of any race ≥ 18 years of age with a subject-reported history of DED in both eyes were randomized at 27 sites in the US to receive treatment with Vevizye or vehicle in a 1:1 ratio. The trial was composed of two periods: a 14-day run-in period and a 29-day treatment period. Visits: Visit 0 (Screening: Day -14), Visit 1 (Baseline/Randomization: Day 1), Visit 2 (Day 15), Visit 3 (Day 29). DED signs and symptoms were assessed at baseline and at the 2 follow-up visits.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	29 days 14 days not applicable
Hypothesis	Superiority	
Treatments groups	CYC	Vevizye 0.1% 29 days, n = 423
	VEH	Vehicle

			29 days, n = 411
Endpoints and definitions (incl. the most relevant secondary and exploratory endpoints)	Primary endpoint	tCFS	Change from baseline (CFB) in total corneal fluorescein staining score (NEI scale) at Day 29
	Primary endpoint	VAS Dryness	CFB in Dryness score (VAS) at Day 29
	Secondary endpoint	cCFS	CFB in central corneal staining score (NEI scale) at Day 29
	Secondary endpoint	tCFS Resp.	Proportion of Responders in tCFS score (≥3 score improvement on NEI Scale) at Day 29
	Secondary endpoint	LGS	CFB in total conjunctival lissamine green staining score (Oxford scale) at Day 29
	Secondary endpoint	Schirmer	Proportion of Responders in Unanesthetized Schirmer's Tear Test (≥10mm increase) at Day 29
	Secondary endpoint	TBUT	CFB in Tear film break-up time at Day 29
Database lock	<date>		

Results and Analysis

Analysis description	**Primary Analyses**		
Analysis population and time point description	FAS (all subjects randomized and having received at least one dose of study drug) Day 29		
tCFS	Treatment group	CYC	VEH
	Number of subjects	409	395
	Mean (SD)	-4.3 (3.15)	-3.9 (3.44)
	LS Mean	-3.96	-3.55
	LS Mean Difference (CI), ANCOVA Model	-0.41 (-0.77, -0.04)	
	p-value	0.0278	
VAS Dryness	Treatment group	CYC	VEH
	Number of subjects	409	395
	Mean (SD)	-12.6 (23.72)	-13.7 (23.41)
	LS Mean	-12.2 (1.29)	-13.6 (1.31)
	LS Mean Difference (CI), ANCOVA Model, Vevizye – vehicle	1.4 (-1.8, 4.6)	
	p-value	0.3842	
Analysis description	**Secondary analysis:**		
cCFS	Treatment group	CYC	VEH
	Number of subjects	409	395
	Mean (SD)	-0.9 (0.95)	-0.8 (0.99)
	LS Mean (SE)	-0.79 (0.045)	-0.67 (0.046)
	LS Mean Difference (CI), ANCOVA Model, Vevizye – vehicle	-0.12 (-0.23, 0.00)	
	p-value	0.0410	

tCFS Resp.	Treatment group	CYC	VEH
	Number of subjects	409	395
	Number of subjects with ≥3 improvement tCFS score D29: n (%)	293 (71.6%)	236 (59.7%)
	Predictive Marginal Proportions	77.78%	65.16%
	Difference in Predictive Marginal Proportions (CI)	12.62% (5.98%, 19.26%)	
	p-value	0.0002	
LGS	Treatment group	CYC	VEH
	Number of subjects	409	395
	Mean (SD)	-1.3 (1.83)	-1.0 (1.74)
	LS Mean (SE)	-1.24 (0.078)	-0.91 (0.079)
	LS Mean Difference (CI), ANCOVA Model, Vevizye - vehicle	-0.33 (-0.53, -0.14)	
	p-value	0.0009	
Schirmer	Treatment group	CYC	VEH
	Number of subjects	409	395
	Number of Subjects with ≥ 10 mm increase from baseline: n (%)	44 (10.8%)	27 (6.8%)
	Predictive Marginal Proportions	10.76%	6.84%
	Difference in Predictive Marginal Proportions (CI), Vevizye - vehicle	3.92% (0.02%, 7.82%)	
	p-value	0.0487	
TBUT	Treatment group	CYC	VEH
	Number of subjects	409	395
	Mean (SD)	0.5359 (1.68850)	0.5068 (1.59980)
	LS Mean (SE)	0.5263 (0.08195)	0.4397 (0.08383)
	LS Mean Difference (CI), ANCOVA Model	0.0865 (-0.1178, 0.2909)	
	p-value	0.4060	

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analysis of efficacy data from the two pivotal studies CYS-003 and CYS-004 were conducted, enabled by similar study designs and populations, as well as by the common primary sign endpoint (change from baseline in tCFS at Day 29) and several common secondary endpoints.

Primary efficacy endpoints for pooled analysis were:

- Change from baseline (CFB) in tCFS score (NEI scale) at Day 29;
- Proportion of responders in tCFS score (≥3 score improvement on NEI scale) at Day 29.

Key secondary endpoints:

- CFB in tCFS score (NEI scale) at Day 15;
- CFB in total conjunctival lissamine green staining score (Oxford scale) at Day 29;
- Proportion of responders in central corneal fluorescein staining (cCFS) score (≥1 score improvement on NEI scale) at Day 29;
- CFB in cCFS score (NEI scale) at Day 29;
- CFB in dryness score (VAS) at Day 29;
- CFB in blurred vision score (VAS) at Day 29;

- CFB in blurred vision score (VAS) at Day 29 in subjects with baseline cCFS score = 3.

The primary assessment of Schirmer's test responders was performed at the end of the two studies, at Day 85 in CYS-003 and at Day 29 in study CYS-004. Thus, no pooled analysis was conducted.

Study population

The same analysis populations as defined for the individual studies were used for the pooled analysis, i.e., the FAS and the Per-Protocol Set (PPS) populations. The FAS included 1162 subjects, including 328 subjects randomized in study CYS-003 and 834 subjects randomized in study CYS-004. Of the 1162 randomized subjects, 1135 (97.7%) completed the studies. The percentage of subjects discontinuing the studies was balanced between the Vevizye 0.1% and vehicle groups.

Main baseline demographic and disease characteristics of the pooled studies are provided in Table 23 and Table 24, respectively.

Table 23: Demographics (FAS) - pooled CYS-003 + CYS-004

	Pooled	
	Vevizye 0.1% (N=585) n (%)	**Vehicle (N=577) n (%)**
Age (years)		
Mean (SD)	58.7 (14.98)	57.9 (15.48)
Median (range)	61 (18, 93)	60 (18, 93)
18 to < 65 years	365 (62.4%)	352 (61.0%)
≥ 65 years	220 (37.6%)	225 (39.0%)
Sex, n (%)		
Male	163 (27.9%)	155 (26.9%)
Female	422 (72.1%)	422 (73.1%)
Ethnicity, n (%)		
Hispanic or Latino	77 (13.2%)	71 (12.3%)
Not Hispanic or Latino	506 (86.5%)	503 (87.2%)
Unknown/ not reported	2 (0.3%)	3 (0.5%)
Race, n (%)		
American Indian or Alaska Native	3 (0.5%)	1 (0.2%)
Asian	54 (9.2%)	58 (10.1%)
Black or African American	69 (11.8%)	69 (12.0%)
Native Hawaiian or Other Pacific Islander	2 (0.3%)	1 (0.2%)
White	453 (77.4%)	439 (76.1%)
Other	1 (0.2%)	2 (0.3%)
Multiple race*	2 (0.3%)	6 (1.0%)
Unknown	0	1 (0.2%)
Not reported	1 (0.2%)	0
Dryness score (VAS), n (%)		
< 75	353 (60.3%)	345 (59.8%)
≥ 75	232 (39.7%)	232 (40.2%)

FAS=full analysis set, N=number of subjects in group, VAS=visual analog scale

Table 24: Baseline characteristics (FAS) - pooled CYS-003 + CYS-004

	Pooled	
	Vevizye 0.1% (N=585) n (%)	**Vehicle (N=577) n (%)**
Study eye, n (%)		
OD	326 (55.7%)	317 (54.9%)
OS	259 (44.3%)	260 (45.1%)
Disease duration (years)		
Mean (SD)	10.8 (9.87)	11.0 (10.45)
Dryness score VAS (0-100)		
Mean (SD)	69.9 (15.60)	69.9 (15.26)
Median (range)	70.0 (3, 100)	70.0 (0, 100)
Blurred vision score VAS (0-100)		
Mean (SD)	52.4 (27.42)	52.0 (26.02)
Median (range)	58.0 (0, 100)	59.0 (0, 100)
tCFS (0-15)		
Mean (SD)	11.5 (1.37)	11.5 (1.33)
Median (range)	11.0 (10, 15)	11.0 (8, 15)
cCFS (0-3)		
Mean (SD)	2.1 (0.60)	2.1 (0.60)
Median (range)	2.0 (1, 3)	2.0 (1, 3)
Total conjunctival lissamine green staining (0-10)		
Mean (SD)	3.9 (1.71)	3.9 (1.71)
Median (range)	4.0 (2, 10)	4.0 (2, 8)
Schirmer's test (mm)		
Mean (SD)	5.1 (2.92)	4.8 (2.74)
Median (range)	5.0 (1, 10)	4.0 (1, 10)
Tear film break-up time (sec)		
Mean (SD)	3.0769 (1.39538)	2.9915 (1.49040)
Median (range)	2.7500 (0.730, 10.200)	2.6600 (0.915, 17.205)
Total OSDI (0-100)		
Mean (SD)	47.03 (19.947)	47.14 (18.493)
Median (range)	45.83 (0.0, 100.0)	47.50 (0.0, 93.2)
Visual acuity (ETDRS- logMAR)		
Mean (SD)	0.113 (0.1623)	0.114 (0.1577)
Median (range)	0.100 (-0.24, 0.68)	0.100 (-0.30, 0.72)
Intraocular pressure (mmHg)		
Mean (SD)	15.7 (2.80)	15.5 (2.86)
Median (range)	16.0 (8, 23)	16.0 (6, 26)

cCFS=central corneal fluorescein staining, ETDRS=early treatment of diabetic retinopathy study, FAS=full analysis set, logMAR=logarithm of the minimum angle of resolution, N=number of subjects in group, NEI=National Eye Institute, OD=left eye, OS=right eye, OSDI=ocular surface disease index, SD=standard deviation, tCFS=total corneal fluorescein staining, VAS=visual analog scale.

Note: Eye-level assessments were summarized for the study eye. In the case that both eyes were eligible for analysis, the study eye was the eye with higher mean tCFS score (NEI Scale) at Day 1. If the mean tCFS score was the same in both eyes, then the right eye was selected as the study eye.

Pooled analysis main results

Primary efficacy endpoints

In the pooled studies, LS mean change from baseline in **tCFS score** (NEI scale) at Day 29 (based on ANCOVA model) was -3.83 and -3.30 in the Vevizye 0.1% and vehicle groups, respectively. The between-treatment difference (Vevizye 0.1% - vehicle) was -0.53 and statistically significant (p=0.0003).

With regards to proportion of **responders in tCFS score** (≥ 3 score improvement on NEI scale) at Day 29 in the pooled studies, 66.4% of subjects in the Vevizye group were tCFS responders, compared to 54.1% of subjects in the vehicle group. In the logistic regression analysis, a higher proportion of responders was in the Vevizye 0.1% compared to vehicle (i.e., estimated between-treatment difference of 15.26%).

Analysis on the PPS population yielded similar results.

Key secondary efficacy endpoints

In the pooled studies, the LS mean CFB in tCFS score (NEI scale) at Day 15 (based on ANCOVA model) was -3.24 and -2.71 in the Vevizye 0.1% and vehicle groups, respectively. The between-treatment difference (Vevizye 0.1% - vehicle) was -0.52 and statistically significant (p=0.0003).

The LS mean CFB in total conjunctival lissamine green staining score (Oxford scale) at Day 29 (based on ANCOVA model) was -1.20 and -0.80 in the Vevizye 0.1% and vehicle groups, respectively. The between-treatment difference (Vevizye 0.1% - vehicle) was -0.40 and significant (p<0.0001).

With regards to the proportion of responders in central corneal fluorescein staining (cCFS) score (defined as ≥ 1 score improvement on NEI scale) at Day 29, 64.8% of subjects in the Vevizye group were cCFS responders, compared to 55.0% of subjects in the vehicle group. In the logistic regression analysis, a statistically significantly higher proportion of responders was observed in the Vevizye 0.1% compared to the vehicle group (i.e., between-treatment difference of 12.25%).

The LS mean CFB in cCFS score (NEI scale) at Day 29 (based on ANCOVA model) was -0.78 and -0.63 in the Vevizye 0.1% and vehicle groups, respectively. The between-treatment difference (Vevizye 0.1% - vehicle) was -0.15 and statistically significant (p=0.0008).

Pooled analysis of CFB in dryness score (VAS) at Day 29 and CFB in blurred vision score (VAS) at Day 29 showed comparable treatment effects in both treatment groups which were not statistically significant between treatments. LS mean CFB in blurred vision score (VAS) at Day 29 in subjects with baseline cCFS score = 3 (based on ANCOVA model) was -12.6 and -4.1 in the Vevizye 0.1% and vehicle groups, respectively. The between-treatment difference (Vevizye vs vehicle) was -8.5 and significant (p=0.0028).

Supportive studies

Supportive data for efficacy of Vevizye are provided by three clinical studies, i.e. study CYS-002, study CYS-005, and study SHR8028-301. Details of study CYS-002 (dose-finding study) are provided in Section 3.3.4.1 of this document.

Study **CYS-005** (ESSENCE-2 OLE) was a Phase 3, multi-center, open-label, single-arm clinical study primarily designed to assess long-term safety of topical Vevizye 0.1% for the treatment of DED. Efficacy measures were acquired as exploratory endpoints.

A subset of subjects (N=202) ≥18 years of age, of either sex and any race who completed study CYS-004 (Phase 3, double-masked, randomized) and who were treated with either Vevizye or vehicle over

29 days, were enrolled at 14 investigative sites in the US to receive treatment with Vevizye OU BID for 52-weeks (1 year).

The study was set out to investigate long-term safety and tolerability of Vevizye over 52 weeks. Efficacy measures were assessed as secondary endpoints.

Efficacy endpoints included the following signs and symptoms measures of DED: CFS total and per region scores (NEI scale), conjunctival lissamine green staining total and per region score (Oxford scale), VAS scores for dryness and blurred vision, OSDI, TBUT, unanesthetized Schirmer's tear test, proportion of subjects with improvement in unanesthetized Schirmer's tear test ≥ 10 mm, proportion of subjects with improvements in tCFS (NEI scale) score of 1, 2 and 3 units, and proportion of subjects with improvements in cCFS (NEI scale) score of 1 unit.

Efficacy endpoints were assessed at all study visits, i.e. Visit 1 (Day 1, corresponding to the final visit of study CYS-004), Visit 2 (Week 4), Visit 3 (Week 12), Visit 4 (Week 26), Visit 5 (Week 40), Visit 6 (Week 52). Change from baseline (CFB), defined as the CYS-004 study baseline, and change from visit 1 (CFV1) of CYS-005 (= Visit 3 of CYS-004) were calculated.

Main results

Of the 202 subjects enrolled, 200 were included in the SAF. In total, 27 subjects discontinued from the study, 15 subjects in the group that received Vevizye in CYS-004 and 12 in the group that received vehicle in CYS-004.

Main efficacy results of study CYS-005 are summarized in Table *25*.

Table 25: Main efficacy results of study CYS-005

	Vevizye 0.1% to Vevizye 0.1% (N=98)	**Vehicle to Vevizye 0.1% (N=102)**	**All (N=200)**
CFB mean (SD), p-value*			
tCFS			
Day 1	-4.8 (3.04), <0.0001	-4.0 (3.31), <0.0001	-4.4 (3.20), <0.0001
Week 12	-6.1 (2.72), <0.0001	-6.0 (3.14), <0.0001	-6.0 (2.94), <0.0001
Week 26	-6.1 (3.00), <0.0001	-5.8 (3.05), <0.0001	-5.9 (3.02), <0.0001
Week 52	-5.8 (2.83), <0.0001	-5.4 (3.54), <0.0001	-5.6 (3.21), <0.0001
cCFS			
Day 1	-1.1 (0.89), <0.0001	-0.8 (1.00), <0.0001	-0.9 (0.95), <0.0001
Week 12	-1.3 (0.96), <0.0001	-1.2 (0.95), <0.0001	-1.3 (0.95), <0.0001
Week 26	-1.2 (0.94), <0.0001	-1.2 (0.85), <0.0001	-1.2 (0.89), <0.0001
Week 52	-1.2 (0.95), <0.0001	-1.1 (1.01), <0.0001	-1.1 (0.98), <0.0001
Conjunctival lissamine green staining (Oxford)			
Day 1	-1.7 (1.74), <0.0001	-1.0 (1.37), <0.0001	-1.4 (1.60), <0.0001
Week 12	-1.6 (1.89), <0.0001	-1.4 (1.99), <0.0001	-1.5 (1.94), <0.0001
Week 26	-1.8 (1.81), <0.0001	-1.6 (1.99), <0.0001	-1.7 (1.90), <0.0001
Week 52	-1.5 (1.95), <0.0001	-1.5 (1.94), <0.0001	-1.5 (1.94), <0.0001
Dryness score (VAS)			
Day 1	-15.8 (27.39), <0.0001	-16.3 (24.90), <0.0001	-16.0 (26.09), <0.0001

	Vevizye 0.1% to Vevizye 0.1% (N=98)	Vehicle to Vevizye 0.1% (N=102)	All (N=200)
Week 12	-19.8 (25.80), <0.0001	-12.7 (24.60), <0.0001	-16.1 (25.37), <0.0001
Week 26	-22.9 (25.83), <0.0001	-22.3 (26.68), <0.0001	-22.6 (26.20), <0.0001
Week 52	-26.6 (27.24), <0.0001	-24.2 (25.62), <0.0001	-25.4 (26.37), <0.0001
Blurred vision (VAS)			
Day 1	-7.5 (25.02), 0.0038	-5.2 (24.65), 0.0371	-6.3 (24.79), 0.0004
Week 12	-9.4 (25.00), 0.0005	-6.0 (28.07), 0.0366	-7.6 (26.62), 0.0001
Week 26	-11.7 (24.67), <0.0001	-9.6 (31.14), 0.0038	-10.6 (28.16), <0.0001
Week 52	-15.7 (28.37), <0.0001	-12.6 (30.42), 0.0002	-14.1 (29.40), <0.0001
Response rates, n (%)			
tCFS responders (≥3 score improvement on NEI scale)			
Day 1	77 (78.6%)	69 (67.6%)	146 (73.0%)
Week 12	85 (92.4%)	87 (87.9%)	172 (90.1%)
Week 26	73 (85.9%)	80 (87.0%)	153 (86.4%)
Week 52	73 (85.9%)	69 (76.7%)	142 (81.1%)
cCFS responders (≥1 score improvement on NEI scale)			
Day 1	73 (74.5%)	66 (64.7%)	139 (69.5%)
Week 12	77 (83.7%)	76 (76.8%)	153 (80.1%)
Week 26	65 (76.5%)	75 (81.5%)	140 (79.1%)
Week 52	66 (77.6%)	60 (66.7%)	126 (72.0%)
Schirmer responders (≥10 mm increase)			
Day 1	11 (11.2%)	10 (9.8%)	21 (10.5%)
Week 12	12 (13.0%)	5 (5.1%)	17 (8.9%)
Week 26	11 (12.9%)	9 (9.8%)	20 (11.3%)
Week 52	15 (17.6%)	9 (10.0%)	24 (13.7%)

CFB=change from baseline, cCFS=central corneal fluorescein staining, NEI=National Eye Institute, SAF=safety population, SD=standard deviation, tCFS=total corneal fluorescein staining, VAS=visual analog scale.
Note: Day 1 refers to the final visit of study CYS-004 (i.e., after 29 days of double-blind treatment with Vevizye 0.1% or vehicle in study CYS-004). *based on paired t-test.

At Visit 1, CFB in total CFS score (NEI Scale), CFB in CFS of most corneal sub-region scores, and conjunctival lissamine green staining score (Oxford scale), showed higher improvements in the group that received active Vevizye in the CYS-004 trial compared to the group that received vehicle.

At Visit 2 of CYS-005, both groups continued to improve. The magnitude of effect was higher in the group that received vehicle previously. From Visit 2 onwards, staining parameters stabilized on a lower staining level (mean tCFS score 5 to 6).

At Visit 1, the proportion of subjects with improvements in tCFS score ≥ 3 units and the proportion of subjects with improvements in central corneal fluorescein staining (cCFS) score of ≥ 1 unit in the study eye were generally high but higher in the group that received Vevizye in CYS-004 (78.6% and 74.5%) compared to the group that received vehicle (67.6% and 64.7%).

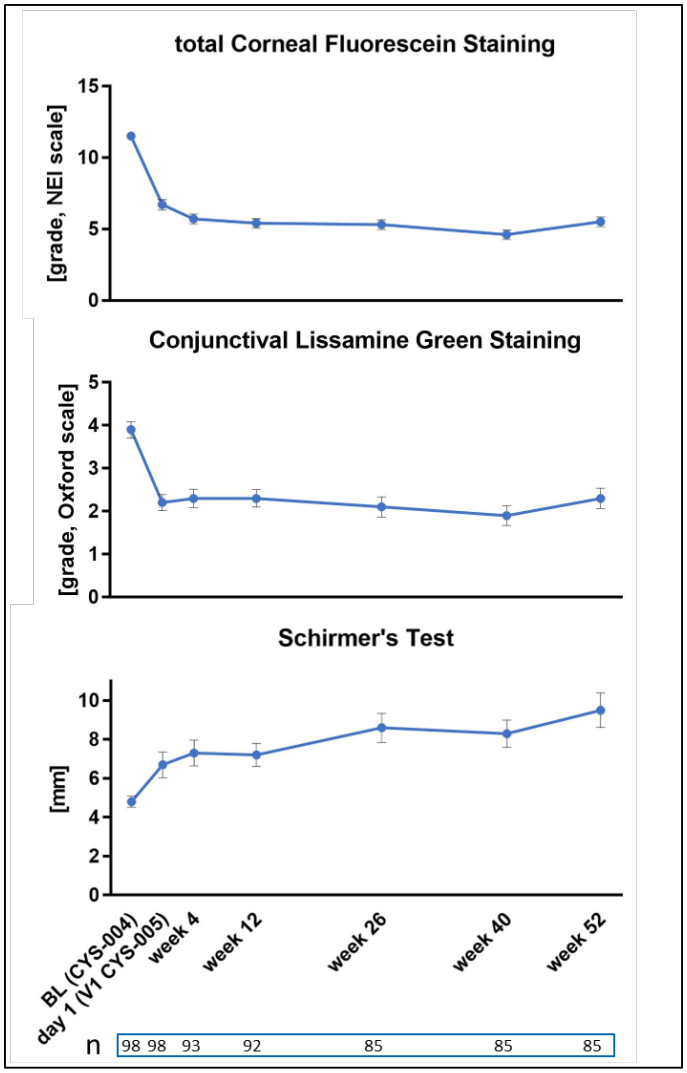
Responder rates increased further in both groups with a higher gain in the group that previously received vehicle. From Visit 2 onwards, responder rates stabilized on a high level (> 80% tCFS responders and > 70% cCFS responders).

Schirmer's tear test scores showed comparable and significant improvements from baseline (= CYS-004 baseline) in all subjects and in both groups. The treatment effect increased over the course of the CYS-005 trial and reached statistical significance over Visit 1 of the CYS-005 trial after 26 weeks of treatment and remained statistically significant until the end of the trial (Week 52). The proportion of responders in unanesthetized Schirmer' s tear test score with ≥ 10 mm improvement from baseline were around 10% in both groups at Visit 1 of CYS-005 and remained relatively stable throughout the trial.

Tear film break-up time showed comparable and statistically significant improvements from baseline (= CYS-004 baseline) in all subjects and in both groups. The treatment effect increased over the course of the CYS-005 trial and reached statistical significance over Visit 1 of the CYS-005 trial at Visit 4 (Week 26) and Visit 5 (Week 40).

Graphical illustration of the main sign endpoints measured in the group that received Vevizye in CYS-004 is provided in Figure 7.

Figure 7: Sign endpoints in study CYS-005 (subjects treated with CyclASol in CYS-004).

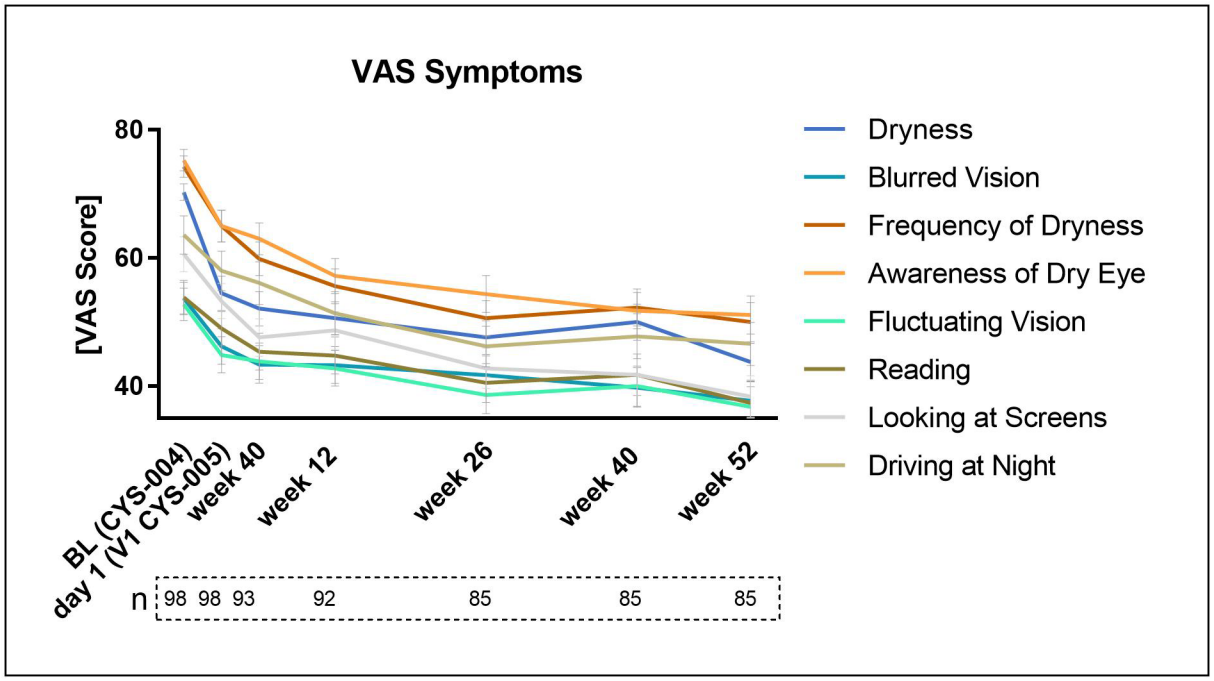


Mean values per timepoint, error bars showing SEM: n denotes observations at each visit.

Symptom endpoints as measured by VAS or OSDI generally improved over the course of study CYS-005, with improvements from baseline (= CYS-004 baseline) in both groups at each visit. Symptoms reached their minimum at the last visit (Week 52). Improvements were generally significant over Visit 1 of CYS-005 from Visit 4 (Week 26) onwards.

Graphical illustration of the symptom endpoints measured by VAS in the group that received Vevizye in CYS-004 is provided in Figure 8.

Figure 8: Symptom endpoints in study CYS-005 (subjects treated with Vevizye in CYS-004)



Mean subject values per timepoint with error bars showing SEM. Note, for the driving at night questions subjects had the possibility to tick NA, therefore for this parameter n is lower than denoted in the graph.

Study SHR8028-301 was a Phase 3, multi-center, randomized, double-blind, parallel-group, vehicle-controlled efficacy and safety study conducted in patients with DED by the Applicant's partner in China. The study consisted of two stages:

- Stage I: multi-center, randomized, double-blind, parallel-group, vehicle-controlled study, including a run-in period with artificial tears one drop OU BID, and a 4-weeks treatment period (mirroring study CYS-004);
- Stage II: 12-week safety follow-up treatment period with open label Vevizye (without vehicle control or blinding) in a subset of the patients.

In stage I, N 206 subjects, representing the full analysis set population (FAS), were randomized to receive either HR8028 eye drops (=Vevizye 0.1%) or vehicle (perfluorobutylpentane and ethanol) in a 1:1 ratio, at the dose of one drop OU BID for 29 days.

Mirroring pivotal study CYS-004, main inclusion criteria were: ≥18 years old; use within 30 days before visit 0 of over-the-counter eye drops, lubricating gels or tear neurostimulator device for dry eye symptoms; dryness score (VAS) of ≥ 50 at visit 0 and visit 1; total corneal fluorescein staining (tCFS)

score (NEI scale) of ≥ 10 at visit 0 and visit 1; total conjunctival lissamine green staining (tLGCS) score (Oxford scale) of ≥2 (sum of nasal and temporal regions) at visit 0 and visit 1; unanesthetized Schirmer's I test score of 1-10 mm (inclusive) at visit 0 and visit 1; have at least one eye meeting all the sign scores criteria.

Primary efficacy endpoints were:
- Change from baseline (CFB) in tCFS score (NEI scale) on D29;
- CFB in eye dryness score (VAS) on D29.

Main secondary endpoints were:
- CFB in total conjunctival lissamine green staining score (Oxford scale) on D29;
- Response rate of central corneal fluorescein staining (cCFS) score on D29 (defined as a decrease of ≥ 1 point in cCFS score (NEI scale));
- Response rate of tCFS score on D29 (defined as a decrease of ≥ 3 points in tCFS score (NEI scale));
- CFB in cCFS score (NEI scale) on D29;
- CFB in tCFS score (NEI scale) on D15;
- CFB in blurred vision score (VAS) on D29.

Main results

Based on the FAS population (N 206), mean age of all subjects was 47.8 years, females accounted for 89.8% (185), and the mean course of dry eye disease was 54.6 months. At baseline, means ± standard deviations (SD) of the tCFS scores in the treatment group and the control group were 12.2 ± 1.85 and 12.3 ± 1.83, respectively, and the means ± SD of the eye dryness scores (VAS) were 73.6 ± 12.17 and 72.4 ± 13.33, respectively.

Primary efficacy results

Results in the treatment group vs the control group at D29: means ± SD of changes in the tCFS scores of study eyes from baseline were -4.8 ± 3.22 (Vevizye) and -3.0 ± 3.01 (vehicle), and the least squares means ± standard errors (LSMean ± SE) were -4.8 ± 0.31 (Vevizye) and -3.0 ± 0.30 (vehicle), with a least squares mean ± standard error of -1.8 ± 0.43 between the two groups, suggesting statistically significant difference (P < 0.0001). The primary sign endpoint was met.

Means ± standard deviations of changes in the eye dryness scores (VAS) from baseline were -19.4 ± 22.89 (Vevizye) and -15.3 ± 15.59 (vehicle), and the least squares means ± standard errors (LSMean ± SE) were -19.2 ± 1.95 (Vevizye) and -15.4 ± 1.92 (vehicle), with a LSMean ± SE of -3.8 ± 2.74 between the two groups, suggesting no statistically significant difference (p = 0.1661). The primary symptom endpoint was not met.

Main secondary efficacy results (FAS) of study SHR8028-301 are summarized in Table 26.

Table 26: Main secondary efficacy results (FAS) of study SHR8028-301

	SHR8028	**Vehicle**	**Group difference**	**p-value**
	LS Mean of CFB		**LS Mean (95% CI)**	
Conjunctival Staining (Oxford) D29	-1.4 ± 0.15	-0.8 ± 0.15	-0.6 (-1.1, -0.2)	0.0033
cCFS (NEI) D29	-1.0 ± 0.10	-0.6 ± 0.10	-0.4 (-0.6, -0.1)	0.0135
tCFS (NEI) D15	-4.0 ± 0.31	-2.8 ± 0.31	-1.2 (-2.0, -0.3)	0.0079
Blurred Vision (VAS) D29	-9.2 ± 1.71	-2.8 ± 1.68	-6.4 (-11.1, -1.7)	0.0085

Observed Response Rate				
Response in cCFS (≥1 Point) D29	61.6%	52.0%	9.47% (-4.19%, 23.13)	0.1770
Response in tCFS (≥ 3 Points) D29	77.8%	47.1%	31.36% (18.46%, 44.25%)	< 0.0001

2.10.6. Discussion on clinical efficacy

In support of efficacy for the claimed indication, the Applicant has provided the results of a Phase 2 dose selection study (CYS-002), and of two pivotal Phase 2b-3 clinical studies (CYS-003 and CYS-004) conducted in the US. Supportive data for efficacy are provided by a one year open label extension study (CYS-005), and by an additional Phase 3 RCT conducted in China (SHR8028-301).

Design and conduct of clinical studies

Dose finding: Study CYS-002 was a Phase 2, multi-center, randomized, double-masked, placebo(vehicle)-controlled clinical study that included a total of 207 adult subjects with a reported history of DED in both eyes for ≥6 months and use of eye drops for dry eye symptoms within 30 days.

Primary objective of study CYS-002 was to compare the safety, efficacy, and tolerability of Vevizye ophthalmic solutions (0.05% and 0.1%) to vehicle for the treatment of the signs and symptoms of dry eye disease (DED) in subjects not adequately responding to artificial tears. This was a double-masked study, with exception of the open label Restasis arm.

Overall, inclusion criteria of the dose response study were adequate for diagnostic confirmation of DED, from mild to severe corneal impairment. Exclusion criteria were sufficient to not expose study participants to unnecessary safety concerns.

The use of any eye drops within two hours before visit 0 and before visit 1 was listed as an exclusion criterion. Concurrent therapies were recorded, and disallowed medications/treatments were outlined in the exclusion criteria. Use of lubricating eye drops was not permitted during study CYS-002. All treatment groups showed a compliance rate of > 98%, where compliance was defined as ≥ 80% of planned doses taken.

The predefined primary and secondary efficacy endpoints were suitable to demonstrate efficacy of Vevizye on both signs and symptoms of DED, by assessing both objective and subjective relevant clinical parameters of the disease.

Pivotal studies CYS-003 and CYS-004 were two sizable (N 328 and N 834, respectively), multicenter, randomized, double-masked and vehicle-controlled studies conducted sequentially in several investigative sites in the United States. The two studies employed similar study designs with partially overlapping inclusion criteria.

Study population (inclusion/exclusion criteria)

Both studies included adult subjects (≥18 years old) with a reported history of DED in both eyes for ≥6 months and use of eye drops for dry eye symptoms within 30 days. Moreover, subjects were eligible if, both at screening and after a 14-day run-in period with artificial tears, had at least one eye with tCFS ≥10 (NEI scale), total lissamine green conjunctival score ≥2 (Oxford scale), and unanesthetized Schirmer's tear test score between ≥1 and ≤10 mm. As the NEI scale ranges from 0-15 (absent to severe corneal damage), the tCFS ≥10 sign inclusion criterion permitted to define a patient population with moderate to severe corneal damage (keratitis). Accordingly, the two pivotal studies shared their

primary sign endpoint, namely CFB in tCFS score on the NEI scale at Day 29. The primary sign endpoint is accepted, as corneal staining is a critical sign of the disease, and the NEI scale a commonly used grading scale.

However, prior use of ocular lubricants within 30 days plus 14-days run-in period with artificial tears does not necessarily define a period of time sufficient to establish whether tear substitutes would be ineffective in DED. Artificial tears do not address the underlying inflammatory pathophysiology of DED, however they often alleviate the symptoms within a month of regular use, whereas for signs it may take several months. It is generally recommended that, if there is no benefit with artificial tears after one month of compliant use, an alternative treatment, such as ciclosporin, should be considered (Semp et al., 2023). The vast majority of the subjects used artificial tears for longer period of time before the screening, and approximately ¾ of the subjects for longer than 6 months. This is considered long enough for artificial tears to show their efficacy for subjects with mild DED.

Exclusion criteria of the pivotal studies were sufficient to not expose study participants to unnecessary safety concerns. In particular, patients with ocular or periocular malignancy or infection were excluded. Accordingly, and consistent with the product information of Ikervis, therefore the following contraindication is included in section 4.3 of the SmPC: Ocular or peri-ocular malignancies or premalignant conditions. Active or suspected ocular or peri-ocular infection.

Study treatment

Pivotal studies compared Vevizye 0.1% to a vehicle composed of the same excipients, i.e. perfluorobutylpentane and ethanol, in the same quantitative amounts as in Vevizye. Though no clear differentiation between the 0.05% and the 0.1% dose was seen, a trend favoring the 0.1% was seen for the symptoms without any added safety concerns. This provides a rational for the selected dose.

Concomitant medications which were not allowed during pivotal trials included topical anti-glaucoma medication, and any topical ocular, facial, or systemic steroids or immunomodulating agents. In line with this and the product information of Ikervis, proper warnings in patients with glaucoma or using other immunomodulators is included in section 4.4 of the SmPC.

Vehicle was chosen as comparator based on global regulatory guidance and advice as well as based on practical aspects of masking. Moreover the global DED market environment, e.g., using Ikervis as comparator, would restrict the study population as the proposed target population is wider than the approved indication for these comparators.

Subjects were not allowed to use artificial tears during the course of the pivotal trials, to eliminate potential confounding factors on symptoms and tolerability. Subjects in study CYS-005 were permitted to use artificial tears after 4 weeks, however, only 3% (n=6) added artificial tears to their treatment.

Outcomes/endpoints

Main differences between pivotal studies include the use of a different assessment instrument for symptoms of DED, both for determining patient eligibility as well as primary symptom endpoint. In study CYS-003, subjects were eligible if, both at screening and following a 14-day run-in period with artificial tears, they had an Ocular Surface Disease Index (OSDI) total score ≥20, whereas in study CYS-004 subjects were required to have a VAS dryness score ≥ 50. Accordingly, primary symptom endpoints were CFB in total OSDI score at Day 29 in study CYS-003, and CFB in dryness score (VAS) at Day 29 in study CYS-004. The VAS is a scale used widely in ophthalmic research particularly related to DED.

Though OSDI and VAS are very different instruments for assessing DED symptoms, the populations in the two pivotal studies are comparable in terms of baseline disease characteristics.

Overall, the predefined primary and secondary efficacy endpoints were suitable to demonstrate efficacy of Vevizye on both signs and symptoms of DED, by assessing both objective and subjective clinical parameters of the disease. Relevant clinical parameters were included. According to recommendations from the European panel of experts in DED (Messmer et al., 2023), disease severity should be primarily determined based on symptoms severity, corneal and conjunctival staining, low tear production, and short tear film break-up time. Accordingly, the parameters most commonly used in clinical trials on topical ocular ciclosporin to assess effects on signs in DED (including the SANSIKA pivotal study for IKERVIS), are CFS, lissamine green conjunctival staining, Schirmer's test, and TBUT. Therefore, these measures were considered as the most relevant sign endpoints for Vevizye. Corneal staining is considered a critical sign of the disease (and especially in the central region), hence change in total CFS on the NEI scale (a commonly used grading scale) is accepted as a primary sign endpoint.

Methods

Methodologically, pivotal studies were complex, due to the large sample sizes and multicenter study design. Both studies underwent GCP inspection from FDA.

In study CYS-003, a protocol amendment (12/2017) has been made that clarified that total corneal fluorescein staining score (NEI scale) and total OSDI score were not to be considered co-primary endpoints.

The sample size calculations used reasonable assumptions and the calculations could be followed.

Randomisation and blinding procedures are considered acceptable. Subjects, investigators, site staff, sponsor staff, and staff of the CROs were masked to the treatment group assignments during the randomization process and for the duration of the study, which is considered appropriate. Subjects were stratified based on site and symptom score at baseline. In study CYS-003, subjects were stratified based on baseline total OSDI score <36 or ≥36 /100. In study CYS-004, subjects were stratified based on baseline VAS dryness score <75 or ≥75 /100. The cut-offs used were based on the median values of similar patients in previous studies.

The definition of the study populations was considered acceptable. The primary analysis model, using ANCOVA is acceptable as well.

Multiplicity for the two primary endpoints in both studies was handled by hierarchical testing. This will formally protect the overall type I error rate. However, this does mean the primary symptom endpoint should be seen more as a secondary endpoint rather than primary.

Pivotal studies CYS-003 and CYS-004 included a total of 1.162 patients with DED who were randomized and included for efficacy analyses. The total sample size is considered sufficient to support the application for marketing authorization.

Overall, demographic characteristics of the two pivotal studies populations were representative of moderate to severe DED population. Most subjects enrolled were female (72-73%), and aged >45 years. This reflects epidemiologic studies showing that DED is more prevalent in women, and elderly population, with prevalence linearly increasing with age (Stapleton et al, DEWS II Epidemiology, 2017). Though less than 2% of the patients enrolled had a history of Sjogren disease. The applicant provided a rational for the immunological properties that allows extrapolation to this population. No warning, precautions are dose adjustments are considered needed.

Within studies, demographic characteristics were balanced across treatment arms. Between studies, patients in study CYS-004 were on average 4.3 years younger (CYS-004 Mean age 57.1 y, CYS-003 Mean age 61.4 y), and with a 1.8 years shorter duration of the disease (CYS-004 Mean duration DED 10.4 y, CYS-003 Mean duration DED 12.26 y). This did not lead to differences at baseline and the populations in the two studies can be considered comparable.

Efficacy data and additional analyses

Dose finding: Study CYS-002 did not meet its primary objective. Primary efficacy analyses found no differences between the Vevizye and the vehicle group in either the co-primary sign (tCFS) and symptom (dryness score) endpoint. Analysis on the PP population yielded consistent results.

Secondary analyses of DED *signs* showed reduction in CFS in most CFS sub-regions (NEI scale) and conjunctival lissamine green staining (Oxford scale), with numerical difference compared to vehicle reaching significance for some parameters and timepoints. The modelling analysis over all timepoints confirmed a significant treatment effect.

Tear production, as measured by unanesthetized Schirmer's tear test I, increased in all treatment groups over the course of the study, with no differences between Vevizye and vehicle.

TBUT and tear osmolarity did not change over the course of the study in any of the treatment groups.

Secondary analyses of DED *symptoms* did not show a statistically significant improvement of Vevizye treatments over vehicle in any symptom as measured by VAS. In PP analysis, when compared to the vehicle group, the Vevizye 0.05% group showed a significant difference in CFB on reading as measured by OSDI at Visit 5 (-0.36, P = 0.0334 [Wilcoxon rank sum test]). In addition, the modelling analysis suggests a significant effect on OSDI informing the CYS-003 symptom endpoint selection.

Moreover, there were no differences between the two different concentrations of Vevizye (0.05% and 0.1%), and neither the statistical analysis on the total population, nor the modelling and simulation analysis, identified a clear dose-response for sign or symptoms between the two Vevizye strengths. The Applicant claimed that Vevizye 0.1% showed 'some trends' over Vevizye 0.05% in symptoms in all subjects and in the target population for the subsequent studies (subjects having tCFS ≥10 at baseline).

Overall, study treatments were well tolerated. Most frequently reported TEAE was decreased visual acuity, which was reported with comparable frequencies between treatment arms. The study drug was generally well tolerated, therefore the higher dose was presumably selected.

Pivotal studies CYS-003 and CYS-004 met their primary sign endpoint, showing significant reductions of tCFS score (NEI scale) at Day 29 in patients treated with Vevizye compared to vehicle. Efficacy of Vevizye for relieving signs of DED was supported by improvements in other relevant signs of the disease, specifically fluorescein staining in the central region of the cornea (cCFS), lissamine green conjunctival staining, and unanaesthetised Schirmer's test (assessing tear production). Supportive analyses provided consistent results. With regard to corneal integrity, improvements on tCFS $\geqslant$ 3 on the NEI scale (not a linear scale) are considered meaningful for the patient considering its association with symptom improvement. Secondary responder analysis for tCFS $\geqslant$ 3 responders showed significant differences between treatment groups (CYS-003: tCFS responders Vevizye 52.9 %, Vehicle 40.6%, P=0.0032, cCFS responder Vevizye 52.9 %, Vehicle 40.6%, P=0.0032; CYS-004: tCFS responders Vevizye 71.6 %, Vehicle 59.7%, P=0.0002, Vevizye 52.9 %, Vehicle 40.6%, P=0.0032), thereby demonstrating clinically meaningfulness of the improvement on corneal integrity.

As observed in the Ikervis procedure (EMA/CHMP/473489/2014), clinical severity may impact on efficacy, i.e., treatment effects may be more pronounced in (=driven by) the subgroup of patients with severe disease. The applicant submitted analyses demonstrating efficacy in both moderate and severe DED.

Analysis performed across trials

Consistent with analyses in individual studies, pooled analysis confirmed treatment effect of Vevizye on relevant signs of DED, but no difference between Vevizye and vehicle in relieving symptoms. There

was however a positive effect of Vevizye on blurred vision in subjects with cCFS scores of 3 at baseline compared to vehicle, confirming that improvement on central corneal staining is meaningful as it impacts visual functioning.

Supportive data

Supportive data for efficacy of Vevizye are provided by studies CYS-002, CYS-005 and SHR8028-301 (Stage I and II).

Stage I of study SHR8028-301 mirrored pivotal study CYS-004, where the same main inclusion criteria and primary efficacy endpoints were employed in a Chinese, and on average younger, patient population (SHR8028-301 mean age 47.8 years; CYS-004 mean age 57.1 years). Consistent with study CYS-004, study SHR8028-301 stage I found a significant improvement from baseline after treatment with Vevizye on the primary sign endpoint (tCFS score on the NEI scale) but not the symptom endpoint (dryness score on the VAS) of DED at Day 29 compared to vehicle.

The open label extension of study CYS-004 (study CYS-005) was set out to primarily investigate long-term safety and tolerability of Vevizye over 52 weeks. Efficacy measures were assessed as secondary endpoints. CYS-005 subjects showed improvements in all prespecified efficacy endpoints compared to baseline (= CYS-004 baseline) at each study visit, however the open label and single arm design of the study hamper the interpretability of the results.

2.10.7. Conclusions on clinical efficacy

The Applicant submitted the data of two sizable (total N = 1162), randomized, double-masked, vehicle-controlled pivotal trials with similar study design, to demonstrate efficacy of Vevizye 0.1% for the treatment of dry eye disease in adult patients, which has not improved despite treatment with tear substitutes. Pivotal studies have demonstrated efficacy on relevant clinical signs of the disease in patients with moderate to severe condition.

2.10.8. Clinical safety

2.10.8.1. Patient exposure

The Vevizye clinical development programme includes five clinical studies in subjects with DED and one study in healthy volunteers. 841 patients with DED were exposed to at least one dose of Vevizye during the clinical development program. Safety data has been presented for 139 patients exposed to Vevizye for at least one year.

The main body of evidence for safety of Vevizye originates from the two Phase 3 vehicle-controlled clinical studies CYS-003 and CYS-004. Data from these studies has also been pooled (Pool A).

The other three studies providing safety data in patients with DED include a multiple-dose dose-response study CYS-002, open-label extension study CYS-005 and a multiple-dose efficacy and safety study SHR8028-301 in Chinese patients SHR8028-301. Data from CYS-002 and CYS-005 has been pooled together with the pivotal studies (Pool B).

In pool B, subjects in extension study CYS-005 also have been subjects in CYS-004. Subjects in CYS-005 who received ciclosporin in CYS-004 were included once in the integration pool using the CYS-004 Day 1 as the reference day for initiation of treatment (i.e., Day 1). However, subjects in CYS-005 who received vehicle in CYS-004 were included twice in the integration pool:

- As a vehicle-treated subject for CYS-004, using the CYS-004 Day 1 as a reference day for initiation of treatment; and
- As a ciclosporin 0.1%-treated subject for CYS-005, using the CYS-005 Day 1 as a reference day for initiation of treatment.

The Safety data set used for individual studies and pooled analysis included all randomized subjects who received at least one dose of the investigational product (as treated).

The focus of safety assessment in this assessment report lies on Pool A i.e. the vehicle-controlled data with the proposed 0.1% ciclosporin strength.

In Pool A, the median age was 61 years across the treatment arms and the age distribution similar. Most patients were white (77.4% in the Vevizye 0.1% and 76.1% in the vehicle group).

Both groups were characterized by high corneal surface staining, with a mean tCFS score of 11.5 and corresponding high mean central CFS score of 2.1 at baseline. Subjects were highly symptomatic with mean dryness scores of 69.9 and mean blurred vision scores of approximately 52 and a mean total OSDI was about 47 in both treatment groups. This characterizes the population as a moderately to severely dry eye population. Baseline disease characteristics were in general balanced between the treatment groups.

Adverse events

An overview of the adverse events and treatment-emergent adverse events by frequency in Pool A and Pool B is summarized in Table 27.

Table 27: Summary of adverse events – Pool A and Pool B

	Pool A			**Pool B CYS-004**			
Number of Subjects with at least one	**Vevizye 0.1% (N=585)**	**Vehicle (N=577)**	**All subjects (N=1162)**	**Vevizye 0.05% (N=51)**	**Vevizye 0.1% (N=738)**	**Vehicle (N=629)**	**All subjects (N=1418)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
AE	128 (21.9%)	123 (21.3%)	251 (21.6%)	19 (37.3%)	225 (30.5%)	137 (21.8%)	381 (26.9%)
Ocular AE	82 (14.0%)	80 (13.9%)	162 (13.9%)	8 (15.7%)	138 (18.7%)	88 (14.0%)	234 (16.5%)
Non-Ocular AE	53 (9.1%)	52 (9.0%)	105 (9.0%)	14 (27.5%)	120 (16.3%)	61 (9.7%)	195 (13.8%)
TEAE	117 (20.0%)	117 (20.3%)	234 (20.1%)	18 (35.3%)	217 (29.4%)	131 (20.8%)	366 (25.8%)
Ocular TEAE	77 (13.2%)	76 (13.2%)	153 (13.2%)	7 (13.7%)	133 (18.0%)	84 (13.4%)	224 (15.8%)
Non-Ocular TEAE	47 (8.0%)	49 (8.5%)	96 (8.3%)	13 (25.5%)	115 (15.6%)	58 (9.2%)	186 (13.1%)
SAE	2 (0.3%)	6 (1.0%)	8 (0.7%)	2 (3.9%)	6 (0.8%)	6 (1.0%)	14 (1.0%)
TE-SAE	2 (0.3%)	6 (1.0%)	8 (0.7%)	2 (3.9%)	6 (0.8%)	6 (1.0%)	14 (1.0%)
TEAEs by Severity*							
Total	117 (20.0%)	117 (20.3%)	234 (20.1%)	18 (35.3%)	217 (29.4%)	131 (20.8%)	366 (25.8%)
Mild	106 (18.1%)	94 (16.3%)	200 (17.2%)	13 (25.5%)	173 (23.4%)	106 (16.9%)	292 (20.6%)
Moderate	10 (1.7%)	21 (3.6%)	31 (2.7%)	5 (9.8%)	41 (5.6%)	23 (3.7%)	69 (4.9%)
Severe	1 (0.2%)	2 (0.3%)	3 (0.3%)	0	3 (0.4%)	2 (0.3%)	5 (0.4%)

Number of Subjects with at least one	Pool A			Pool B CYS-004			
	Vevizye 0.1% (N=585)	Vehicle (N=577)	All subjects (N=1162)	Vevizye 0.05% (N=51)	Vevizye 0.1% (N=738)	Vehicle (N=629)	All subjects (N=1418)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
TEAEs by Relationship to Study Drug**							
Total	117 (20.0%)	117 (20.3%)	234 (20.1%)	18 (35.3%)	217 (29.4%)	131 (20.8%)	366 (25.8%)
Suspected	55 (9.4%)	49 (8.5%)	104 (9.0%)	2 (3.9%)	77 (10.4%)	55 (8.7%)	134 (9.4%)
Not Suspected	62 (10.6%)	68 (11.8%)	130 (11.2%)	16 (31.4%)	140 (19.0%)	76 (12.1%)	232 (16.4%)
AEs Leading to Treatment Discontinuation	5 (0.9%)	3 (0.5%)	8 (0.7%)	1 (2.0%)	8 (1.1%)	4 (0.6%)	13 (0.9%)
AEs Resulting in Death	0	0	0	0	0	0	0

AE=adverse event, N=number of subjects in group, SAE=serious adverse event, TEAE=treatment-emergent adverse event, TE-SAE=treatment-emergent serious adverse event.
Note: Subjects who participated in CYS-005 and who received vehicle in CYS-004 are counted in both the Vevizye 0.1% and Vehicle treatment arms.
Any TEAE that begins or worsens during the study is recorded as a new TEAE. Percentages are based on the total number of subjects in each treatment group and integration pool. TEAEs are AEs that started or worsened on or after the date of first dose.
* If a subject experienced more than one TEAE, the subject is counted only once for the maximal severity. TEAEs with missing severities are counted as severe.
** If a subject experienced more than one TEAE, the subject is counted only once for the strongest relationship to study drug. In CYS-002, the relationship of each AE to the investigational product was determined by the investigator using the following classifications: Definite, Probable, Possible, None, and Unclassified. For summarization in this integration, the relationship of each AE to the investigational product in CYS-002 was considered suspected if the relationship was recorded as Definite, Probable, Possible, or Unclassified, and considered Not Suspected if the relationship was recorded as None.

The incidences of treatment-emergent **ocular AEs** in Pool A and Pool B by SOC and PT are listed in Table 28

Table 28: Most common ocular treatment-emergent adverse events (in > 2 subjects)– Pool A and Pool B

	Pool A			Pool B			
System Organ Class (SOC) Preferred Term (PT)	CyclASol 0.1% (N=585) n (%)	Vehicle (N=577) n (%)	All Subjects (N=1162) n (%)	CyclASol 0.05% (N=51) n (%)	CyclASol 0.1% (N=738) n (%)	Vehicle (N=629) n (%)	All Subjects (N=1418) n (%)
Number of Ocular TEAEs	**99**	**98**	**197**	**9**	**184**	**110**	**303**
Number of Subjects with at Least One Ocular TEAE	**77 (13.2%)**	**76 (13.2%)**	**153 (13.2%)**	**7 (13.7%)**	**133 (18.0%)**	**84 (13.4%)**	**224 (15.8%)**
Eye disorders	**34 (5.8%)**	**40 (6.9%)**	**74 (6.4%)**	**6 (11.8%)**	**75 (10.2%)**	**44 (7.0%)**	**125 (8.8%)**
Visual acuity reduced	12 (2.1%)	16 (2.8%)	28 (2.4%)	2 (3.9%)	20 (2.7%)	17 (2.7%)	39 (2.8%)
Vision blurred	4 (0.7%)	6 (1.0%)	10 (0.9%)	0	7 (0.9%)	6 (1.0%)	13 (0.9%)
Vitreous detachment	1 (0.2%)	0	1 (0.1%)	0	10 (1.4%)	0	10 (0.7%)
Eye irritation	2 (0.3%)	3 (0.5%)	5 (0.4%)	0	3 (0.4%)	5 (0.8%)	8 (0.6%)
Conjunctival haemorrhage	2 (0.3%)	2 (0.3%)	4 (0.3%)	1 (2.0%)	4 (0.5%)	2 (0.3%)	7 (0.5%)
Eye pain	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (2.0%)	3 (0.4%)	2 (0.3%)	6 (0.4%)
Eye pruritus	2 (0.3%)	3 (0.5%)	5 (0.4%)	0	3 (0.4%)	3 (0.5%)	6 (0.4%)
Dry eye	1 (0.2%)	3 (0.5%)	4 (0.3%)	0	2 (0.3%)	3 (0.5%)	5 (0.4%)
Lacrimation increased	2 (0.3%)	0	2 (0.2%)	1 (2.0%)	4 (0.5%)	0	5 (0.4%)
Eyelid margin crusting	2 (0.3%)	2 (0.3%)	4 (0.3%)	0	2 (0.3%)	2 (0.3%)	4 (0.3%)
Vitreous floaters	2 (0.3%)	2 (0.3%)	4 (0.3%)	0	2 (0.3%)	2 (0.3%)	4 (0.3%)
Chalazion	0	1 (0.2%)	1 (0.1%)	1 (2.0%)	1 (0.1%)	1 (0.2%)	3 (0.2%)
Conjunctival hyperaemia	1 (0.2%)	0	1 (0.1%)	0	2 (0.3%)	1 (0.2%)	3 (0.2%)
Foreign body sensation in eyes	1 (0.2%)	2 (0.3%)	3 (0.3%)	0	1 (0.1%)	2 (0.3%)	3 (0.2%)
Ocular hyperaemia	1 (0.2%)	0	1 (0.1%)	1 (2.0%)	2 (0.3%)	0	3 (0.2%)
Posterior capsule opacification	0	0	0	0	3 (0.4%)	0	3 (0.2%)
Visual impairment	2 (0.3%)	0	2 (0.2%)	0	3 (0.4%)	0	3 (0.2%)
General disorders and administration site conditions	**47 (8.0%)**	**39 (6.8%)**	**86 (7.4%)**	**1 (2.0%)**	**60 (8.1%)**	**41 (6.5%)**	**102 (7.2%)**
Instillation site pain	46 (7.9%)	37 (6.4%)	83 (7.1%)	1 (2.0%)	58 (7.9%)	38 (6.0%)	97 (6.8%)
Instillation site pruritus	1 (0.2%)	1 (0.2%)	2 (0.2%)	0	1 (0.1%)	2 (0.3%)	3 (0.2%)
Infections and infestations	**2 (0.3%)**	**2 (0.3%)**	**4 (0.3%)**	**0**	**4 (0.5%)**	**3 (0.5%)**	**7 (0.5%)**
Conjunctivitis	0	0	0	0	2 (0.3%)	1 (0.2%)	3 (0.2%)
Hordeolum	2 (0.3%)	1 (0.2%)	3 (0.3%)	0	2 (0.3%)	1 (0.2%)	3 (0.2%)
Injury, poisoning and procedural complications	**0**	**0**	**0**	**0**	**1 (0.1%)**	**2 (0.3%)**	**3 (0.2%)**
Investigations	**1 (0.2%)**	**0**	**1 (0.1%)**	**0**	**3 (0.4%)**	**0**	**3 (0.2%)**

N=number of subjects in group, TEAE=Treatment-Emergent Adverse Event.
Note: Subjects who participated in CYS-005 and who received vehicle in CYS-004 are counted in both the Vevizye 0.1% and Vehicle treatment arms.
Percentages are based on the total number of subjects in each treatment group and integration pool.
TEAEs are AEs that started or worsened on or after the date of first dose.
SOCs and PTs within a SOC are listed in order of descending frequency for All Subjects in the Pool B population.
Subjects experiencing more than one TEAE within a given SOC or PT are counted once within that SOC or PT.

The incidences of treatment-emergent **non-ocular AEs** in Pool A and Pool B by SOC and PT are listed in *Table 29*.

Table 29: Most common non-ocular treatment-emergent adverse events (in > 2 subjects)– Pool A and Pool B

	Pool A			Pool B			
System Organ Class (SOC) Preferred Term (PT)	CyclASol 0.1% (N=585) n (%)	Vehicle (N=577) n (%)	All Subjects (N=1162) n (%)	CyclASol 0.05% (N=51) n (%)	CyclASol 0.1% (N=738) n (%)	Vehicle (N=629) n (%)	All Subjects (N=1418) n (%)
Number of Non-Ocular TEAEs	**55**	**69**	**124**	**15**	**205**	**80**	**300**
Number of Subjects with at Least One Non-Ocular TEAE	**47 (8.0%)**	**49 (8.5%)**	**96 (8.3%)**	**13 (25.5%)**	**115 (15.6%)**	**58 (9.2%)**	**186 (13.1%)**
Infections and infestations	**27 (4.6%)**	**24 (4.2%)**	**51 (4.4%)**	**7 (13.7%)**	**58 (7.9%)**	**29 (4.6%)**	**94 (6.6%)**
Nasopharyngitis	8 (1.4%)	8 (1.4%)	16 (1.4%)	3 (5.9%)	11 (1.5%)	11 (1.7%)	25 (1.8%)
Upper respiratory tract infection	8 (1.4%)	7 (1.2%)	15 (1.3%)	0	10 (1.4%)	7 (1.1%)	17 (1.2%)
Sinusitis	2 (0.3%)	2 (0.3%)	4 (0.3%)	0	5 (0.7%)	2 (0.3%)	7 (0.5%)
Bronchitis	0	0	0	1 (2.0%)	5 (0.7%)	0	6 (0.4%)
COVID-19	0	0	0	0	6 (0.8%)	0	6 (0.4%)
Urinary tract infection	1 (0.2%)	2 (0.3%)	3 (0.3%)	1 (2.0%)	3 (0.4%)	2 (0.3%)	6 (0.4%)
Pneumonia	0	1 (0.2%)	1 (0.1%)	0	3 (0.4%)	1 (0.2%)	4 (0.3%)
Cellulitis	1 (0.2%)	1 (0.2%)	2 (0.2%)	0	2 (0.3%)	1 (0.2%)	3 (0.2%)
Herpes zoster	1 (0.2%)	0	1 (0.1%)	0	3 (0.4%)	0	3 (0.2%)
Influenza	2 (0.3%)	1 (0.2%)	3 (0.3%)	0	2 (0.3%)	1 (0.2%)	3 (0.2%)
Tooth abscess	0	2 (0.3%)	2 (0.2%)	0	1 (0.1%)	2 (0.3%)	3 (0.2%)
Injury, poisoning and procedural complications	**3 (0.5%)**	**6 (1.0%)**	**9 (0.8%)**	**2 (3.9%)**	**17 (2.3%)**	**7 (1.1%)**	**26 (1.8%)**
Contusion	1 (0.2%)	1 (0.2%)	2 (0.2%)	0	5 (0.7%)	1 (0.2%)	6 (0.4%)
Ligament sprain	0	1 (0.2%)	1 (0.1%)	0	2 (0.3%)	1 (0.2%)	3 (0.2%)
Gastrointestinal disorders	**4 (0.7%)**	**4 (0.7%)**	**8 (0.7%)**	**0**	**15 (2.0%)**	**5 (0.8%)**	**20 (1.4%)**
Abdominal pain upper	2 (0.3%)	0	2 (0.2%)	0	3 (0.4%)	0	3 (0.2%)
Nausea	0	0	0	0	3 (0.4%)	0	3 (0.2%)
Musculoskeletal and connective tissue disorders	**1 (0.2%)**	**7 (1.2%)**	**8 (0.7%)**	**0**	**11 (1.5%)**	**7 (1.1%)**	**18 (1.3%)**
Arthralgia	0	0	0	0	4 (0.5%)	0	4 (0.3%)
Nervous system disorders	**1 (0.2%)**	**7 (1.2%)**	**8 (0.7%)**	**0**	**8 (1.1%)**	**8 (1.3%)**	**16 (1.1%)**
Dizziness	0	3 (0.5%)	3 (0.3%)	0	1 (0.1%)	4 (0.6%)	5 (0.4%)
Headache	1 (0.2%)	2 (0.3%)	3 (0.3%)	0	2 (0.3%)	2 (0.3%)	4 (0.3%)
Respiratory, thoracic and mediastinal disorders	**3 (0.5%)**	**3 (0.5%)**	**6 (0.5%)**	**1 (2.0%)**	**9 (1.2%)**	**3 (0.5%)**	**13 (0.9%)**
Cough	1 (0.2%)	0	1 (0.1%)	0	3 (0.4%)	0	3 (0.2%)
Investigations	**3 (0.5%)**	**3 (0.5%)**	**6 (0.5%)**	**0**	**9 (1.2%)**	**3 (0.5%)**	**12 (0.8%)**
SARS-CoV-2 test positive	1 (0.2%)	2 (0.3%)	3 (0.3%)	0	5 (0.7%)	2 (0.3%)	7 (0.5%)
Cardiac disorders	**0**	**0**	**0**	**2 (3.9%)**	**4 (0.5%)**	**0**	**6 (0.4%)**
General disorders and administration site conditions	**0**	**1 (0.2%)**	**1 (0.1%)**	**2 (3.9%)**	**2 (0.3%)**	**2 (0.3%)**	**6 (0.4%)**
Metabolism and nutrition disorders	**1 (0.2%)**	**0**	**1 (0.1%)**	**0**	**6 (0.8%)**	**0**	**6 (0.4%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (0.3%)**	**0**	**2 (0.2%)**	**0**	**5 (0.7%)**	**1 (0.2%)**	**6 (0.4%)**
Psychiatric disorders	**0**	**2 (0.3%)**	**2 (0.2%)**	**0**	**4 (0.5%)**	**2 (0.3%)**	**6 (0.4%)**
Vascular disorders	**1 (0.2%)**	**2 (0.3%)**	**3 (0.3%)**	**0**	**4 (0.5%)**	**2 (0.3%)**	**6 (0.4%)**
Hypertension	1 (0.2%)	1 (0.2%)	2 (0.2%)	0	2 (0.3%)	1 (0.2%)	3 (0.2%)
Renal and urinary disorders	**1 (0.2%)**	**1 (0.2%)**	**2 (0.2%)**	**0**	**4 (0.5%)**	**1 (0.2%)**	**5 (0.4%)**
Endocrine disorders	**1 (0.2%)**	**1 (0.2%)**	**2 (0.2%)**	**0**	**3 (0.4%)**	**1 (0.2%)**	**4 (0.3%)**
Hypothyroidism	1 (0.2%)	1 (0.2%)	2 (0.2%)	0	2 (0.3%)	1 (0.2%)	3 (0.2%)
Reproductive system and breast disorders	**0**	**0**	**0**	**0**	**4 (0.5%)**	**0**	**4 (0.3%)**
Skin and subcutaneous tissue disorders	**3 (0.5%)**	**0**	**3 (0.3%)**	**0**	**3 (0.4%)**	**0**	**3 (0.2%)**

N=number of subjects in group, SAF=safety set, TEAE=Treatment-Emergent Adverse Event.

Note: Subjects who participated in CYS-005 and who received vehicle in CYS-004 are counted in both the Vevizye 0.1% and Vehicle treatment arms.
Percentages are based on the total number of subjects in each treatment group and integration pool.
TEAEs are AEs that started or worsened on or after the date of first dose.
SOCs and PTs within a SOC are listed in order of descending frequency for All Subjects in the Pool B population.
Subjects experiencing more than one TEAE within a given SOC or PT are counted once within that SOC or PT.

All AEs reported during the studies were assessed by the Investigators for relationship to the study treatment (i.e. not related or related). The most commonly reported related ocular TEAEs by SOC and PT in Pool A and Pool B are presented in

Table 30: Most common ocular treatment-related treatment-emergent adverse events in Pool A and Pool B

	Pool A			Pool B			
System Organ Class (SOC) Preferred Term (PT)	CyclASol 0.1% (N=585) n (%)	Vehicle (N=577) n (%)	All Subjects (N=1162) n (%)	CyclASol 0.05% (N=51) n (%)	CyclASol 0.1% (N=738) n (%)	Vehicle (N=629) n (%)	All Subjects (N=1418) n (%)
Number of Ocular Treatment-related TEAEs	**66**	**62**	**128**	**4**	**96**	**72**	**172**
Number of Subjects with Ocular Treatment-Related TEAEs	**55 (9.4%)**	**49 (8.5%)**	**104 (9.0%)**	**2 (3.9%)**	**76 (10.3%)**	**55 (8.7%)**	**133 (9.4%)**
General disorders and administration site conditions	**47 (8.0%)**	**38 (6.6%)**	**85 (7.3%)**	**1 (2.0%)**	**60 (8.1%)**	**40 (6.4%)**	**101 (7.1%)**
Instillation site pain	46 (7.9%)	36 (6.2%)	82 (7.1%)	1 (2.0%)	58 (7.9%)	37 (5.9%)	96 (6.8%)
Instillation site pruritus	1 (0.2%)	1 (0.2%)	2 (0.2%)	0	1 (0.1%)	2 (0.3%)	3 (0.2%)
Instillation site erythema	0	0	0	0	1 (0.1%)	1 (0.2%)	2 (0.1%)
Instillation site foreign body sensation	0	1 (0.2%)	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)
Eye disorders	**13 (2.2%)**	**14 (2.4%)**	**27 (2.3%)**	**1 (2.0%)**	**22 (3.0%)**	**18 (2.9%)**	**41 (2.9%)**
Vision blurred	3 (0.5%)	4 (0.7%)	7 (0.6%)	0	6 (0.8%)	4 (0.6%)	10 (0.7%)
Eye irritation	2 (0.3%)	3 (0.5%)	5 (0.4%)	0	2 (0.3%)	5 (0.8%)	7 (0.5%)
Eye pain	0	1 (0.2%)	1 (0.1%)	1 (2.0%)	2 (0.3%)	2 (0.3%)	5 (0.4%)
Visual acuity reduced	1 (0.2%)	1 (0.2%)	2 (0.2%)	0	3 (0.4%)	2 (0.3%)	5 (0.4%)
Eye pruritus	2 (0.3%)	2 (0.3%)	4 (0.3%)	0	2 (0.3%)	2 (0.3%)	4 (0.3%)
Lacrimation increased	2 (0.3%)	0	2 (0.2%)	1 (2.0%)	3 (0.4%)	0	4 (0.3%)
Dry eye	0	2 (0.3%)	2 (0.2%)	0	0	2 (0.3%)	2 (0.1%)
Eyelid margin crusting	1 (0.2%)	1 (0.2%)	2 (0.2%)	0	1 (0.1%)	1 (0.2%)	2 (0.1%)
Foreign body sensation in eyes	1 (0.2%)	1 (0.2%)	2 (0.2%)	0	1 (0.1%)	1 (0.2%)	2 (0.1%)
Ocular hyperaemia	1 (0.2%)	0	1 (0.1%)	1 (2.0%)	1 (0.1%)	0	2 (0.1%)
Photophobia	0	2 (0.3%)	2 (0.2%)	0	0	2 (0.3%)	2 (0.1%)
Conjunctival hyperaemia	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Corneal epithelium defect	0	1 (0.2%)	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)
Erythema of eyelid	1 (0.2%)	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Eye discharge	0	1 (0.2%)	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)
Oculogyric crisis	0	0	0	0	1 (0.1%)	0	1 (0.1%)
Swelling of eyelid	1 (0.2%)	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Visual impairment	0	0	0	0	1 (0.1%)	0	1 (0.1%)
Infections and infestations	**0**	**0**	**0**	**0**	**1 (0.1%)**	**0**	**1 (0.1%)**
Conjunctivitis	0	0	0	0	1 (0.1%)	0	1 (0.1%)
Injury, poisoning and procedural complications	**0**	**0**	**0**	**0**	**0**	**1 (0.2%)**	**1 (0.1%)**
Chemical burns of eye	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Investigations	**0**	**0**	**0**	**0**	**1 (0.1%)**	**0**	**1 (0.1%)**
Intraocular pressure increased	0	0	0	0	1 (0.1%)	0	1 (0.1%)

N=number of subjects in group, SAF=safety set, TEAE=Treatment-Emergent Adverse Event.
Note: Subjects who participated in CYS-005 and who received vehicle in CYS-004 are counted in both the Vevizye 0.1% and Vehicle treatment arms.
Percentages are based on the total number of subjects in each treatment group and integration pool.
TEAEs are AEs that started or worsened on or after the date of first dose.SOCs and PTs within a SOC are listed in order of descending frequency for All Subjects in the Pool B population.
Subjects experiencing more than one TEAE within a given SOC or PT are counted once within that SOC or PT.

Only two non-ocular TEAEs were considered related to study treatment by the Investigator. In pool A, one subject (0.2%) in the vehicle group experienced a non-ocular treatment-related TEAE of headache. In pool B, in addition to this subject, one subject in the Vevizye 0.1% group (0.1%) reported a non-ocular treatment-related TEAE of sinusitis.

Serious adverse events, deaths, and other significant events

No patient died during the performed clinical studies.

The incidence of serious adverse events per SOC and PT in Pool A and Pool B are presented in Table 31. Most common serious adverse events occurred in SOC infections and infestations. None of the serious adverse events was considered related to the study treatment.

Table 31: Serious adverse events – Pool A and Pool B

	Pool A			Pool B			
System Organ Class (SOC) Preferred Term (PT)	CyclASol 0.1% (N=585) n (%)	Vehicle (N=577) n (%)	All Subjects (N=1162) n (%)	CyclASol 0.05% (N=51) n (%)	CyclASol 0.1% (N=738) n (%)	Vehicle (N=629) n (%)	All Subjects (N=1418) n (%)
Number of SAEs	**2**	**6**	**8**	**2**	**9**	**6**	**17**
Number of Subjects with at Least One SAE	**2 (0.3%)**	**6 (1.0%)**	**8 (0.7%)**	**2 (3.9%)**	**6 (0.8%)**	**6 (1.0%)**	**14 (1.0%)**
Infections and infestations	**1 (0.2%)**	**3 (0.5%)**	**4 (0.3%)**	**0**	**4 (0.5%)**	**3 (0.5%)**	**7 (0.5%)**
Pneumonia	0	1 (0.2%)	1 (0.1%)	0	2 (0.3%)	1 (0.2%)	3 (0.2%)
Appendicitis	0	1 (0.2%)	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)
Cellulitis	0	0	0	0	1 (0.1%)	0	1 (0.1%)
Localised infection	1 (0.2%)	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Ophthalmic herpes simplex	0	1 (0.2%)	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)
Cardiac disorders	**0**	**0**	**0**	**2 (3.9%)**	**1 (0.1%)**	**0**	**3 (0.2%)**
Acute coronary syndrome	0	0	0	1 (2.0%)	0	0	1 (0.1%)
Atrial fibrillation	0	0	0	0	1 (0.1%)	0	1 (0.1%)
Myocardial infarction	0	0	0	1 (2.0%)	0	0	1 (0.1%)
Gastrointestinal disorders	**0**	**2 (0.3%)**	**2 (0.2%)**	**0**	**0**	**2 (0.3%)**	**2 (0.1%)**
Intestinal obstruction	0	1 (0.2%)	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)
Small intestinal obstruction	0	1 (0.2%)	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)
Nervous system disorders	**0**	**0**	**0**	**0**	**2 (0.3%)**	**0**	**2 (0.1%)**
Cerebrovascular accident	0	0	0	0	1 (0.1%)	0	1 (0.1%)
Transient ischaemic attack	0	0	0	0	1 (0.1%)	0	1 (0.1%)
Blood and lymphatic system disorders	**0**	**0**	**0**	**0**	**1 (0.1%)**	**0**	**1 (0.1%)**
Anaemia	0	0	0	0	1 (0.1%)	0	1 (0.1%)
Hepatobiliary disorders	**1 (0.2%)**	**0**	**1 (0.1%)**	**0**	**1 (0.1%)**	**0**	**1 (0.1%)**
Cholelithiasis	1 (0.2%)	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Musculoskeletal and connective tissue disorders	**0**	**1 (0.2%)**	**1 (0.1%)**	**0**	**0**	**1 (0.2%)**	**1 (0.1%)**
Intervertebral disc degeneration	0	1 (0.2%)	1 (0.1%)	0	0	(0.2%)	1 (0.1%)

N=number of subjects in group, SAE=serious adverse event.
Note: Subjects who participated in CYS-005 and who received vehicle in CYS-004 are counted in both the Vevizye 0.1% and Vehicle treatment arms.
Percentages are based on the total number of subjects in each treatment group and integration pool.
SOCs and PTs within a SOC are listed in order of descending frequency for All Subjects in the Pool B population.
Subjects experiencing more than one SAE within a given SOC or PT are counted once within that SOC or PT.

Laboratory findings

Clinical laboratory evaluations were performed in the Phase I study CYS-001 in healthy volunteers (hematology, clinical chemistry, and urinalysis) and in the Phase II study CYS-002 (hematology and blood chemistry). Only temporary increases in CK, CK-MB, AST and ALT were observed in two subjects in study CYS-001. In study CYS-002, no laboratory results of clinical concern were reported. No clinically significant shifts in laboratory hematology or blood chemistry occurred in any treatment group.

Ophthalmologic examination findings

Visual acuity, slit-lamp biomicroscopy, intraocular pressure, dilated fundoscopy examinations and drop comfort assessments were performed and are briefly discussed for Pool A and Pool B.

Best-corrected visual acuity (logMAR) was assessed at each study visit using an ETDRS chart. No meaningful and consistent differences were seen between the study visits in any of the treatment groups or between the treatment groups in either of the eyes.

Slit-lamp biomicroscopy examinations of the cornea, conjunctiva, anterior chamber, iris, lens, and lid were performed at all visits. Results were graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). Abnormal clinically significant values were reported in only a very few subjects, only concerning lens and cornea. These included 8 cases in cyclosporine 0.1% treated eye after baseline. The number of abnormal clinically significant values was balanced between the vehicle and the cyclosporine 0.1% groups.

The vast majority of findings remained stable throughout the studies. Shifts at regular study visits were only seen for two individual subjects:

- Cornea: in the vehicle group in one subject for the study eye and the fellow eye on Day 29 (Subject 31-049 in CYS-004), the SAE related to these abnormalities was ophthalmic Herpes simplex
- Lens: in the Vevizye 0.1% group in one subject for the fellow eye (Subject 31-036 in CYS-004) had not clinically significant nuclear sclerosis at baseline in both eyes, at Day 29 it was assessed as clinically significant in the right eye

Subjects' **IOP** was assessed by contact tonometry in each eye at select visits in each trial. No meaningful and consistent differences were seen between the study visits in any of the treatment groups or between the treatment groups in either of the eyes.

A **dilated fundoscopy** examination of the vitreous, retina, macula, choroid, and optic nerve was performed at select visits in each study. The results were graded as normal, abnormal NCS, and abnormal CS. In Pool A, there were no abnormal CS findings in dilated fundoscopy reported for any of the parameters at any of the timepoints. In Pool B, an abnormal CS finding was only reported for vitreous in one subject in the Vevizye 0.1% group for the study eye on Day 309. This was also the only shift from normal at baseline to abnormal CS post-baseline that was seen.

The **drop comfort** scale was assessed for each eye immediately upon instillation, and at 1 minute and 2 minutes following initial dosing. The drop comfort scale ranges from 0 to 10, with 0 indicating very comfortable and 10 indicating very uncomfortable. In general, the drop comfort scores are highly similar across the treatment arms and time points in both Pools.

Safety in special populations

The age range in the studies was 18 to 93 years of age. The percentage of subjects with AEs and TEAEs was in general higher in older subjects (aged ≥ 65 years) than in younger subjects (aged 18 to < 65 years), see Table 32.

Table 32: Incidence of (serious) adverse events in the cyclosporine 0.1% group in Pool A1 by age group.

MedDRA Terms Age	Age 18 <65 N=365 (62.4%)	Age 65-74 N=147 (25.1%)	Age 75-84 N=66 (11.3%)	Age ≥85 N=7 (1.2%)
Total AEs	58 (15.9%)	40 (27.2%)	15 (22.7%)	4 (57.1%)
Serious AEs – Total	1 (0.3%)	1 (0.3%)	0	0
AE leading to drop-out	1 (0.3%)	3 (2.0%)	1 (1.5%)	0
Ocular TEAEs	42 (11.5%)	23 (15.6%)	11 (16.7%)	1 (14.3%)
Non-ocular TEAEs	20 (5.5%)	20 (16.6%)	4 (6.1%)	3 (42.9%)

Safety related to drug-drug interactions and other interactions

Drug interactions were not examined. In the performed studies, only a very few patients used concomitant corticosteroids (N=4) and none IOP-lowering agents as per exclusion criteria.

For topically applied medications, it is recommended to keep a time distance of at least 15 minutes between the applications of Vevizye and any other eye medication concomitantly used.

Discontinuation due to adverse events

In pool A, the overall incidence of TEAEs leading to treatment discontinuation was 0.9% in the Vevizye 0.1% group and 0.5% in the vehicle group. TEAEs leading to treatment discontinuation were most frequently reported in the SOC eye disorders: 0.5% in the Vevizye 0.1% group and 0.2% in the vehicle group reported TEAEs leading to treatment discontinuation in this SOC.

At PT level, TEAEs leading to treatment discontinuation occurred in individual subjects only in any one treatment group. One subject in each treatment group was withdrawn from treatment due to instillation site reactions.

In pool B, the overall incidence of TEAEs leading to treatment discontinuation was 2.0% in the Vevizye 0.05% group, 1.1% in the Vevizye 0.1% group and 0.6% in the vehicle group. Similar to pool A, TEAEs leading to treatment discontinuation were most frequently reported in the SOC eye disorders and occurred in individual subjects only in any one treatment group, with the exception of instillation site pain which was reported in two subjects (0.3%) in the Vevizye 0.1% group and one subject (0.2%) in the vehicle group.

Post marketing experience

N.A.

2.10.9. Discussion on clinical safety

Vevizye contains new excipient, perfluorobutylpentane, that has not been used in a human medicinal product before. The clinical studies CYS-001 and CYS-002 showed systemic absorption of perfluorobutylpentane through ocular administration of Vevizye. Non-clinical PK data further show limited, but not zero association or accumulation of perfluorobutylpentane within tissues. However, reproductive organs are not the specific target of compound retention or toxicity. Epidemiological studies have also documented multiple associations between exposure to some poly- or perfluoroalkyl substances (PFAS) and a variety of health effects, in particular with relation to carcinogenicity, hormone imbalance and reproductive toxicity.

The Applicant justified that perfluorobutylpentane (a semifluorinated alkane) has a benign safety profile compared to PFAS with known toxicity. However, the provided discussion on studies performed with a structural surrogate and mode of action related to semifluorinated alkanes is convincing in showing that reproductive toxicity is not expected. Routine risk minimisation measures are considered sufficient to address the potential risks during pregnancy. SmPC section 4.6 does not recommend use during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. This is aligned with other cyclosporine containing eye drops on the market and acceptable considering the available data on cyclosporine and the provided discussion regarding the excipient perfluorobutylpentane.

The Vevizye clinical development programme includes five clinical studies in subjects with DED and one study in healthy volunteers. The main body of evidence for safety of Vevizye originates from the two

Phase 3 vehicle-controlled clinical studies CYS-003 and CYS-004. Data from these studies has also been pooled (Pool A). Data from dose-response study CYS-002 and the open-label extension study CYS-005 has been pooled together with the pivotal Phase 3 studies in Pool B.

A total of 738 patients with DED were exposed to at least one dose of Vevizye in the vehicle-controlled studies and their extensions (Pool B). Only a limited number of patients has been exposed to Vevizye for ⩾1 year (N=139 (9.8%)). Mean exposure to Vevizye 0.1% was 133 days and median 84 days (Pool B). The size of the safety dataset is considered acceptable, considering the known adverse event profile of ciclosporin.

Approximately 20% of patients in both Vevizye 0.1% arm (n=117, 20%) and vehicle arm (n=117, 20.3%) experienced a treatment-emergent adverse event in Pool A. Approximately 90% of these events were mild in the Vevizye arm (n= n=106/117) as compared to approximately 80% in the vehicle arm (n=94/117). In Pool B the maximal severity of TEAEs was balanced between the Vevizye 0.1% and vehicle arm. Discontinuation due to adverse events was rare i.e. 5 (0.9%) in Vevizye 0.1% arm and 3 (0.5%) in the vehicle arm in pool A. This was similar in pool B (overall 132 (0.9%).

Specifically in study CYS-003, the number of subjects with ocular TEAEs was higher in Vevizye 0.1% group when compared to vehicle (20; 12.3% vs 14; 8.4%, respectively). Similarly, the incidence of ocular TEAEs with mild severity was higher in Vevizye 0.1% group when compared to vehicle (31; 19.1% vs 22; 13.3%, respectively). However there was no single term driving the imbalances between Vevizye group and vehicle group and the overall number of subjects with ocular TEAEs in the Vevizye program was low.

Instillation site pain was the most commonly reported treatment-emergent adverse event, with a similar incidence in the Vevizye 0.1% and the vehicle arm (7.9% (n=46) vs. 6.4% (n=37) in Pool A, respectively), followed by visual acuity reduced, also with a similar incidence between study arms (2.1% (n=12) vs. 2.8% (n=16) in Pool A, respectively). In overall, ocular TEAEs and non-ocular TEAEs occurred infrequently and the incidences were comparable between Vevizye 0.1% and vehicle. Ocular infections were rare: iritis N=1 (0.1%) (Vevizye 0.1% arm), conjunctivitis N=3 (0.2%) (two in Vevizye 0.1% arm and one in vehicle arm) and hordeolum N=3 (0.2%) (two in Vevizye 0.1% arm and one in vehicle arm). Neoplasms occurred also rarely (N=6) (0.6%) and were not considered related to the study drug. However, due to the known effects of cyclosporine and in line with other ocular cyclosporine products registered in the EU, use of Vevizye is contraindicated in ocular or peri-ocular malignancies or premalignant conditions and in active or suspected ocular or peri-ocular infection.

Vitreous detachment occurred in Pool B in 10 subjects (0.7%) in the Vevizye 0.1% group in comparison to none in the vehicle group. However, the longer follow-up time in CYS-005 with regular eye examinations may have impacted the disbalance seen in occurrence of vitraeous detachment between the Vevizye and vehicle group. Furthermore, the characteristics of patients with vitraeous detachment match the population susceptible to this event. It is also questionable whether cyclosporine or the excipient perfluorobutylpentane will reach the retina or vitreous humor in human eye. Altogether, causality to Vevizye cannot be concluded.

In addition, posterior capsule opacification occurred in Pool B in 3 subjects in the Vevizye 0.1% group (0.4%) as compared to none in the vehicle group. All patients with posterior capsule opacification had undergone cataract surgery in the past, as expected. For one patient this was already noted at baseline. Causality to Vevizye cannot be concluded based on the available evidence. Some infections occurred more frequently in the Vevizye arm as compared to the vehicle arm (COVID-19, Herpes zoster, Bronchitis). The majority of the infections discussed occurred in study CYS-005 i.e. the open-label follow-up study. With respect to COVID-19, half of the cases reported occurred during the peak in confirmed COVID-19 cases between January-February 2022. The overall incidence of COVID-19 in the study was not increased in comparison to the overall incidence in the USA at the time of the study.

Herpes zoster was reported in 3 patients, from which 2 during CYS-005. One patient was taking hydroxychloroquine with immunosuppressive properties. All patients were women around 50 years of age or above, thus with a higher risk of herpes zoster infection.

Six cases of bronchitis were reported, from which five in CYS-005. Three patients had risk factors for developing bronchitis (asthma, COPD, seasonal allergy).

Causality between the above discussed infections and Vevizye cannot be concluded based on the available data and therefore addition of these adverse events to the SmPC is not warranted. An overall warning on immunosuppressive effects of cyclosporin has been added to the SmPC, as was requested previously.

The applicant has presented a selection of adverse events in SmPC section 4.8, based on treatment-emergent adverse events which were considered treatment related and were reported in >2 subjects in the overall study population. This approach can be accepted considering the low incidence of individual adverse events in overall and the similar rates between the Vevizye 0.1% and vehicle arm.

In the study CYS-002 one subject in the vehicle group discontinued due to an adverse event of chemical eye injury. The reason for discontinuation was conjunctivitis due to administered vehicle, which resolved after 4 days when treated. As isolated cases of local intolerabilities can occur with any eye drops, no concern is raised

Vevizye contains ethanol as excipient. Taking into consideration the fact that the proposed formulation was well tolerated, the presence of alcohol in the eyedrops can be accepted.

Serious adverse events were rare and the incidence of serious adverse events was similar in Vevizye 0.1% (n=6, 0.8%) and vehicle arms (n=6, 1.0%) in Pool B. It is agreed with the applicant that the relationship to study drug is unlikely. No serious ocular infections or malignancies occurred in the cyclosporine arms during the studies.

Ophthalmologic examinations including visual acuity, tonometry, slit-lamp examination and fundoscopy revealed no clinically relevant differences between Vevizye 0.1% and vehicle, also in terms of shifts from baseline. In general the drop comfort scores were comparable between Vevizye 0.1% and vehicle.

Data provided on laboratory findings is sufficient and did not raise concerns.

Comparison of adverse event profiles between genders and races is hampered by the fact that the majority of included patients were female and white. In general, treatment-emergent adverse events tended to occur more often in females than males and less frequently in Asian patients as compared to Black or African American patients and White patients.

The age range in the studies was up to 93 years of age. Comparison of adverse event profiles in different age subgroups has been presented in patients 18-⩽65 year of age versus patients 65-74, 75-84 and 85+ years of age. From these, the highest age group of >85 years of age includes a limited number of 17 patients in total in Pool A.

In overall, patients in all subgroups of older patients experienced more TEAEs than patients under 65 years of age. Within the different subgroups above 65 years of age, while there seems to be a higher incidence of ocular and other TEAEs in patients between 75 and 84 years of age as compared to those between 65 and 74 years of age, the incidence in Vevizye 0.1% group is lower than in the vehicle group in Pool A. When examining data on non-ocular TEAEs in Pool B, the longer follow-up time for patients in Vevizye 0.1% group and the comorbidities in older population should be taken into account when comparing the incidence of TEAEs to the vehicle group. Altogether the provided data does not point towards differential safety profile within older patient subgroups.

Instillation site pain was more frequent in patients ⩾65 years of age as compared to younger patients (9.5% vs. 6.8%, respectively). This difference is stated in SmPC section 4.8.

No interaction studies have been performed and only very few patients in the studies used concomitant ocular medications. As patients with dry-eye disease may use concomitant ocular medications such as corticosteroids or IOP-lowering agents and risks in concomitant use cannot be ruled out, these medications are addressed in the SmPC section 4.5. With respect to use in patients with glaucoma, the text was moved to section 4.4. (SmPC).

2.10.10. Conclusions on clinical safety

The safety profile of Vevizye is characterised by mild instillation site reactions and ocular adverse events, which were transient in nature. Severe adverse events were rare. Potential risks associated with concomitant use with other ophthalmic treatments were appropriately reflected in the SmPC.

2.11. Risk Management Plan

2.11.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.12. Pharmacovigilance

2.12.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.12.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.13. Product information

2.13.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the

applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-risk balance

3.1. Therapeutic Context

Vevizye 1 mg/mL eye drops, solution is intended for "the treatment of moderate to severe dry eye disease in adult patients, which has not improved despite treatment with tear substitutes.".

Dry eye disease (DED), also known as keratoconjunctivitis sicca, is defined as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (international Dry Eye Workshop – DEWS, Craig et al., 2017).

Clinically, DED is characterized by a persistently unstable and/or deficient tear film causing discomfort and/or visual impairment, accompanied by variable degrees of ocular surface epitheliopathy, inflammation, and neurosensory abnormalities (Tsubota et al 2020).

DED patients present ocular discomfort signs (e.g., redness, reduction in tear production, mucus discharge, fast tear break-up time) and symptoms (e.g., burning, irritation) of increasing frequency, although there is usually poor correlation between signs and symptoms. If untreated or undertreated, DED progressively damages the ocular surface with possible major ocular complications such as infections or ulcers, and potentially irreversible impairments of visual functions (Rouen et al 2018). DED has been associated with a substantial impact on vision, quality of life (Buchholz et al 2006; Leonardi et al 2021; Morthen et al 2021), and work productivity, and carries a significant physical and psychological burden (Messmer et al., 2023, Morthen et al 2021).

Goal of DED management is to restore homeostasis of the ocular surface which can be achieved by breaking the inflammatory vicious circle of pathophysiology (Messmer et al., 2023).

3.2. Available therapies and unmet medical need

The therapeutic approach in DED is typically multistage. Initially, environmental factors that increase tear evaporation and may decrease tear production should be minimized. Tear supplementation with artificial tears / lubricants is usually the first line treatment for mild to moderate cases of DED (Craig et al 2017). When the first line approach provides insufficient control of the disease, anti-inflammatory treatments should be employed. Treatments recommended by the International Dry Eye Workshop (DEWS) of the Tear Film and Ocular Surface Society and multiple treatment guidelines include ciclosporin and corticosteroids (Jones et al 2017, German Leitlinie BVA und DOG, 2019; Guias espanolas Ojo Seco).

Topical corticosteroids are effective anti-inflammatory agents in DED, but can be used only for short-term periods due to potential adverse events. Topical ocular ciclosporin may be employed as a second line treatment in DED for a more extended period of time (Messmer et al. 2023, Leitlinie von BVA und DOG Trockenes Auge, 2019). Ikervis is currently the only topical ocular ciclosporin product, centrally approved in the EU for the treatment of DED (EMA/CHMP/473489/2014). Ikervis is indicated for "*the treatment of severe keratitis in adult patients with DED, which has not improved despite treatment with tear substitutes."* The approved target population of Ikervis represents only a subset of the moderate to severe DED patients who may benefit from topical ciclosporin based on international treatment recommendations. About 10-15% of patients treated with Ikervis discontinue the treatment due to

intolerance to the product (Ikervis EMA EPAR 2015; Deshmukh et al 2022). To mitigate local intolerance and overcome late onset of effect, Ikervis is frequently bridged with topical corticosteroids, which are tapered off over 4-8 weeks.

There is an unmet medical need for topical anti-inflammatory treatments particularly for moderate DED patients not responding to first line therapies such as artificial tears. For patients with moderate and severe DED, there is need for treatments with improved tolerability that could reduce concurrent use of corticosteroids.

3.3. Main clinical studies

The main evidence of efficacy is derived from two multicenter, randomized, double-masked and vehicle-controlled studies (i.e., CYS-003 and CYS-004) with similar study design comparing efficacy and safety of Vevizye 0.1% versus its own vehicle. The patients included were of both sexes and ≥18 years of age. The patients had a reported history of DED in both eyes for at least 6 months, and used tear substitutes within 30 days. Subjects were eligible when they met both the symptoms and signs outcome criteria. The symptom criteria that had to be met was a total OSDI score ≥20/100 (study CYS-003) or a VAS dryness score ≥50/100 (study CYS-004). In addition the signs criteria that had to be met were; at least one eye with total corneal fluoresceine score (tCFS) ≥10/15 (NEI scale), total lissamine green conjunctival score ≥2 (Oxford scale), and unanesthetized Schirmer's tear test score ≥1 and ≤10 mm. These criteria had to be met both at screening and after a 14-day run-in period where they were treated with artificial tears.

A total of 1162 patients (n=328 patients (CYS-003) and n=834 patient (CYS-004)) were randomized to receive treatment with either Vevizye 0.1% ophthalmic solution (Vevizye) or vehicle in a 1:1 ratio for 84 days (CYS-003) or 29 days (CYS-004).

Primary efficacy endpoints were assessed for both studies at day 29. Common primary sign endpoint was change from baseline (CFB) in total corneal fluorescein staining score (tCFS, NEI) at Day 29. Primary symptom endpoint was CFB in total OSDI score at Day 29 in study CYS-003, and CFB in dryness score (VAS) at Day 29 in study CYS-004.

3.4. Favourable effects

Both pivotal studies showed a significant reduction of tCFS score (NEI scale) from baseline to Day 29 in patients treated with Vevizye compared to vehicle (CYS-003: LS Mean Difference (CI) -0.8 (-1.3, -0.4), p=0.0002; CYS-004: LS Mean Difference (CI) -0.41 (-0.77, -0.04), p=0.0278). This was confirmed by secondary analysis of responders in tCFS, defined as proportion of subjects with ≥3 tCFS score improvement (CYS-003: responders Vevizye 52.9 %, Vehicle 40.6%, P=0.0032; CYS-004: responders Vevizye 71.6 %, Vehicle 59.7%, P=0.0002).

This finding was supported by improvements in other key secondary outcomes of DED, including corneal fluorescein staining of the central region (cCFS), conjunctival lissamine green staining, and unanesthetized Schirmer's test (tear production).

In both pivotal studies, cCFS scores were reduced in the Vevizye 0.1% group compared to vehicle at Day 29 (CYS-003: Δ in mean CFB (CI) -0.2 (-0.4, 0.0), P ≤ 0.001; CYS-004: LS Mean Difference (CI) -0.12 (-0.23, 0.00), p=0.0410).

Conjunctival lissamine green staining scores decreased in the Vevizye 0.1% group compared to vehicle from baseline to Day 29 in both pivotal studies (CYS-003: Δ in mean CFB (CI) -0.5 (-0.9, -0.2), P ≤ 0.001; CYS-004: LS Mean Difference (CI) -0.33 (-0.53, -0.14), p=0.0009).

Difference in proportion of responders in unanesthetized Schirmer's Tear Test (≥10mm increase) between the Vevizye and vehicle group at Day 29 was significant in study CYS-004 (p= 0.0487), whereas in study CYS-003 was not significant at Day 29 (p= 0.9243), but significant at Day 85 (p= 0.0344).

3.5. Uncertainties and limitations about favourable effects

Improvement in signs (corneal and conjunctival integrity, and tear production) was not accompanied by symptom relief in comparison to vehicle.

3.6. Unfavourable effects

The main safety data for Vevizye 0.1% originates from two Phase 3 vehicle-controlled studies CYS-003 and CYS-004 which have been pooled (Pool A). Altogether, 738 patients with dry-eye disease have been exposed to at least one dose of Vevizye during the clinical development program. 139 patients have been exposed to Vevizye for ⩾1 year.

No deaths were reported during the studies. Serious adverse events were rare and the incidence of serious adverse events was similar in Vevizye 0.1% (n=6, 0.8%) and vehicle (n=6, 1.0%) arms. Discontinuation due to adverse events was also rare (0.9%) and similar between treatment arms.

Approximately 20% of patients in both Vevizye 0.1% arm (n=117, 20%) and vehicle arm (n=117, 20.3%) experienced a treatment-emergent adverse event in Pool A. Approximately 90% of these events were mild in the Vevizye arm as compared to approximately 80% in the vehicle arm.

Instillation site pain was the most commonly reported treatment-emergent adverse event, with a similar incidence in the Vevizye 0.1% and the vehicle arm (7.9% vs. 6.4% in Pool A, respectively), followed by visual acuity reduced, also with a similar incidence between study arms (2.1%, n=12 vs. 2.8%, n=16) in Pool A, respectively). Overall, ocular TEAEs and non-ocular TEAEs occurred infrequently and the incidences were comparable between Vevizye 0.1% and vehicle. Of note, only two non-ocular treatment emergent adverse events were considered related to study treatment by the Investigator.

Ocular infections were rare: five were reported in the Vevizye 0.1% arm and two in the vehicle arm. Neoplasms occurred also rarely (N=6) and were not considered related to the study drug.

Visual acuity, slit-lamp biomicroscopy, intraocular pressure and dilated fundoscopy examinations were performed and did not reveal clinically meaningful differences between Vevizye 0.1% and vehicle arms.

The overall incidence of adverse events and treatment-emergent adverse events was higher in older patients. Instillation site pain was more frequent in patients ≥65 years of age as compared to younger patients (9.5% vs. 6.8%, respectively).

3.7. Uncertainties and limitations about unfavourable effects

n.a.

3.8. Effects Table

Table 33: Effects Table for VEVIZYE 1 mg/mL eye drops, solution, for the treatment of dry eye disease in adult patients, which has not improved despite treatment with tear substitutes

Effect	Short Description	Unit	Vevizye 0.1%	Vehicle	Strength of evidence	Uncertainties	References
Favourable Effects							
tCFS	CFB to Day 29, Mean (SD). NEI scale total score (0-15)		-2.9 (2.59)	-2.2 (2.73)	p=0.0002	Study populations had moderate to severe corneal damage (tCFS 10-15 NEI scale)	CYS-003
			-4.3 (3.15)	-3.9 (3.44)	p=0.0278		CYS-004
tCFS resp.	Proportion of responders at Day 29	%	52.9	40.6	P=0.0032		CYS-003
			71.6	59.7	P=0.0002		CYS-004
cCFS	CFB to Day 29, Mean (SD). NEI scale total score (0-3)		-0.6 (0.87)	-0.4 (0.86)	p≤0.001		CYS-003
			-0.9 (0.95)	-0.8 (0.99)	p=0.0410		CYS-004
LGS	CFB to Day 29, Mean (SD). Oxford scale score (0-10)		-1.0 (1.49)	-0.5 (1.49)	p≤0.001		CYS-003
			-1.3 (1.83)	-1.0 (1.74)	p=0.0009		CYS-004
Shirmer	Proportion of responders at Day 85	%	12.3	5.5	P=0.0344		CYS-003
	Proportion of responders at Day 29	%	10.8	6.8	P=0.0487		CYS-004
Unfavourable Effects							
SAE's	Serious adverse events	%	0.3%	1.0%			Pool A
Eye disorders		%	5.8%	6.9%			Pool A
- infections		%	0.3%	0.3%			
Installation site reactions		%	8.0%	6.8%			Pool A

Abbreviations: tCFS = Total Corneal Fluorescein Staining; cCFS = Central Corneal Fluorescein Staining; LGS = Conjunctival Lissamine Green Staining; NEI = National Eye Institute; SAE = serious adverse events. Abbreviations: CFB = change from baseline; SD = standard deviation; CI = confidence interval.

Notes: Sample size CYS-003 N = 328, CYS-004 N = 834; Proportion of responders in tCFS was defined as number (%) of subjects with ≥3 improvement tCFS score; Proportion of responders was defined as number (%) of subjects with ≥ 10 mm increase from baseline.

3.9. Benefit-risk assessment and discussion

3.9.1. Importance of favourable and unfavourable effects

Clinical efficacy

Vevizye showed efficacy on different objective signs of DED. The signs assessed in the clinical studies are included in international therapeutic guidelines in DED. They are measures also used in clinical practice for determining and monitoring disease severity and progression (Messmer et al., 2023). These measures include assessments of corneal and conjunctival staining and tear production.

Reduction on total corneal staining after treatment with Vevizye is an objective measure of improved corneal surface. Improvement on the central region of the cornea is of particular relevance for the patients, as it is associated with visual functioning (Kaido et al, 2011). Reductions on conjunctival staining and increased tear production are additional beneficial effects in support of efficacy on the broad ocular surface and lacrimal apparatus.

There were significant effects on DED signs in the Vevizye group compared to vehicle. With regard to corneal integrity, improvements on tCFS ≥ 3 and cCFS ≥ 1 on the NEI scale (not a linear scale) are considered meaningful for the patient. In the Vevizye group, mean change from baseline (SD) at Day 29 in tCFS was -2.9 (2.59) in study CYS-003 and -4.3 (3.15) in CYS-004, whereas mean change from baseline (SD) at Day 29 in central CFS was -0.6 (0.87) and -0.9 (0.95) in pivotal study CYS-003 and CYS-004, respectively. However, compared to vehicle, differences seem small. In study CYS-003 and study CYS-004 the difference in reduction of the total CFS (NEI scale) at day 29 was -0.8 (p=0.0002) respectively -0.41 (p=0.0278) both favouring Vevizye when compared to the vehicle. While these differences on the NEI scale seem small, the responder analysis confirmed clinical meaningful benefit.

Analysis of unanesthetized Schirmer's tear test score responders showed a higher proportion of patients with clinically meaningful improvement of tear production (≥ 10 mm increase) in the Vevizye group compared to vehicle in both pivotal studies, although at two different time points.

Generally, efficacy results were consistent across two independent, adequate and well-controlled pivotal studies (total N= 1.162), and supported by a third adequate and well-controlled clinical study in a Chinese population (N=206).

The improvement on signs not accompanied by an improvement in symptom was also seen and discussed for Ikervis. It was generally acknowledged that symptom improvement lags far behind sign improvement.

Currently, Ikervis is approved for treatment of patients with severe keratitis. For Ikervis efficacy in moderate keratitis was not evident. Vevizye, however, was tested in patients with moderate to severe corneal impairment (tCFS ≥10/15 NEI scale). Subgroup analyses confirmed efficacy in both moderate and severe DED subjects, regardless of definition used, i.e., based on tCFS (on NEI scale), cCFS (on NEI scale), Schirmer's tear test or Dryness scoreHence, Vevizye could fill an unmet medical need in moderate DED as well.

Effectiveness of Vevizye was adequately evaluated after short-term treatment (29 and 84 days in CYS-004 and CYS-003 study, respectively). Long-term efficacy over the course of one year was a secondary objective of the open label and single arm supportive study CYS-005. Though the data can only be interpreted to a limited extent, long term efficacy is considered demonstrated. Moreover, the applicant has included a statement in the SmPC to evaluate the effectiveness of Vevizye and the severity of DED every 3 months. This is in line with clinical practice and reflects the clinical data.

Clinical safety

The safety profile of Vevizye is characterised by mild and transient instillation site reactions and ocular adverse events which in the majority of cases were manageable as only in a few cases these effects led to treatment discontinuation. Considering the already existing ocular discomfort in patients with dry-eye disease, the low number of ocular adverse events is beneficial. Severe adverse events were rare.

The immunosuppressive effect of cyclosporine is well known. In the performed studies with Vevizye, ocular infections occurred rarely and none of these were severe. Susceptibility to (ocular) infections and malignancies is adequately described in the product information.

Ocular adverse events were more common in older patients as compared to younger patients. Considering the changes in ocular surface with increasing age, these adverse events may be more bothersome in older patients than others. Instillation site pain was more common in older patients and is addressed in the SmPC.

3.9.2. Balance of benefits and risks

From the clinical point of view, short-term efficacy of Vevizye has been shown on different signs of moderate to severe DED. This effect is confirmed in subgroup analyses for both moderate and severe DED patients across different efficacy endpoints. The SmPC contains a statement to review DED severity every 3 months, which allows long term use and reflects clinical practice.

Mild and transient instillation site reactions and ocular adverse events are of limited clinical relevance.

The positive effects on corneal, conjunctival integrity and tear production outweigh the relatively mild adverse events observed with Vevizye.

3.9.3. Additional considerations on the benefit-risk balance

Not applicable

3.10. Conclusions

The overall benefit/risk balance of the medical product Vevizye is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vevizye is favourable in the following indication(s):

Treatment of moderate to severe dry eye disease (keratoconjunctivitis sicca) in adult patients, which has not improved despite treatment with tear substitutes (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.